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**FACTORES ASOCIADOS A LA
DISMINUCIÓN DE LA FUNCIÓN FÍSICA
EN ADULTOS MAYORES**

TESIS DOCTORAL

Alejandro Álvarez Bustos

DIRECTORES

Dr. Leocadio Rodríguez
Mañas

Dra. Cristina Alonso
Bouzón

TUTOR

Dr. Fernando Rodríguez
Artalejo

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*“Saber envejecer es la obra maestra de
la sabiduría y una de las partes más
difíciles del gran arte de vivir”*

Henri-Frédéric Amiel

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Acronyms and abbreviations

AWGOS: Asian Working Group on Sarcopenia.

ADL: Activities of Daily Living.

AKT: Protein Kinase B.

ALM: Appendicular Lean Mass.

BMI: Body Mass Index.

COPD: Chronic Obstructive Pulmonary Disease.

CI: Confidence Interval.

CC: Coyoacan Cohort.

CRP: C-Reactive Protein.

DHEA: Dehydroepiandrosterone sulfate.

DQI-I: Diet Quality Index-International.

EWGSOP: European Working Group on Sarcopenia in Older People.

FCA: Federal Council on Ageing.

FI: Frailty Index.

FIBRA-RJ: Frailty in Brazilian Older People Study—Rio de Janeiro.

FNIH: Foundation for the National Institutes of Health.

FRADEA: FRAilty and DEpendence in Albacete study.

FTS: Frailty-Trait Scale.

FTS-3: Frailty-Trait Scale shortest form (3 items).

FTS-5: Frailty-Trait Scale short form (5 items).

Hb: Hemoglobin.

IGF-1: Insulin-like Growth Factor-1.

IL6: Interleukin-6.

ICD-10: International Classification of Diseases-10.

IWGS: International Working Group on Sarcopenia.

MMSE: Mini-Mental State Examination.

mTOR: mammalian target of rapamycin.

MUFAs: Mono-Unsaturated Fatty Acid.

PI3K: Phosphatidylinositol-3-Kinase.

ROS: Reactive Oxygen Species.

s-FNIH: standardized Foundation for the National Institutes of Health.

SHARE: Survey of Health, Aging and Retirement in Europe.

TSHA: Toledo Study of Healthy Ageing.

TNF- α : Tumor Necrosis Factor-alpha.

USA: United States of America.

WHO: World Health Organization.

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Summary

The world's population is ageing. Thanks to medical and technological advances over the last century, life expectancy has approached biological limits. The older adult population has doubled in fifty years and, according to some predictions, this trend will continue until at least 2050. By that year, people over 80 will triple their current number, growing from 126 million to 447 million.

The ageing process is characterized by various physiological as well as socio-economic and cultural changes, which can lead to increased morbidity and physical limitation. However, ageing is not necessarily linked to these two conditions. As we age, function becomes the most relevant factor related to adverse outcomes, such as mortality, hospitalization, institutionalization, falls, decreased quality of life, or increased healthcare resources.

In this conceptual framework in which function is intimately related to adverse events in older adults, and should lead the clinical approach in older adults, understanding the pathways that deteriorate physical function (disability) is a necessity. In the spectrum of function, from robustness to disability, frailty is the link between this condition of the two opposites. Frailty has been understood as a state of increased vulnerability, where any minor stressor could trigger the threshold of disability. In the first objective of this thesis, we conducted a narrative review of the mechanisms involved in frailty, derived from the ageing process itself and/or from the affection of different organs and systems.

Fortunately, it has been shown that frailty is reversible. In the first objective, we also show how, through physical activity and exercise, some of these mechanisms are hindered, thus reducing frailty, and increasing different factors of physical function.

Nevertheless, the progression of frailty (the trajectories of frailty, or the transition between frailty and non-frailty states) over time and the factors related to these changes in frailty levels remain to be elucidated. In the second objective, we determined the risk of certain adverse events, such as disability, hospitalization, and mortality, based on frailty trajectories. We found that those with moderate frailty scores who become increasingly frail as they age, have no added adverse risk of these events relative to those with lower frailty scores at baseline. This seems to confirm that it is the current functional status what confers the risk of adverse events.

However, the age-related low muscle mass and function, termed sarcopenia, could be one of the biological substrates in the deterioration of function. In the third objective, we determined that

the presence of sarcopenia is a risk factor in the development of frailty, as well as an impediment to its reversal. However, the presence of sarcopenia does not appear to increase the risk of death associated with frailty.

Finally, we explored healthcare cost expenditures associated to frailty, sarcopenia, or the coexistence of both entities in older adults. While sarcopenia was associated only with the likelihood of being hospitalized, frailty was associated with an increased use of hospital resources, such as the likelihood of hospitalization, number of hospital admissions and length of hospital stay, and may mediate the potential effects of sarcopenia.

Therefore, there is a need to promote early detection strategies and multidisciplinary interventions that reduce frailty and sarcopenia, to positively impact on reducing the risk of adverse events in older adults, as well as in healthcare systems.

Resumen

La población mundial está envejeciendo. Gracias a los avances médicos y tecnológicos logrados durante el último siglo, la esperanza de vida se ha acercado a los límites biológicos. La población adulta mayor se ha duplicado en cincuenta años y, según algunas predicciones, esta tendencia continuará al menos hasta 2050. Para ese año, las personas mayores de 80 años triplicarán el número actual, creciendo de los 126 a los 447 millones de personas.

El proceso de envejecimiento se caracteriza por diversos cambios fisiológicos, así como socioeconómicos y culturales, que pueden desembocar en aumento de morbilidad y la limitación física. Sin embargo, el envejecimiento no está necesariamente ligado a estas dos condiciones. A medida que envejecemos, la función se convierte en el factor más relevante relacionado con resultados adversos, como la mortalidad, la hospitalización, la institucionalización, las caídas, la disminución de la calidad de vida o el aumento de los recursos sanitarios.

En este marco conceptual en el que la función está íntimamente relacionada con eventos adversos en adultos mayores, y debe liderar el abordaje clínico en los adultos mayores, entender las vías que conducen al deterioro de la función física (discapacidad) es una necesidad. En el espectro de la función, desde la robustez hasta la discapacidad, la fragilidad es el enlace entre esta condición de dos opuestos. La fragilidad se ha entendido como un estado de mayor vulnerabilidad, en el que cualquier estresor menor podría disparar el umbral de la discapacidad. En el primer objetivo de esta tesis, realizamos una revisión narrativa sobre los mecanismos implicados en la fragilidad, derivados del propio proceso de envejecimiento y/o de la afectación de diferentes órganos y sistemas.

Afortunadamente, se ha demostrado que la fragilidad es reversible. En el primer objetivo también exponemos cómo mediante la actividad física y el ejercicio algunos de esos mecanismos se ven obstaculizados, reduciendo así la fragilidad y aumentando diferentes factores de la función física.

Sin embargo, la progresión de la fragilidad (las trayectorias de la misma, o la transición entre los estados de fragilidad y no fragilidad) a lo largo del tiempo y los factores relacionados con estos cambios en los niveles de fragilidad siguen sin dilucidarse. En el segundo objetivo, determinamos el riesgo de sufrir determinados eventos adversos, tales como la discapacidad, la hospitalización y la mortalidad, en base a las trayectorias de la fragilidad. Encontramos que aquellos con puntuaciones de fragilidad moderadas que revierten dicha condición a medida que envejecen, no presentan un riesgo adverso añadido de sufrir estos eventos en relación con aquellos que se encontraban con menores puntuaciones de fragilidad al inicio. Esto parece confirmar que es la situación funcional actual la que confiere el riesgo de eventos adversos.

Por otro lado, la baja masa y función masa muscular asociada a la edad, denominada sarcopenia, podría ser uno de los sustratos biológicos en el deterioro de la función. En el tercer objetivo, determinamos que la presencia de sarcopenia es un factor de riesgo en el desarrollo de fragilidad, así como un impedimento a la hora de revertir la misma. Sin embargo, la presencia de sarcopenia no parece aumentar el riesgo de muerte asociado a la fragilidad. Por último, exploramos si la presencia de fragilidad, la sarcopenia o la coexistencia de ambas entidades en los adultos mayores afectan a los costes relacionados con la hospitalización. Mientras que la sarcopenia tan sólo se asoció con la probabilidad de ser hospitalizado, la fragilidad se relacionó con mayor uso de los recursos hospitalarios, como la probabilidad de hospitalización, el número de admisiones hospitalarias y la duración de la estancia hospitalaria, pudiendo mediar en los efectos potenciales de la sarcopenia.

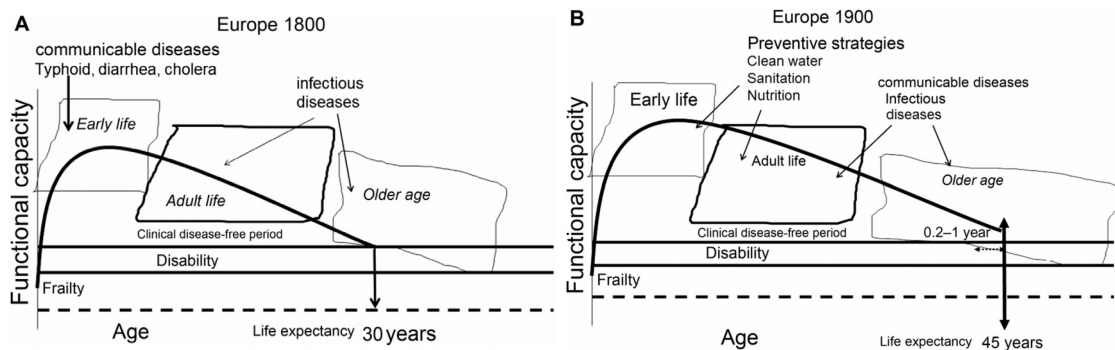
Por tanto, es necesario promover estrategias de detección precoz e intervenciones multidisciplinares que reduzcan el estado de fragilidad y sarcopenia, con el fin de impactar de manera positiva en la reducción del riesgo de eventos adversos en los adultos mayores, así como en los sistemas de salud.

Background

Ageing population

World population has increased exponentially. By 1500, the overall population was around 400 million people, reaching 1 billion when the 19th century started[1] and has grown to reach the 7.8 billion people in 2021[2]. Technological, nutritional, lifestyle and healthcare changes (such as sewage and safe drinking water[3], vaccination, and drugs) as well as improvement of living and environmental conditions, especially during the latest centuries, have allowed this spectacular increase of world population and have extended life expectancy to almost natural constraints[1,4], even exceeding last century predictions[5] (Figure 1).

These facts, together with the changing role of women in society and their inclusion in the world of work has led to a decline in the fertility rate, reshaping the demographic distribution resulting in ageing populations, especially in more developed societies, where in fact, more than 75% of the population die after the age of 75 [1] (Figure 2). While people aged 65 and older represent 9,3% of the overall population, this percentage exceeds 20% in countries as Spain[2] and is predicted to reach a third of the Spanish population by 2060 (Figure 3) [6]. Moreover, people aged 80 or older tripled their population from 1950 to 1980 and have tripled again in 50 years, reaching 145 million people[2] and according to prospect prediction, will triple again by 2050 [7].



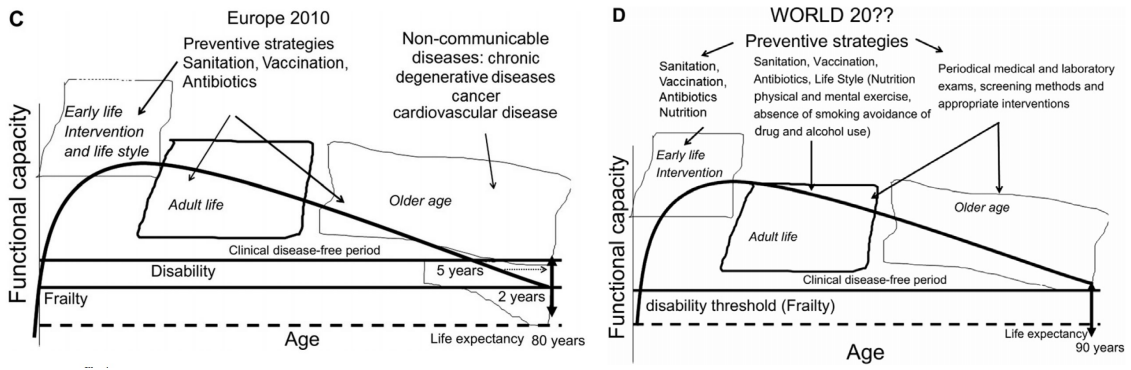


Figure 1. Life expectancy in Europe in 1800, 1900, 2010 and projections worldwide. Figure from Lunenfeld and Stratton, 2013[8].

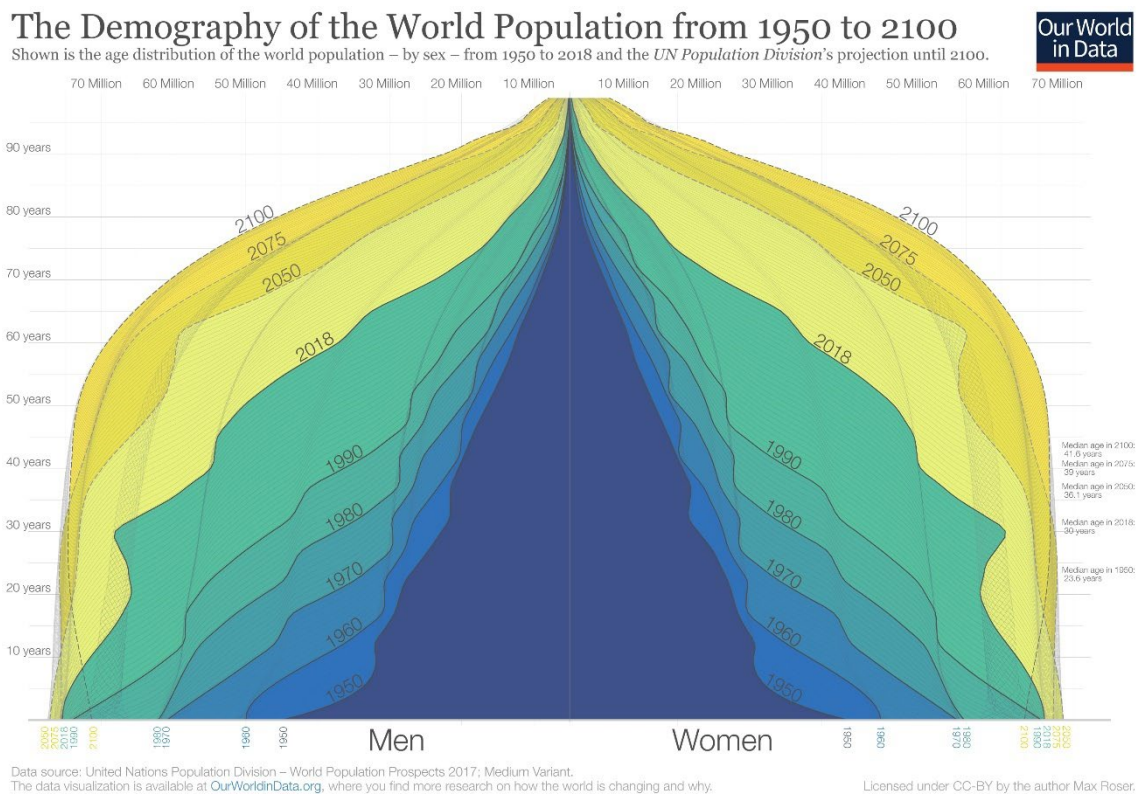


Figure 2. World population distributed by age and sex from 1950 and 2018 and projections until 2100. Data from OurWorldinData.org [9].

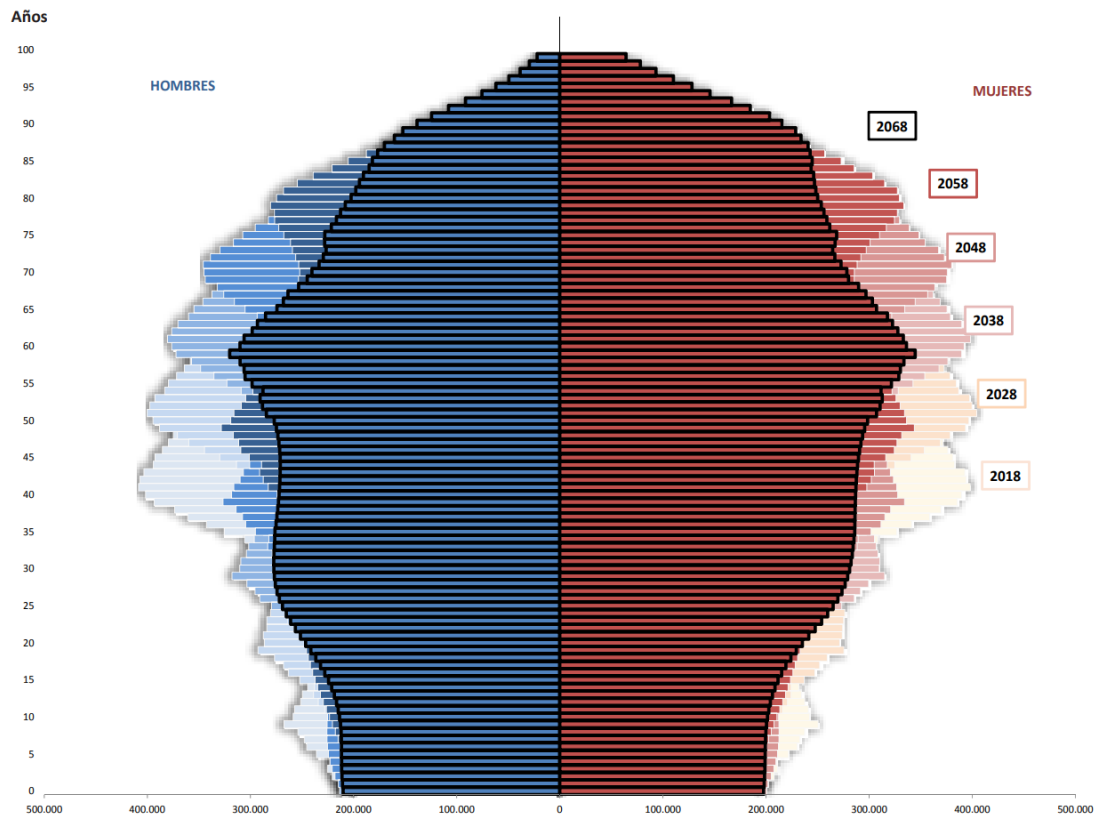


Figure 3. Spanish population projections by age and sex, 2018-2068. Figures from Informes Envejecimiento en red, 2020[6].

Importance of physical function in ageing

Ageing is a physiological process characterized by several changes, depending upon cultural and socio-economic conditions, including higher prevalent rates of morbidity and physical function limitation[10]. However, aging is not necessarily linked with these two conditions[11,12]. As we age, physical function becomes the most relevant factor related to adverse outcomes, such as mortality, hospitalization, institutionalization, falls, a decreased quality of life or an increment of health care resources[13].

In 1980, the World Health Organization (WHO) [14], based on previous models[15], proposed a conceptual model of disability in which disease impacts the individual causing an impairment, which in turn, leads to disability. For example, diabetes (disease) cause peripheral neuropathy which impact diminishing balance (impairment) causing the disability to the patient by not being able to shower (disability)[16]. This direct linkage with disability is not so clear, with some

diseases being highly prevalent in older adults, such as hypertension, which has prompted the proposal of several conceptual models [17,18]. Moreover, this traditional view failed to recognize disability as a static and unidirectional entity [19].

Focusing on this idea, in 2015, WHO released its first report on aging and health [20], recognizing the function relevance in the aging process. In this report, WHO defines Healthy Aging as “the process of developing and maintaining the functional ability that enables wellbeing in older age”. Thus, Healthy Aging paradigm is not linked with the absence of disease, but it is linked with the maintenance and enhancement of functional ability, which is a true milestone in the conception and the practical approach of health in older people[21,22].

In this conceptual functioning-based framework, in which biological age is not the same as chronological age[23], understanding the pathways leading to a lack of physical function (disability) is a necessity. To explain this, WHO[20] purpose the “functional ability”, determined by two factors: environment and intrinsic capacity. The environment will be the place which individuals live in and interact between other individuals and their own environment. So, if the environment is stable, functional ability depends on the intrinsic capacity, defined as “all the physical and mental capacities that an individual can draw on at any point in time”.

Intrinsic capacity starts declining after the third decade of life [24]. In parallel of intrinsic capacity, decrease the functional reserve. Functional reserve is the physiological capacity of avoiding or resisting against stressors. When this functional reserve is low, any stressor (such as acute diseases, hospitalization) could trigger the disability process, in which challenges from the environment, are too stressful for the individual who cannot perform them. Disability has appeared.

In the development of the so-called non-catastrophic disability, which is the usual model proposed for the disabling process in older population, the functional spectrum, ranging from robustness to disability, frailty seems to be the link between these two-opposite conditions, in which some capacities are impaired but could be improved yet[25–27] (Figure 4).

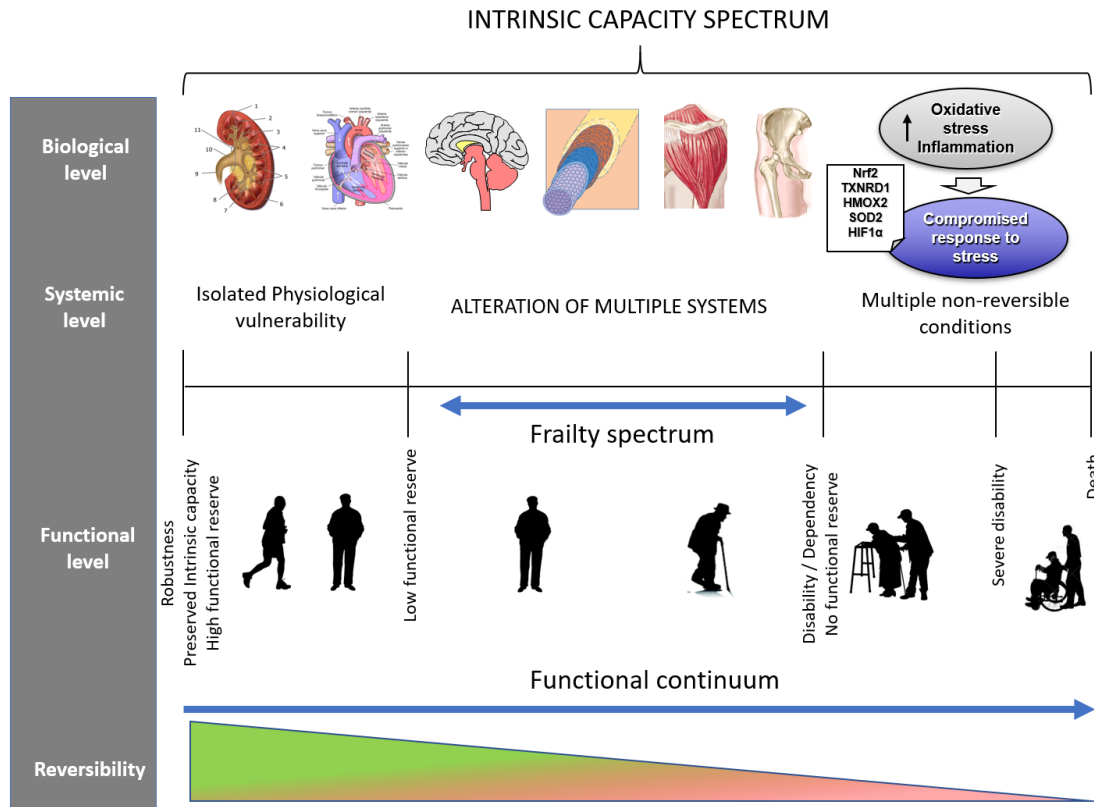


Figure 4. The spectrum of intrinsic capacity from the perspectives of organ and systemic level, and their clinical manifestations at functional level and chance of reversibility. Adapted from Angulo et al. 2020 [28]

Disentangling the disabling process

Disability has been defined as the need for personal assistance in their basic activities of daily living[29]. It represents the last link in the chain of mobility and functional independence, which not only diminishes the quality of life of the individual, but also their informal caregivers[30,31]. In addition, disabled patients have higher mortality[32] and institutionalization risks[33] and burden the system by suffering more hospitalizations or increasing health care resources[34,35]. Thus, disability is presented as a major problem to be avoided in public health policies[35]. However, there is evidence showing that individuals at birth will spend around a fifth of their lives with disability levels in the community. Although life expectancy has increased over the last 50 years, disability-free life expectancy has not, but rather the increase in life expectancy corresponds almost entirely to a greater time within disability levels, especially at older ages (Table 1) [36].

Table 1. Expected Years of Life Spent in Various States of Health, at Birth and at Ages 20–64, 65, and 85 Years, by Gender: United States, 1970–2010.

State of Health	1970, Mean (95% CI)	2010, Mean (95% CI)	Change, 1970–2010
Males			
At birth			
Total	67.0	76.2	9.2
Free of disability	56.5 (56.4, 56.6)	61.0 (60.9, 61.2)	4.5
With disability in community	10.0 (9.8, 10.1)	14.7 (14.6, 14.9)	4.7
Institutionalized	0.6 (0.6, 0.6)	0.4 (0.4, 0.5)	–0.2
At age 65 y			
Total	13.0	17.7	4.7
Free of disability	6.6 (6.6, 6.8)	9.3 (9.1, 9.4)	2.7
With disability in community	5.8 (5.7, 5.9)	8.0 (7.8, 8.1)	2.2
Institutionalized	0.5 (0.5, 0.5)	0.4 (0.4, 0.5)	–0.1
At age 85 y			
Total	4.7	5.8	1.1
Free of disability	1.4 (1.3, 1.6)	1.9 (1.8, 2.1)	0.5
With disability in community	2.7 (2.5, 2.8)	3.5 (3.3, 3.6)	0.8
Institutionalized	0.6 (0.5, 0.7)	0.4 (0.4, 0.5)	–0.2
Females			
At birth			
Total	74.6	81.0	6.4
Free of disability	62.7 (62.6, 62.8)	65.4 (65.3, 65.6)	2.7
With disability in community	10.9 (10.7, 11.0)	14.8 (14.6, 15.0)	3.9
Institutionalized	1.1 (1.0, 1.2)	0.8 (0.8, 0.9)	–0.3
At age 65 y			
Total	16.8	20.3	3.5
Free of disability	9.1 (9.0, 9.2)	11.5 (11.4, 11.6)	2.4
With disability in community	6.6 (6.5, 6.7)	8.0 (7.8, 8.1)	1.4
Institutionalized	1.1 (1.0, 1.2)	0.9 (0.8, 0.9)	–0.2
At age 85 y			
Total	5.6	6.9	1.3
Free of disability	1.4 (1.3, 1.6)	2.2 (2.1, 2.4)	0.8
With disability in community	3.0 (2.9, 3.2)	3.7 (3.6, 3.9)	0.7
Institutionalized	1.2 (1.1, 1.3)	0.9 (0.8, 1.0)	–0.3

Note. CI = confidence interval. Sum of life expectancy in states sometimes does not add to total expectation of life because of rounding.

Modified from Crimmins et al. 2016 [36].

It has been distinguished into three main disability groups: in the basic Activities of Daily Living (ADLs) disability[29,37,38]; mobility disability[39] and disability in the instrumental ADLs [29,40,41]. Other studies proposed to measure social factors and sensory aspects like visual, hear or the ability to speak[42].

About 10% of nondisabled community dwellings older than 64 develop disability, although incidence and prevalence depend on the type of activity assessed, disability is higher with aging

and among women [29,37,43]. By using limitations in daily living activities, disability prevalence has ranged from 16 to 54% in the low- and middle-income countries [44].

In Spain, Graciani et al. found rates of almost 73% of some type of disability in non-institutionalized older adults older than 60 years[42]. Other studies have reported that the disability prevalence among older adults older than 74 is 15.31% for moderate and 10.14% for severe or extreme disability[45].

Being women, older, living in rural areas, lower educational, physical activity, lower perceived health levels, being hospitalized in the last year, comorbidity or impairments in cognitive status had been related with disabled status[42]. Chronical entities like cardiovascular diseases (angina and previous stroke), lung diseases (asthma), metabolic disease (diabetes), musculoskeletal diseases (like sarcopenia or arthritis) or sensory diseases were significantly related with disability. Met prefrail, frail or sarcopenia criteria were also associated with severe disability[42].

Other studies have investigated the relevance of different factors on the speed of developing disability. Factors like older ages (≥ 85 years), hearing and cognitive impairment, be frail, low peak expiratory flow and low functional self-efficacy were associated with progressive disability. On the other hand, 4 factors (visual and hearing impairment, low physical and peak flow performance) were related to catastrophic disability, defined as the one that occurred from one month to the other [46].

On the other hand, higher educational or socioeconomic status was proved as protectors in developing disability[42].

Frailty

Frailty concept

“How easily the wind overturns a frail tree” thought Buddha 2500 years ago [47]. Instinctively, something weak, delicate and flimsy comes to mind when we think of something “frail”. In fact, “frêle” the French word which “frailty” comes from, means little resistance. This notion of little

resistance to stressors and the exhaustion of physiological reserves has been exploited by the geriatric medicine.

Since Monsignor Charles F. Fahey and the Federal Council on Aging (FCA) in the United States of America (USA) introduced the “frail elderly” term to describe a specific older adult population during the 1970s[48,49], lots of definition have been proposed to designate what we know today as frailty. Vaupel and colleagues defined “frailty” in 1979 as the unmeasured variability in the risk of death within the same age individuals[50]. But it is not until 1997, when frailty is taken into consideration as a clinical issue, thanks to the seminal paper of Campbell and Buchner[51]. Since then, two main conceptual concepts have dominated the field of frailty. The first one, led by the group of Rockwood and Mitninski in Canada, supports that frailty was the final outcome of accumulation of deficits[52,53]. The second one, led by Fried and Walston in Hopkins (USA), supports that frailty is a pre-disability phenotype with several underlying causes, able to predict several adverse outcomes[54]. In this same line of thinking, in 2013, Rodriguez-Mañas and other experts in frailty proposed a Delphi method-based consensus statement for defining frailty as “an age-associated, biological syndrome characterized by decreased biological reserves, which puts an individual at risk when facing minor stressors, and is associated with adverse outcomes (ie, disability, death, and hospitalization)” [55].

Except if indicated, the conceptual framework of frailty used in this PhD Thesis is the one of the Frailty Phenotype[54].

Prefrailty concept

Prefrailty status has been framed between robustness and frailty [56], emerging from theory[57] as an entity that increase the risk of adverse events compared to robustness[25], and precluding frailty status whereby interventions could be effective in preventing or delaying frailty[58].

Fried described that early frailty stages may be silent until the trigger was shot and the threshold of reserves was loss, resulting in frailty[59]. This idea was in line with Lang et al. [60] and Fusco et al.[61] opinion, defining prefrailty as a clinical silent process in which individuals could recover from stressors if they had sufficient physiological reserves. Frailty has been described as an

increased vulnerability [59,61], transitional stage [61,62], dynamic process [61–63] and physical frailty[57,64–67].

A recent review by Sezgin et al.[68] on the multidimensional construct of frailty proposes that the concept of frailty should also include factors that are not purely physical, but also cognitive or social factors that could secondarily affect these physical factors, as it had been proposed earlier [69]. In this same regard, recent findings show impairment in some cerebral areas in older frail people, connected to alterations in motor[70] and executive function[71]. On the other hand, although other scales such as the Frailty Index or the Frailty-Trait Scale (in its different versions) did not initially foresee a state of pre-frailty, some authors have proposed looking for this stage before frailty. For example, the continuum of the Frailty Index was adapted to robustness, pre-frailty and frailty stages in some studies[72,73], although in some others the results suggest that the category of prefrail could be simply a problem of misclassification of the subjects. In fact, almost two in three patients pigeonholed as prefrail according the Fried Phenotype may have the same risk for adverse events as robust, something that could be simply a problem of misclassification of the subjects[74].

Frailty as a global health problem

Millions of older adults all over the world present frailty. However, the lack of a universal definition with multiple tools to assess it and the paucity of research in low-income countries difficult the knowledge of overall prevalence and incidence.

Frailty incidence

While prevalence rates focus on periods in which a patient is affected by a particular disease, incidence tries to deal with transitions from disease to health. This concept is particularly interesting in frailty [75], due to during the aging process, transitions between frailty states are common [76,77].

A systematic review published in 2018, concluded that surprisingly, few studies have studied frailty incidence what limited the possibility of drawing a conclusion of incident frailty in the future from a public health perspective [75]. Articles included in this review reported that frailty

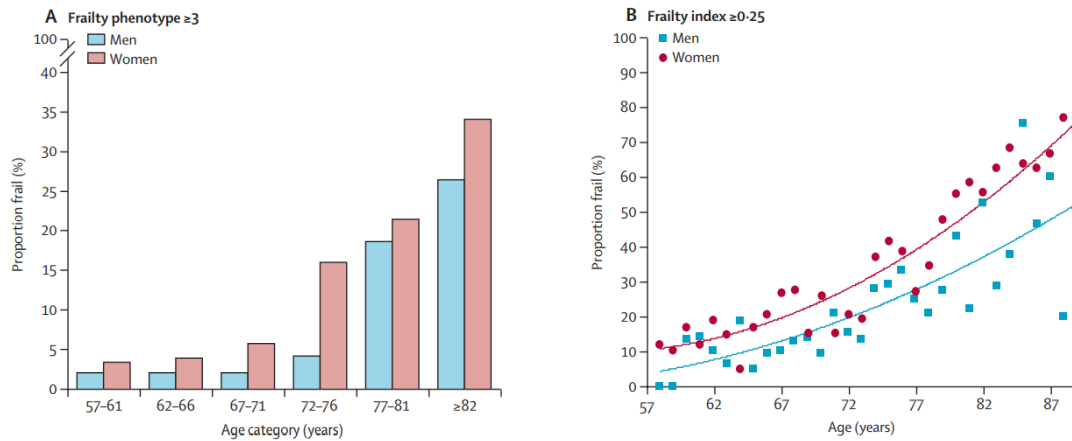
incidence rates ranging from 3.9% at 3 years follow-up [78], 5% at 22[79], 7.5% at 3.5 [80] to 7.8% at 9.9 years [81] when the Fried Phenotype was the tool used and by using Frailty Index frailty incidence ranged from 13% [82] at 1 year follow-up to 51.4% in aboriginal people with 6.7 mean years of follow-up [83]. On the other hand, prefrailty incidence showed higher rates, rising from 21% [78] at 3 years to 36 at 22 years follow-up [79].

These incidences were lower than those obtained by a similar systematic review in community-dwelling older adults aged 60 or more published in 2019. Among the non-frail subjects who completed the median follow-up time of 3 years, 13.6% developed frailty, with a pooled incidence rate of 43.4 cases per 1000 person-years, which was significantly higher in prefrail (62.7) than in robust (12.0). Among the robust, almost one in three became prefrail (30.9%), with a pooled incidence rate of 150.6 per 1000 person-years. Moreover, the pooled incidence rate among gender was significantly higher in women than in men for frailty (44.8 vs 24.3) and prefrailty (173.2 vs 129.0) cases per 1000 person-years[84].

Frailty prevalence

One systematic review pooled data from 21 studies and 61500 older community-dwelling adults and estimated the overall frailty prevalence in a 10.7% (95% Interval Confidence (CI)= 10.5%-10.9%) and a 41.6% (95% CI = 41.2%–42.0%) overall weighted average for prefrailty[85]. However, discrepancies between the studies were obvious, ranging between 4% to 59%. The overall weighted average prevalence was 9.9% and 44.2% for frailty and prefrailty respectively, when the Frailty Fried Phenotype was used [85]. Only one study included in this systematic review used the Frailty Index to assess frailty, founding a frailty prevalence of the 22.7%[86]. Nevertheless, a recent systematic review, using data from 240 studies including 1755497 individuals aged ≥ 50 years established the prevalence for the deficit accumulation model in 24% (95% CI = 22%-26%) and 12% (95% CI = 11-13%) by using the Fried Phenotype[87]. Recently, some tools have been proposed in the Toledo Study of Healthy Aging (TSHA). While the Fried Frailty Phenotype classified 8.5% as frail, the Frailty Trait Scale (FTS) and their short forms, Frailty Trait Scale 5 (FTS5) and Frailty Trait Scale 3 (FTS3) found 28.36%, 24.82% and 20.09% as frail[74].

Independently the tool used, the prevalence of frailty has been observed to be higher in women and rises with ageing (Figures 5). For Fried Scale, the prevalence among females is 15% and 11% for men, while by using Frailty Index prevalence are 29% and 20%, respectively.



Figures 5. Frailty prevalences according to age and gender .
From Hoogendijk et al. 2019 [88]

Factors associated with the presence of frailty

The prevalence of frailty is also affected by sociodemographic and clinical aspects. The Survey of Health, Aging and Retirement in Europe (SHARE) assessed frailty uniformly across Europe and observed a lower prevalence of frailty in higher-income countries than in lower-income countries [89]. The same conclusions were found in the systematic review and meta-analysis by Siriwardhana and colleagues, in which frailty reached rates of 51.4% in Cuba and prefrailty 71.6% in Brazilians[90]. The wide difference might be explained by the frailty assessment method with and without the standardization of the different tools and the geographic region with inequalities in health, educational and lifestyle access[90–92] or even ethnic groups, in which African Americans and Aboriginal Australians could present a higher frailty prevalence and others, such as Mexican-Americans a lower one[93].

These figures refer to the prevalence of the condition in community-dwelling older people. But when this population is approached in different clinical settings the numbers increased dramatically. In nursing homes, prevalence rates of 52.3% (95% CI 37.9%–66.5%) and 40.2% (28.9%–52.1%) of frailty and prefrailty, respectively, were found in a systematic review

and meta-analysis [94]. Among older hospitalized, 47% (37%-57%) and 36% (29%-44%) present frailty and prefrailty criteria[95]. Likewise, according to data from the European multicentre study FRAILTOOLS, between 7 and 32% of older adults attended in primary care would meet frailty criteria, while the prevalence of outpatient clinic would range between 10 and 42%[96].

Moreover, frailty prevalence is higher among older patients with specific diseases. In this way, systematic reviews have found that 10-25%% of people with diabetes [93], 19% in Chronic Obstructive Pulmonary Disease (COPD)[99], 22% in persons with cerebrovascular disease[100], 24% in anaemics[101], 31,9% in mild to moderate Alzheimer's disease[102], 37% among patients with end-stage renal disease [103] or 42% in patients with solid and haematological malignancies [104].

In Spain, frailty prevalence has been explored by some cohorts. Alonso-Bouzon and coworkers determined using the TSHA data that frailty prevalence varied according to the tool used by 24.12% when the Frailty Phenotype was not standardized to 6.68% when it was. Something similar occurred identifying the prefrail subjects, moving from 66.40% to 47.81%[91]. Moreover, discrepancies between tools using this cohort have previously been commented. In the FRAilty and DEpendence in Albacete (FRADEA) study, a ≥ 70 years community-dwellers older adult cohort, the prevalence of frailty and prefrailty according to Frailty Phenotype was 16,91% and 48,54% [105]. In the ≥ 65 cohort of Peñagrande, frailty obtained a prevalence of 10,3%[106]. In older cohorts, with subjects older than 74 years old, prevalences of 20,4% and 8,5% have been reported in Leganés [107] and Lérida[108], respectively.

Frailty instruments

The assessment of frailty in different settings of care, such as clinical care and research, focusing on different patient characteristics has allowed different underlying concepts of frailty with a wide spectrum of frailty assessment tools with a poor agreement between them[109,110] and different sensitivity and specificity depending on the setting and the event studied[108].

Linda P Fried and coworkers proposed frailty as an age-associated biological syndrome characterized by the reduction in the functional reserve and resistance against stressful factors,

causing organ impairment which leads to adverse event vulnerability[25]. This definition clearly distinguishes frailty between comorbidity or disability, as entities that could co-exist and influence each other [59] (Figure 6). Fried proposed a frailty phenotype assessing five aspects of frailty: unintentional weight loss (10 lb in past year), self-reported exhaustion, weakness in the grip strength test, slow walking speed and low physical activity [25]. Subjects who met 3 or more criteria were considered as frail, those who met 1 or 2 were considered prefrail and those who met none were considered as robust[25].

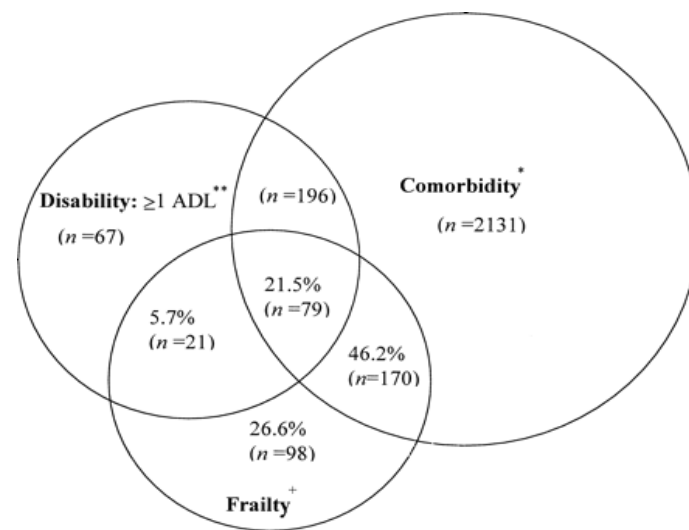


Figure 6. Prevalence, overlaps, definitions and major health care implications between frailty, comorbidity, and disability.

Figure from Fried et al., 2004[59]

Due to its feasibility in methodological and aetiological studies, its predictive value in adverse event outcomes (such as falls, disability, institutionalization, hospitalization or mortality), and the possibility of using it for intervention targets and clinical decision-making, the Frailty Phenotype has been the most used frailty instrument in the literature[111].

In contrast to the Frailty Phenotype, Rockwood and colleagues proposed in 1994 that the accumulation of deficits threaten the independence in older adults, and proposed a dynamic model, in which the balance between assets and deficits would determine the person's independence in the community[115]. This concept was refined years later and using data from the Canadian Study of Health and Aging developed the Frailty Index [53]. This tool is constructed

by a long checklist of symptoms, signs, diseases, disabilities, laboratory, radiographic, or electrocardiographic abnormalities and social characteristics [53,116] and even health utilization[117] and explore how the deficit accumulation of these conditions impacts on the subject. This instrument obtains a result derived from the deficits met by the subject divided by the number of criteria assessed[53].

Alternatively, there were proposed the “Frailty Trait Scale-5” (FTS5), a short form of the previous “Frailty Trait Scale” (FTS)[124]. This tool was constructed considering the simplicity of Fried et al.’s definition and its biological basis, and the predictive characteristics of the FI, improving the tracking ability of frailty assessment by detecting small changes in the biological substrate independently of disease, disability and social burden[124]. The FTS5 includes the Body Mass Index, physical activity assessment by the Physical Activity Scale for the Elderly (PASE) [127,128] and the Progressive Romberg Balance test[129], the walking speed and handgrip strength. This tool showed good diagnostic accuracy for stratifying older adults, monitoring small changes due to interventions or clinical progression and it is feasible to be implemented in daily clinical practice settings[74]. Moreover, FTS5 showed a good prediction ability of different adverse outcomes such as death, hospitalization, incident frailty and disability[74].

These three tools will be the one chosen to answer our research questions.

Frailty as a dynamic condition

Since Gill and colleagues demonstrated the reversibility and dynamism of frailty [76] some studies have explored the transition between frailty states due to the tremendous impact on older adults, their families, and the whole society [117] in the context of an emerging major public health challenge for healthcare systems[118]. Longitudinal studies can provide valuable information addressing transitions and trajectories of changes in frailty while ageing, and factors related to those pathways to ample potential prevent health-related outcomes.

In their work, Gill et al. found that almost a 58% of non-disabled community-dwelling older adults made at least one transition between frailty status. Although transitions to worsen status were more likely (43.3%), a non-negligible 23% improved it [76]. Moreover, this transition in

frailty status could occur even in participants older than 85, and some of them could improve in their frailty status [119]. In a recent systematic review and meta-analysis, which included only articles that defined frailty by using the Fried frailty phenotype, established rates of worsening (29.13%), improving (13.70%) and remaining in the same frailty status (56.54%) (Figure 7). Despite the fact that frail participants are unlikely to end the follow-up as robust, four out of each ten with basal frailty ended up being prefrail, and one out of each four with basal prefrailty, ended up being robust[77]. It is important to remark that these rates were obtained without any intervention, so interventions at early stages of frailty should be considered [77].

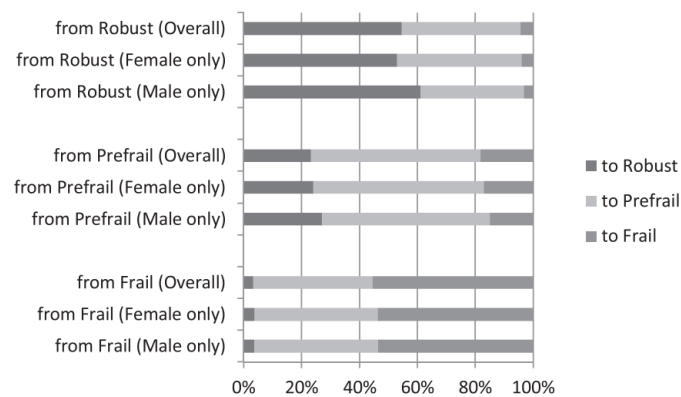


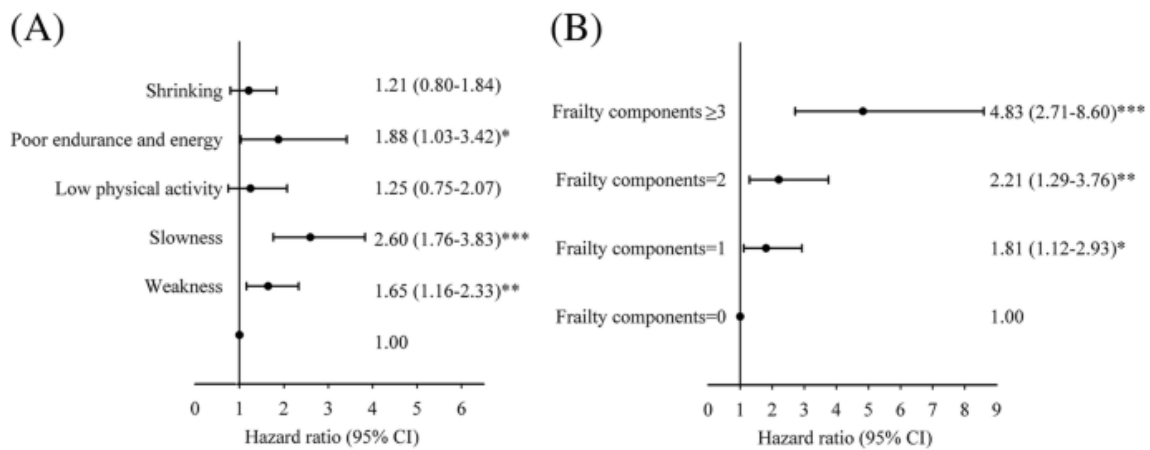
Figure 7. Frailty transition patterns according to basal frailty status in overall sample and stratified by gender.

Figure from Kojima et al., 2019 [77].

Furthermore, Gill et al. evaluated participants each 18 months, and advised about transition occurred mainly between adjacent states and found frailty transitions in this period time advising that probably frailty transitions occurred more frequently. This hypothesis was confirmed by Ahmad and colleagues by evaluating 2324 community-dwellers with 12 months follow-up[120].

In a recent study, Romero-Ortuno and coworkers followed 8504 participants for 8 years, with a mean age at recruitment of 63.1 years. They assessed frailty status of the participants by using the Frailty Phenotype, and found that the easiest domains to reverse were unintentional weight loss and fatigue, with approximately 60%, while weakness (40%), low physical activity (35%) or slow gait speed (23%) were less prevalent of reversing[121]. However, while the prevalence of

domains such as unintentional weight loss (7%-8%), or fatigue (8.95-10.8%) hardly varied between waves, other domains such as walking speed (9.8%-24.9%) or low physical activity (14.2%-33.7%) increased exponentially. Moreover, in the frail participants, low physical activity (85.6%), slowness (78.5), weakness (68.9) were the most prevalent domains met[121]. Alternatively, weakness and fatigue are domains significantly related with mortality (Figure 8)[122].



*: p-value < 0.05; **: p-value < 0.01, ***: p-value < 0.001

Figure 8. Relationship between mortality and Frailty Phenotype domains and number of domains met.

Figure from Wang et al. 2019.

Although Frailty Index was conceived as a continuous scale, some studies have explored frailty transitions according to this scale, setting the cut-off points in $FI \leq 0.10$ for robust, $0.10 < FI \leq 0.21$ for prefrail, and $FI > 0.21$ for frail individuals[123]. Ye et al [124]. found that almost 8% of community dwellers older than 60 years old improved in their frailty status assessed with FI, while 22.2% worsened in their status of frailty. Women and older had higher rates of transition to a worse status of frailty. Liu and coworkers[125] found substantially higher rates of improvement in frailty analysing data from 11,165 Chinese older adults, reaching 11% among patients who started out pre-frail and another 11% among patients who started out frail, despite old age at the start of the study (82.6 mean age at baseline).

Fallah et al.[126] found that after 54 months of follow-up, older adults with poor mobility tend to die (32 vs 15%) earlier, and improve (13 vs 16%) or maintain their frailty status (8 vs 16%) assessed by the FI less often than older adults with better mobility at baseline.

Factors associated with frailty

As abovementioned, frailty is a dynamic continuum state which can worsen or improve over time[77]. Insight into protective (Table 2) and contributor (Table 3) factors should be paramount to create and establish preventive strategies and public health guides identifying targets amenable to improve with specific interventions according to a personalized approach [88].

Table 2. Protective factors for onset and regression in frailty states.

Demographic and social factors	Lifestyle factors
<ul style="list-style-type: none"> • Social and total activity[127], or cultural engagement[128] • Higher income[129,130] • Living alone [131], Having a partner and higher social support [132], positive affect [133] • Neighbourhood with green space [134] • Male sex [132], female sex[130] • Younger age[130] 	<ul style="list-style-type: none"> • Hobbies and sports[127] or higher physical activity [132] • Higher adherence to Mediterranean diet[80,135], higher DQI-I score [136], three fruit and two vegetables portions/day [137], total protein, animal protein and higher MUFAs[138], low fat milk and yogurt[139], higher tertile of habitual resveratrol exposure[140] • Drinking alcohol with meals [141], moderate alcohol intake [131] and heavy drinker compared with no drinker [141] • Combination of higher exercise and dietary varieties ≥ 2[142]

DQI-I: Diet Quality Index-International. MUFAs: Mono-Unsaturated Fatty Acid.

Adapted from Feng et al., 2017[143] and Hoogendijk et al., 2019[88].

Once frailty has developed, some factors have been identified as reducers of chances of improving frailty status. Intrinsic factors include being older [144,145]. Although it could be more difficult to improve in the frailty status according to ageing, it is possible. Mendonça and colleagues found that about a 6% of older adults older than 85 could improve in their frailty status (from prefrail to robust or frail to prefrail)[119]. Moreover, they found that socioeconomic status did not influence the probability of transition and that multimorbidity (considered as four or more diseases) increased the risk of transit from robustness to frailty[119].

Suffering from diabetes[145,146], COPD [146,147], cancer, or having a previous stroke [145–147] have lower chances of improving their frailty status compared with those who have not. Moreover, lifestyle factors like smoking[144,147] have also been proven to a detrimental factor

in improving frailty. According to Lee and co-workers[145], men were less likely to revert their frailty status than be women, however, a recent meta-analysis was not found significant discrepancies between both genders [147].

Table 3. Risk factors for onset and progression of frailty.

Demographic and social factors	Clinical factors	Lifestyle factors	Biological factors
<ul style="list-style-type: none"> • Advanced age [130,148–155] • Female sex [132,149,152] • Ethnic minority [150] • No education[154], Low education [150] or being reared apart[132] • Low income [149,150] and socioeconomic position [149] • Negative affect [152]or Loneliness • High-density neighbourhood [148] • Poor self-rated health [149,154] • Spousal concordance of frailty status[156] 	<ul style="list-style-type: none"> • Multimorbidity and chronic diseases (comorbidity[157], prediabetes[154], diabetes[130,154,155], hypertension[155], previous cancer, chronic lung diseases[130], COPD[97], Framingham cardiovascular risk score[158], previous stroke[130], Alzheimer, lower MMSE/ impaired cognition[129,130,148,152,154,155], higher CES-D score[152], depressive symptoms[129,150,155,157,159] or spouse depression[160], arthritis[154], osteoarthritis[130], chronic kidney disease- related osteoporosis[161], osteoporosis alone[162,163] and with sarcopenia[162–164], and sarcopenia alone[165], low skeletal muscle mass index[155], knee pain[166], hearing impairment[167], decreased vision • BMI <18.5[150], ≥30 [129,149,150] or continuous[152], underweight[132,157], overweight and obese[132] • Malnutrition [168] • ≥1 falls[150] • Impaired cognition [148] • Depressive symptoms • Be hospitalized [130,169] • Hormone use[150] or Polypharmacy [154,157] • ADL functional status 6,140] and reduced function of extremities [152] • Oral function, fewer teeth, lower occlusal force and masseter thickness and oral diadochokinesis[155] 	<ul style="list-style-type: none"> • Physical inactivity [170] • Low energy and protein intake[171], moderate to high nutritional risk (NSI ≥3)[154] • Smoking [129,132,150,152] 	<ul style="list-style-type: none"> • Inflammation (Hb, CRP[154], elevated cytokines or highest CRP tertile[129], Higher white cell count, higher numbers of monocytes or lymphocytes, higher albumin level, lower level of DHEAS, higher cortisol:DHEAS ratio[172] • Endocrine factors (androgen deficiency or IGF-1, lower free testosterone[173] • Micronutrient deficits (low carotenoids, alpha tocopherol[153], albumin[154,155], low vitamin B12, total cholesterol[154], folate[154,171] vitamin B6, vitamin D[129,174], vitamin E or vitamin C[171]) • Serum uric acid [175] • Dysregulation across multiple physiological systems[176] • Metabolic syndrome and insulin resistance[177], serum leptin[178]

ADL: Activities of Daily Living. BMI: Body Mass Index. COPD: Chronic Obstructive Pulmonary Disease. CRP: C-Reactive Protein. DHEA: Dehydroepiandrosterone sulfate. Hb: Hemoglobin. IGF-1: Insulin-like Growth Factor-1. MMSE: Mini-Mental State Examination.

Adapted from Feng et al., 2017[143] and Hoogendijk et al., 2019[88].

In the TSHA, underreporting the amount of alcohol consumed and low grip strength were associated with loss of robustness, whereas a Body Mass Index (BMI) corresponding to moderate-severe obesity decreased the likelihood of becoming robust. In addition, impairments in hearing and cognition, low physical activity and smoking were associated with an increased risk of incident frailty[179].

How could sarcopenia affect frailty status?

Sarcopenia has been proposed as the biological substrate of physical frailty[180]. In fact, the idea of musculoskeletal changes as a core and central aspect of frailty was introduced by Fried and colleagues in the Frailty Phenotype[181]. In the operationalizing purpose of frailty, they included a domain called “shrinking” in which unintentional weight loss and sarcopenia were considered the same idea. However, today we know that frailty and sarcopenia, despite the fact that they are related, are distinct entities[182]. These two conditions share pathogenic mechanisms and some physical items for diagnosis (low grip strength and low gait speed). Nevertheless, few sarcopenic older adults met the frailty criteria and one out of three frail subjects did not meet sarcopenia criteria (Table 4) [182]. In fact, the interaction between these entities seems to predict adverse events in older adults. While frailty or prefrailty predict mortality independently of the presence of sarcopenia, an interaction between frailty (but not prefrailty) and sarcopenia needs to be present to predict worsening in disability (Table 5 and 6)[183].

Table 4. Prevalence of sarcopenia according to different criteria stratified by frailty status.

N=1611	Frailty Status		
	Robust	Prefrail	Frail
EWGSOP			
Sarcopenic	182 (17.25)	141 (29.13)	29 (40.27)
Nonsarcopenic	873 (82.75)	343 (70.86)	43 (59.72)
FNIH			
Sarcopenic	103 (9.76)	177 (36.57)	52 (72)
Nonsarcopenic	946 (89.66)	304 (62.8)	20 (27.7)
sFNIH			
Sarcopenic	198 (18.76)	208 (42.97)	47 (65)
Nonsarcopenic	851 (80.66)	273 (56.40)	25 (34.72)

EWGSOP: European Working Group on Sarcopenia in Older People. FNIH: Foundation for the National Institutes of Health. s-FNIH: standardized Foundation for the National Institutes of Health.

Table from Davies et al., 2018. [182]

Table 5. Multivariate Cox Regression analysis for Mortality.

	Bivariate Models		Model 1 ^a		Model 2 ^b		Model 3 ^c	
	HR (CI 95%)	P Value	HR (CI 95%)	P Value	HR (CI 95%)	P Value	HR (CI 95%)	P Value
Prefrail (ref. robust) ^d	2.25 (1.61–3.13)	<.001	1.68 (1.20–2.37)	.003	1.58 (1.12–2.24)	.010	1.50 (1.06–2.13)	.022
Frail (ref. robust) ^d	5.66 (3.52–9.11)	<.001	3.53 (2.15–5.82)	<.001	3.09 (1.84–5.18)	<.001	2.62 (1.54–4.47)	<.001
Sarcopenia ^e	1.45 (1.07–1.95)	.015	1.57 (1.12–2.20)	.009	1.43 (0.99–2.07)	.057	1.35 (0.93–1.96)	.110

Bold values indicates statistical significant association.

^aIndividual models for frailty and sarcopenia adjusted both for age and sex.

^bModel with frailty, sarcopenia, age, and sex.

^cModel with frailty, sarcopenia, age, sex, and Charlson Index.

^dModel with frailty, sarcopenia, age, sex, Charlson Index, and the interaction term for prefrailty and sarcopenia and frailty and sarcopenia.

Table 6. Multivariate Logistic regression analysis for worsening of disability

	Bivariate Models		Model 1 ^a		Model 2 ^b		Model 3 ^c		Model 4 ^d	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
Prefrail (ref. robust)	1.26 (0.95–1.66)	.105	1.25 (0.93–1.67)	.137	1.16 (0.86–1.56)	.331	1.14 (0.84–1.54)	.402	0.94 (0.65–1.35)	.727
Frail (ref. robust)	2.56 (1.43–4.58)	.002	2.90 (1.49–5.63)	.002	2.51 (1.28–4.94)	.008	2.38 (1.20–4.70)	.013	0.84 (0.25–2.87)	.781
Sarcopenia	1.85 (1.41–2.42)	<.001	1.74 (1.28–2.37)	<.001	1.50 (1.09–2.07)	.014	1.50 (1.08–2.07)	.015	1.02 (0.65–1.62)	.922
Prefrail-sarcopenia interaction									1.86 (1.00–3.49)	.052
Frail-sarcopenia interaction									5.96 (1.39–25.59)	.016

Bold values indicates statistical significant association.

^aIndividual models for frailty and sarcopenia adjusted both for age and gender.

^bModel with frailty, sarcopenia, age, and sex.

^cModel with frailty, sarcopenia, age, sex, and Charlson Index.

^dModel with frailty, sarcopenia, age, sex, Charlson Index, and the interaction term for prefrailty and sarcopenia and frailty and sarcopenia.

Tables from Davies et al. 2022 [183].

Sarcopenia

Concept

Muscle mass and function is paramount in correct health and for preventing diseases. In 1989, Irwin Rosenberg coined the term “sarcopenia”[184], a word that derives from the Greek language. “Sarx” meaning flesh, and “penia” meaning loss or lack of. Sarcopenia terms has evolved from the years, in order to distinguish this term from others like cachexia, malnutrition or even frailty. The European Working Group on Sarcopenia in Older People (EWGSOP) defined three criteria to identify and diagnose sarcopenia. Probable sarcopenia is identified according to low muscle strength. This finding is confirmed when low muscle quantity or quality is present. Moreover, when low physical performance is added to the two previous conditions, sarcopenia is considered as severe[185].

Different studies have shown that people lose 1% of their skeletal muscle mass each year as they age[186]. Added to this reduction of muscle mass, muscle function, evidenced in muscle strength and power, is also diminished even faster than muscle mass[186–189]. In this way, the importance of sarcopenia was recognised with its inclusion in the International Classification of Diseases-10 (ICD-10) code as an independent condition [190,191]. However, different operationalization

definitions and cut-off points had been proposed attending to the population assessed, hindering its suitable use in research and clinical practice.

Prevalence

Although the relevance of sarcopenia has been explored in different settings, the lack of a universal definition has made it a challenge to understand the true impact of this disease on older adults. Nevertheless, some studies have explored the epidemiology of sarcopenia, with obvious uneven results.

In 2015, Lourenço et al. [192] explored the prevalence of sarcopenia according to the EWGSOP in 3260 older adults aged 65 or older included in three cohorts, Frailty in Brazilian Older People Study—Rio de Janeiro (FIBRA-RJ), Brazil; Coyoacan Cohort (CC), Mexico City, Mexico; and Toledo Study for Healthy Aging (TSHA), Toledo, Spain. They found that according to this algorithm, 83.4% were sarcopenic, reaching a rate of 94.4% between the Spanish older adults. The authors themselves indicated that, according to this definition, the extremely high prevalence of the abnormal condition makes it useless for clinical screening to detect adverse events, thus standardizing the cut-off points according to the population seems to be necessary [192].

However, some authors have explored the prevalence of sarcopenia according to different definitions. In a recent systematic review and meta-analyses, Mayhew et al. [193], estimated the presence of sarcopenia between 12.9% (95% CI: 9.9%-15.9%) according to the EWGOS/Asian Working Group on Sarcopenia (AWGOS), 9.9% (95% CI: 3.2%-16.6%) according to the International Working Group on Sarcopenia and 18.6% (95% CI: 11.8%-25.5%) according to the Foundation for the National Institutes of Health (FNIH). Alternatively, the prevalence of sarcopenia reached a 40.4% (95% CI: 19.5%-61.2%) when the appendicular lean mass (ALM)/weight was the chosen definition[193].

Papadopoulou and coworkers[194] found similar results between the prevalence of sarcopenia in community-dwelling older adults independently the tool used, ranging from 8%, 11%, and 12% in men and 5%, 10% and 11% in women using the International Working Group on Sarcopenia

(IWGS), EWGSOP and AWGS, respectively. The pooled prevalence was slightly higher in men than in women (11% vs 9%)[194].

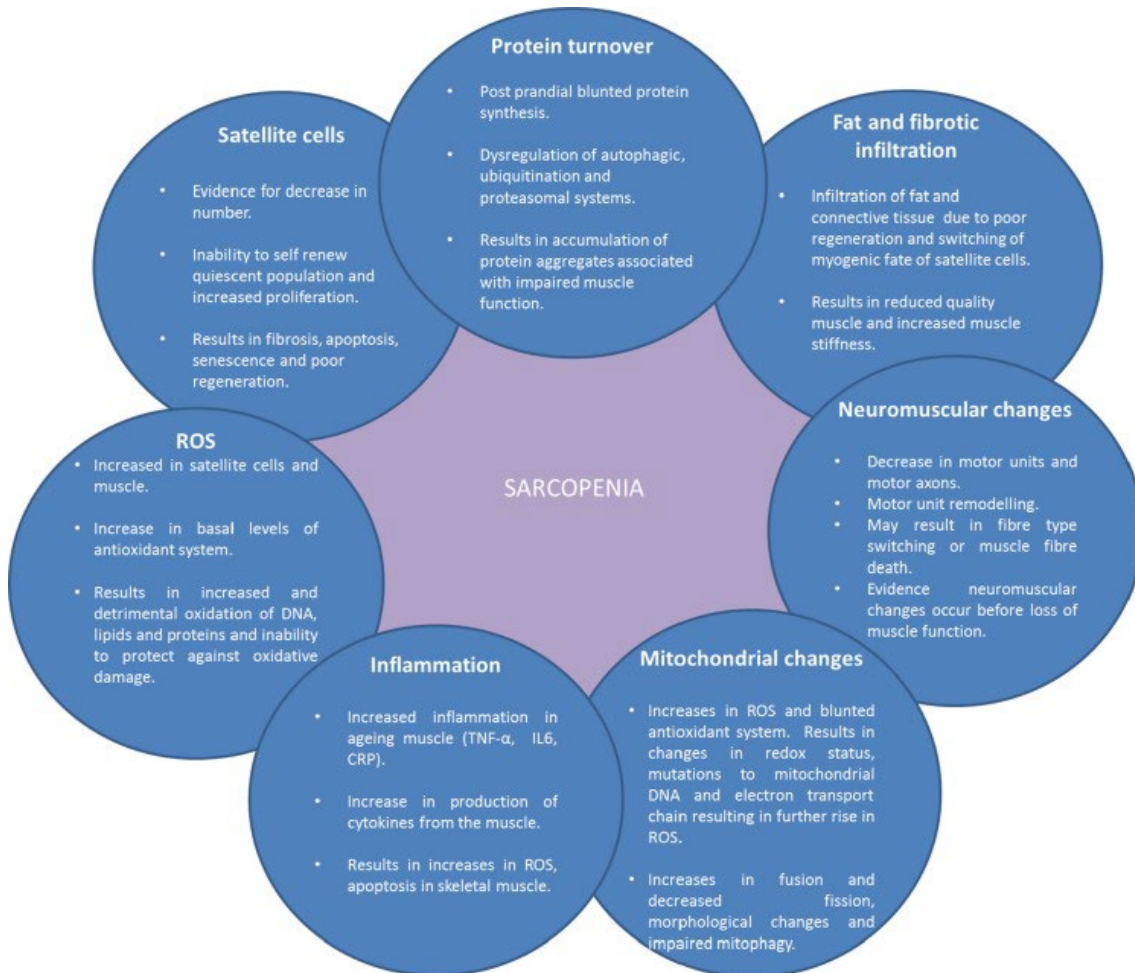
Notwithstanding sarcopenia definitions, its contribution to adverse events such as hospitalization in older adults has been broadly found in different studies. In fact, 44% of the older adults hospitalized in the medical subgroups met sarcopenia criteria, and this percentage low to a 22% in the surgical subgroups[95]. A similar prevalence has been shown in other clinical settings such nursing homes, being sarcopenic 51% of men and 31% of women[194], and post-acute inpatient rehabilitation (56%)[195]. Additionally, sarcopenia shares pathophysiology with other age-related chronic diseases, which increases the incidence of both diseases in a bidirectional manner. So much so that the presence of sarcopenia rises to 26.4% in dementia, 31.1% in diabetes and 26.8% in respiratory diseases[196]. Other conditions like cancer have been intimate related to loss of muscle mass and function, getting a 45% of sarcopenic in breast cancer survivors [197] and 37% among colorectal cancer survivors[198].

Pathophysiology

Pathophysiological mechanisms of sarcopenia are even not well understood. Nevertheless, multiple muscle factors have been identified in sarcopenic individuals (Figure 9). It is noteworthy that many of them are also found in frailty. Decline in lean muscle mass especially affects the lower limb and mobility status. While ageing, muscle protein synthesis and breakdown processes are imbalance, resulting in an anabolic resistance state[199]. In addition, as we age, we probably consume less energy and less protein intake[200,201] and the rate of sedentary lifestyle increases[202], which would support this state of anabolic resistance, but even in the presence of exercise stimuli, a lower rate of muscle protein synthesis is observed in older adults compared to younger subjects[203,204].

Aging could increase inflammation and reactive oxygen species, reducing muscle function. A reduced sensitivity of phosphatidylinositol-3-kinase (PI3K)/ protein-kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway is caused by a reduction in insulin-like growth factor (IGF-1) levels and promoting protein degradation[205,206]. Furthermore, when muscle tissue needs to

be repaired, organisms designed for this action may be compromised. Research on satellite cells, muscle stem cells whose function is promoting skeletal muscle reparation[207], diminished their regenerative capacity and proliferative and regenerative potential in aged muscle [208] what may explain their inability to preserve muscle mass[209].



IL6: Interleukin 6. TNF- α : Tumor Necrosis Factor-alpha. CRP: C-Reactive Protein. ROS: Reactive Oxygen Species.

Figure 9. Summary of aged skeletal muscle changes that are affected in sarcopenia. Figure from McCormick and Vasilaki, 2018[210].

Another underlying molecular mechanism related to skeletal muscle loss is the alteration in autophagy due to aging[211]. Autophagy is a multiple degradation pathway to maintain skeletal muscle homeostasis through the clearance of damaged organelles and macromolecules[211]. So that, loss of control of adequate induction or precise regulation of the autophagic process and a better control of mitochondria by autophagy would favour sarcopenia[215].

Low-grade chronic inflammation is a common feature of aging, characterized by increased circulating levels and cellular production of pro-inflammatory cytokines such as interleukin-6 (IL6), Tumor Necrosis Factor (TNF α), and C-Reactive Protein (CRP), among others[28,216]. These cytokines impair mitochondrial biogenesis [217] and inhibit neurogenesis or reduce the effect of exercise on neurogenesis[216,218,219]. The loss of mitochondrial function integrity-impaired muscle physiology[209]. Although there is unclear if mitochondrial dysfunction is a cause or a consequence of aging[220], it is obvious that mitochondrial dysfunction has been identified among the hallmarks of aging[221] and is a major determinant factor in sarcopenia[222].

However, as mentioned previously, it is well documented that muscle mass is lost much more slowly than muscle strength[190,223], and strength and not mass could explain the association between adverse events, such as mortality [224]. This association between loss of muscle mass and strength could be different between gender, being faster [225,226] and strongly associated with mobility function in men than in women [225,227,228].

In addition to the loss of lean muscle mass, loss of muscle quality has been reported in older adults. Some studies have observed that ageing is associated with the intramuscular infiltration of non-contractile tissue (collagen and fat) [229]. Excessive depots of adipocytes cells are considered to be a pathological phenomenon, termed myosteatorsis. Exists two fat depots mainly within skeletal muscle: lipid infiltration within the fascia surrounding skeletal muscle and fat infiltration within myocytes[230]. Detrimental neuromuscular activation, reduced muscle blood flow and local pro-inflammatory adipokines have been proposed as mechanisms [231] that partly explain intra and intermuscular fatty infiltration reducing muscle quality (defined as the ability to generate force by unit of muscle mass)[232]. This reduction in muscle quality includes quantitative and qualitative changes in muscle cells, but also in the neuromuscular systems [233], mainly because of the age-dependent attenuation in motor axon conduction velocity and myelinated axons[234]. Fast-twitch fiber, those with greater capacity to generate force, change their muscle fibers phenotype from fast to slow muscle fiber [233], due to a reduction in a reinnervation of motor units later of the denervation, especially in these type II fibers. When denervation exceeds the

reinnervation, apoptosis occurs[235]. To avoid motor unit death, adjacent healthy motor neurons (usually type I fibers) could reinnervate these muscle fibers (usually type II) via a terminal axon sprout[236].

Peripheral neuromuscular function is not the only one that is affected when aging. Age-related changes in nervous system[237] and motorneuron such a reduction in spinal excitability and inhibition[238,239] and the variability of the discharge rates of motor units during submaximal contractions what may contribute to reduce the ability of older adults to perform steady muscle contractions[212].

Objectives

Due to the facts that has been previously exposed, the objectives of this doctoral thesis are as follows:

- To review the mechanisms involved in frailty related to the ageing process, as well as chronic diseases. Also, to expose how these mechanisms could be improved or reversed by physical activity and exercise. To analyze the individual components of physical exercise programs and their impact on different components of frailty. And, finally, to synthesize the current evidence for designing and implementing a physical exercise program in frail older people.

- Secondly, to explore the existence of different trajectories of frailty and their associations with adverse events (disability, hospitalization and mortality) in community-dwelling older adults. In this work, we will also assess not only the level of change (trajectory), but also the baseline score on the risk of adverse events.

- Thirdly, we will explore the relationship between sarcopenia and frailty. We will study whether sarcopenia influences frailty transitions, as well as whether its presence increases the risk of death in community-dwelling older adults stratified by frailty status.

- Finally, to analyze the association between healthcare cost expenditures related to frailty, sarcopenia, and its interaction at both cross-sectional and longitudinal levels.

Objetivos

Por todo lo detallado anteriormente, los objetivos de esta tesis doctoral son los siguientes:

- Revisar los mecanismos implicados en la fragilidad relacionados con el proceso de envejecimiento, así como de enfermedades crónicas. Así mismo, exponer cómo esos mecanismos son mejorados o revertidos mediante la actividad física y el ejercicio. Analizar los componentes individuales de los programas de ejercicio físico y su impacto en diferentes componentes de la fragilidad. Y, por último, sintetizar la evidencia actual para diseñar e implementar un programa de ejercicio físico en personas mayores frágiles.
- En segundo lugar, se explorará la existencia de diferentes trayectorias de fragilidad y sus asociaciones con eventos adversos (discapacidad, hospitalización y mortalidad) en adultos mayores que viven en la comunidad. En este trabajo, también se evaluará no sólo el nivel cambio (trayectoria), sino también la puntuación basal en el riesgo de los eventos adversos.
- En tercer lugar, exploraremos la relación entre la sarcopenia y la fragilidad. Se estudiará si la sarcopenia influye en las transiciones de fragilidad, así como si su presencia aumenta el riesgo de muerte en adultos mayores que viven en comunidad estratificándolos por su estado de fragilidad.
- Finalmente, se explorarán los costes relacionados con la hospitalización de adultos mayores que viven en comunidad asociados a la fragilidad, la sarcopenia, y su interacción tanto a nivel transversal como longitudinal.

Chapters

Chapter 1: Physical activity and exercise: Strategies to manage frailty

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Physical activity and exercise: Strategies to manage frailty

Javier Angulo^{a,b}, Mariam El Assar^{b,c}, Alejandro Álvarez-Bustos^c, Leocadio Rodríguez-Mañas^{b,d,*}

^a Servicio de Histología-Investigación, Unidad de Investigación Traslacional en Cardiología (IRYCIS-UFV), Hospital Universitario Ramón y Cajal, Madrid, Spain

^b Centro de Investigación Biomédica en Red de Fragilidad y Envejecimiento Saludable (CIBERFES), Instituto de Salud Carlos III, Madrid, Spain

^c Fundación para la Investigación Biomédica del Hospital Universitario de Getafe, Getafe, Spain

^d Servicio de Geriátria, Hospital Universitario de Getafe, Getafe, Spain

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ABSTRACT

Frailty, a consequence of the interaction of the aging process and certain chronic diseases, compromises functional outcomes in the elderly and substantially increases their risk for developing disabilities and other adverse outcomes. Frailty follows from the combination of several impaired physiological mechanisms affecting multiple organs and systems. And, though frailty and sarcopenia are related, they are two different conditions. Thus, strategies to preserve or improve functional status should consider systemic function in addition to muscle conditioning. Physical activity/exercise is considered one of the main strategies to counteract frailty-related physical impairment in the elderly. Exercise reduces age-related oxidative damage and chronic inflammation, increases autophagy, and improves mitochondrial function, myokine profile, insulin-like growth factor-1 (IGF-1) signaling pathway, and insulin sensitivity. Exercise interventions target resistance (strength and power), aerobic, balance, and flexibility work. Each type improves different aspects of physical functioning, though they could be combined according to need and prescribed as a multicomponent intervention. Therefore, exercise intervention programs should be prescribed based on an individual's physical functioning and adapted to the ensuing response.

1. Introduction

Increasing numbers of people reaching the ranks of the elderly is one of the achievements of the past century. Whereas the early years of the 20th Century saw a life expectancy of about 30 years, this statistic had more than doubled worldwide by the end of the century [1]. Further, this trend will continue at least until the middle of the current century. In 2015, there were 617 million people of the age of 65 or older, and the next 35 years will see a massive increase in the percentage of older people. The fastest growing age group will be those over the age of 80, reaching 447 million individuals by 2050, three times the current number [2]. Based on these predictions, millions of people will endure the aging process, with variations depending upon cultural and socioeconomic conditions [3].

The aging process is a somewhat more complex issue than just the passing of time. Aging is characterized by several highly prevalent changes, including an increase in morbidity and a decrease in functional performance which, although linked, are two separate conditions [4,5]. In fact, as we age, functioning increasingly becomes the factor most strongly associated with quality of life and the risk for several adverse outcomes, including hospitalization, permanent

institutionalization, use of health and social resources, and death [6].

In 2015, the World Health Organisation (WHO) released its first report on aging and health [7] in which it recognized the true relevance of function, the components involved in its preservation or deterioration, and how the relationship between what I am able to do and the challenges of the environment mark the presence of functional autonomy or disability. In that report, WHO defines healthy aging as “the process of developing and maintaining the functional ability that enables wellbeing in older ages.” According to this definition, older people with multiple diseases may enjoy a healthy aging process if they maintain functional ability, i.e., elderly's health status is defined by functional status rather than morbidity. This stance is a true milestone not only in its conception of health with its theoretical consequences but also in its approach to health, with its practical consequences [8,9]. The impact of the latter ones on the elderly is extremely important, as the possibility of prolonging life is dramatically reduced [10] and the potential for improving the quality of life reaches its maximal relevance.

Which factors are associated with function and, secondly, linked to personal autonomy? WHO (2015) distinguishes between two types of factors. The first type falls under what is called *intrinsic capacity* and the

* Corresponding author. Servicio de Geriátria, Hospital Universitario de Getafe, Ctra de Toledo km 12,500, 28905, Getafe, Spain.

E-mail address: leocadio.rodriguez@salud.madrid.org (L. Rodríguez-Mañas).

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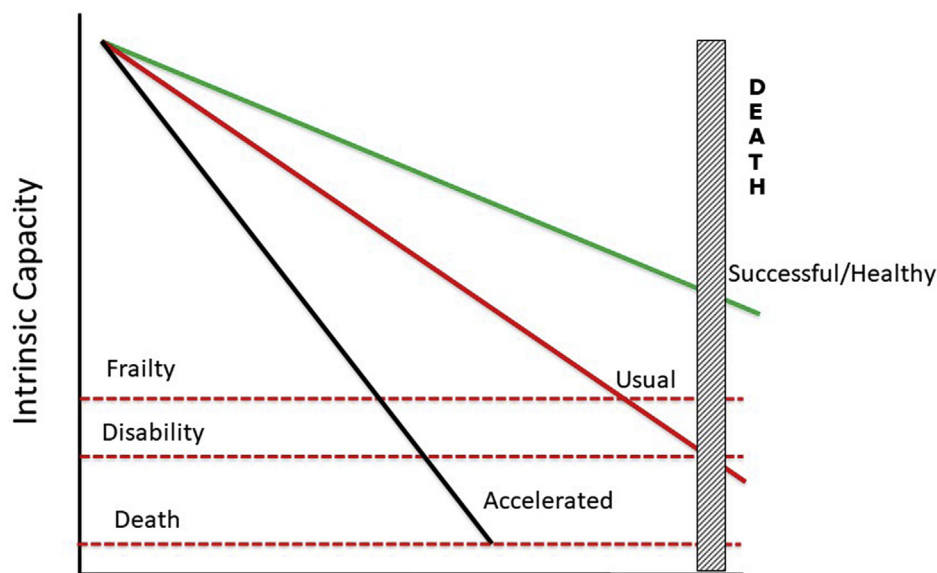


Fig. 1. Three different trajectories of intrinsic capacity along the lifetime: Accelerated aging, usual aging, and successful/healthy aging. Trajectories are suitable for intervention, acting on the rate of decrease in intrinsic capacity.

second type is *environment*. Intrinsic capacity is defined as “the composite of all the physical and mental capacities an individual can draw on” and is the final outcome caused by the joint effect of genetic background, chronic diseases, lifestyles, changes due to aging and broader geriatric syndromes.

Thus, in a stable environment, function is mainly determined by intrinsic capacity. However, intrinsic capacity starts declining at a quite constant rate (1% per year) as soon as the maturity process is completed (in human beings, around 20–25 years of age) [11]. When this declining intrinsic capacity reaches a certain threshold, challenges derived from the environment are no longer possible to be overcome and disability appears (Fig.1). Hence, in older people the transition from a robust state to disability is a long-lasting, continuous process which may take years [12]. Meanwhile, as intrinsic capacity declines an associated

component also decreases: functional reserve (Fig. 2). Functional reserve is essential, among other reasons, to avoid stressors impacting function and, if impacted, to recover the affected function. Consequently, when intrinsic capacity and functional reserve are under minimums, the risk for additional disability is very high and the possibility of recovery is very low. This conceptual framework should include a stage in the pathway from robustness to disability where the intrinsic capacity is low, but still above the disability threshold, and the functional reserve is reduced, but still enough for total or partial function recovery. This stage in the pathway, characterized by high susceptibility to low power stressors and high risk for adverse outcomes (e.g., disability and its associated consequences like hospitalization, institutionalization, or death) while still maintaining potential for recovery, is what it is referred to as frailty [13–15].

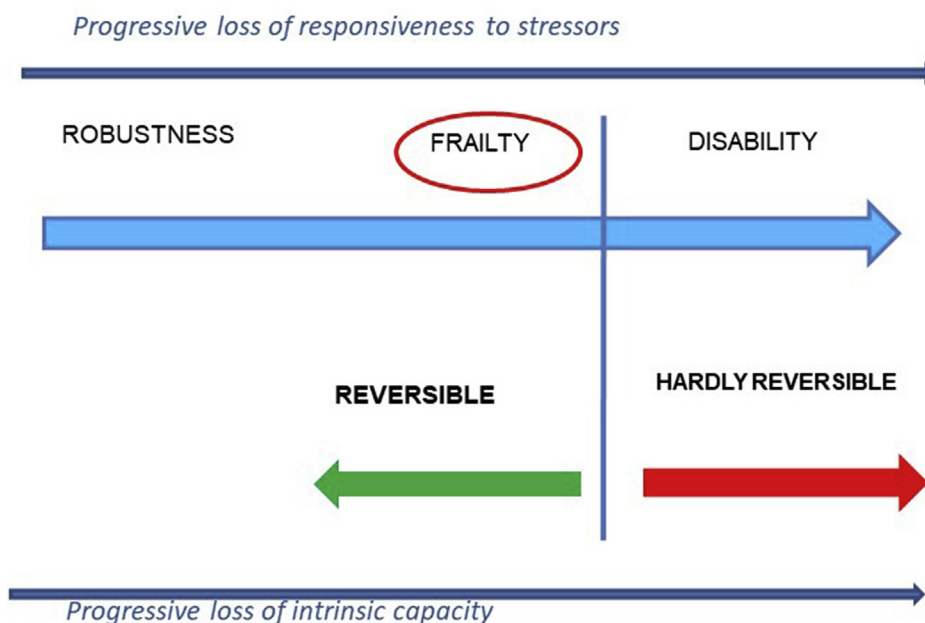


Fig. 2. Shortening of intrinsic capacity and functional reserve leading to frailty and, if no intervention, to disability and death. As these shortages progress, the likelihood of reversing functional impairment decreases. When the threshold for disability is crossed, the possibility of restoring robustness is uncertain.

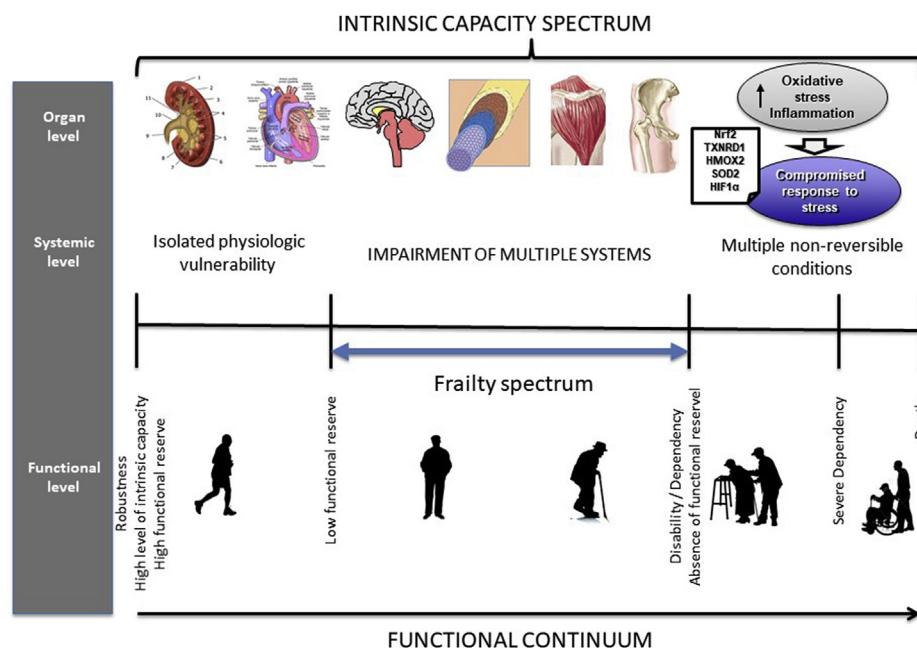


Fig. 3. The spectrum of intrinsic capacity from the perspectives of organ and systemic level, and their clinical manifestations. In the first stages, there are changes in isolated organs that can still be reversed and do not impact function due to a high functional reserve. As the condition progresses, other organs start to deteriorate, due to the aging processes or to the accumulation of chronic diseases sharing similar mechanisms of damage. At this stage frailty status appears: there is still enough functional reserve to maintain functional autonomy, although some deterioration in performance-based tasks can be observed if carefully assessed. If the condition continues progressing, functional reserve is depleted and disability takes hold, with few chances for recovery.

Prevention or delay of functional status decline, progression to disability, with its characteristic loss of personal self-sufficiency has been one of the main classical but also ongoing objectives of geriatric medicine [6,16–18]. Therefore, in the past decades frailty has received increasing attention as a window of opportunity to avoid or postpone disability. Frailty has been examined using two different approaches [15]. One of them, measuring deficit accumulation generates a frailty index; the other one is defining a particular phenotype (the frailty phenotype), which denotes the underlying processes where the effects of the aging process, subclinical and clinical diseases merge (Fig. 3). The frailty phenotype also captures the mechanisms shared by the aging process and certain chronic diseases which affect several organs and systems. These mechanisms are then phenotypically expressed as functional deterioration, including frailty [19]. By either approach, the roads leading to frailty are varied, with different trajectories and rates [20].

Increasing evidence reports the benefits yielded by exercise and multimodal interventions on the functional status of older people, including frailty. Data clearly support early intervention in the pathway from robustness to disability in order to maximize potential benefits [21,22]. This evidence has fostered the assessment of pre-disability conditions, i.e., when individuals are still independent but their performance (as an indicator of the risk for developing disability) is impaired, as it is the case in frailty. Although there are over 50 frailty assessment tools, for the purpose of this review we will use the Frailty Phenotype as designed by Fried and colleagues and its three categories. The Frailty Phenotype evaluates five health- and function-related domains and classifies people into three categories accordingly: Robust (0 domains affected), pre-frail (1–2) and frail (≥ 3) [13].

This review has four main aims. First, to provide data and describe the mechanisms involved in frailty which emerge from the aging process itself and/or chronic diseases affecting certain organs and systems. Second, to show how physical activity and exercise hinder some of those harmful mechanisms, thus improving physical function and delaying or reversing frailty. Third, to analyse the individual components of the physical exercise programs and their best implementation to abate frailty. And, finally, to analyse current evidence and bases for designing, implementing, and evaluating a program of physical exercise for older frail people.

2. Pathophysiology of frailty

Frailty is a clinical syndrome that affects multiple key systems including the endocrine, respiratory, and cardiovascular systems as well as the skeletal muscle. This syndrome often marks the onset of the process known as “Cycle of Frailty” which leads to sarcopenia and other multisystemic failures [23] (Fig. 4). Close knowledge on how the aging process interacts with chronic diseases to impair organic systems function and bring about frailty is key for designing successful preventative strategies.

2.1. Skeletal muscle

Evidence clearly establishes an association between frailty and the structure and function of skeletal muscle. However, although sarcopenia is one of the key risk factors for frailty syndrome, frailty and sarcopenia are distinct conditions [24]. In fact, muscle alterations are detected only in, approximately, 2/3 of frail individuals. This suggests that the frailty phenotype, albeit influenced by skeletal muscle function, is a clinical manifestation of a multisystemic functional impairment [25].

Originally conceptualized as the age-related loss of skeletal muscle mass, the concept of sarcopenia has evolved to stand for the decline of muscle mass and function among older adults [26]. In addition, the aging process compromises both muscle structure and function. The reduction in muscle mass causes an increase in the proportion of maximal power generating capacity of the remaining muscles performing the activities of daily living. This, let's say, overuse of the remaining muscles, leads to an earlier onset of fatigue which, in turn, hastens the shift from an independent to a dependent lifestyle [27].

Lean muscle mass suffers a considerable decline with age. On average, it makes up 50% of total body weight in young adults versus about 25% in 70 to 80 year-olds [28]. This decline, especially that of the lower limb, impacts mobility status significantly. Further, age-related muscle mass loss has been associated to a state of “anabolic resistance” where there is an imbalance of muscle protein synthesis and breakdown processes in response to stimuli, like exercise or nutrition [29]. In fact, reduced rates of cumulative muscle protein synthesis accompanied by blunted mass gains were observed in older adults in response to resistance exercise training when compared to young adults [30,31]. Both cross-sectional and longitudinal studies of older adults of

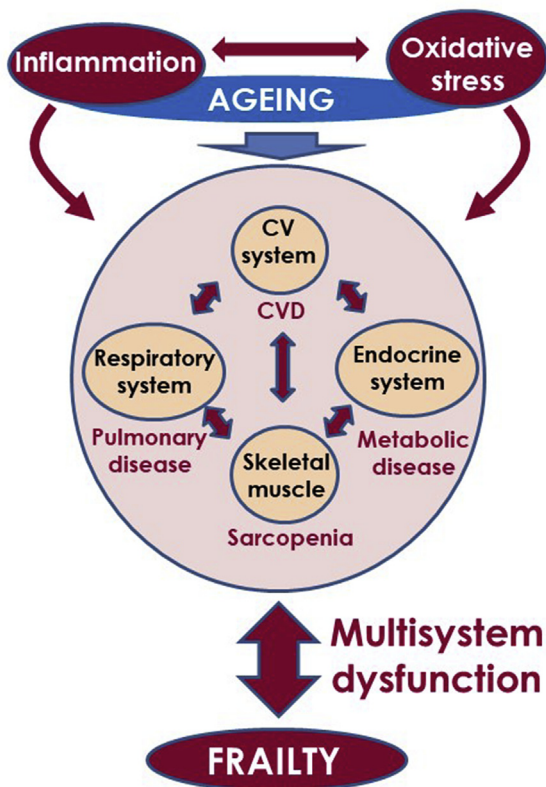


Fig. 4. Aging together with increase in oxidative damage and chronic inflammation represent three interrelated age-dependent processes that provide a background prone to organic systems dysfunction and age-related chronic diseases. The interaction between age-related chronic diseases, aging process, oxidative stress, and inflammation may lead to multisystem dysfunction and frailty phenotype in the elderly.

both genders place the onset of age-related decline in muscle strength on the third or fourth decade of life [32–35]. However, longitudinal studies reveal that muscle mass loss does not fully account for the loss of muscle strength and physical function in older adults [36,37]. In fact, muscle strength is lost much more rapidly than the concomitant muscle mass [38,39]. Thus, muscle strength, the best single measure of age-related muscle changes, is associated with physical disability in instrumental activities of daily living and functional limitation [40].

Additionally, changes in muscle quality (force corrected for size) also take place during aging [41,42]. Muscle power declines earlier and faster with age than strength does [43]. And, unfortunately, muscle power seems to have a stronger association to functional capacity among frail elderly populations than muscle strength [44].

Other authors have reported that age-related muscle power loss may be impacted by a reduced number of motor units, with the denervation of muscle preceding the loss of muscle axons and consecutively motor unit death [45,46]. As a compensatory mechanism, adjacent healthy motor neurons (often type I) reinnervate the denervated muscle fibers (often type II) through terminal axonal sprouting [47]. However, as this mechanism turns defective as we age, it actually triggers muscle loss by increasing myocytes apoptotic potential due to the loss of trophic factors [48]. It has been suggested that age-related changes in the grip and leg extensor strength are not primarily due to muscle atrophy but are reflective of declines in the integrity of the nervous system [26]. Interestingly, well-trained seniors who had exercised regularly in the previous 30 years had two advantages over healthy sedentary age-matched seniors; first, they had retained a greater maximal muscle force and function and, second, they had preserved muscle fibers size resulting from fiber rescue by reinnervation [49].

Further, research on satellite cells (SCs) reveals more potential links between exercise, physical functioning, and muscle health. SCs represent a population of muscle stem cells that reside within muscle tissues in defined niches and promote skeletal muscle repair [50]. Proliferation and differentiation of SCs during muscle regeneration is profoundly influenced by innervation, vasculature, hormones, nutrition, and the extent of tissue damage [51]. SCs may also play an important role in muscle maintenance and muscle growth in response to resistance exercise training [52]. Compared to younger muscle, aged muscle contains fewer SCs and a higher proportion of them display impaired proliferative capacity and regenerative potential, which may explain muscle's failure to regenerate successfully [53] and the inability to maintain its mass [52]. Fortunately, even though SCs density in type II muscle fibers and the size of the fibers themselves declined with age, both magnitudes increased after resistance exercise training for 12 weeks [54]. However, despite reports of a clear correlation between age and impaired regenerative potential of SCs, conflicting results arising from animal models [55,56] keep the debate on the contribution of SCs to sarcopenia alive.

Authors have reported that muscle function alterations not only contribute to an individual's frailty status, but that reduced muscle strength, as measured by grip strength, is associated with an increased risk of mortality [57,58]. Recently, grip strength has revealed as a strong predictor of cardiovascular mortality and a moderately strong predictor of incident cardiovascular disease. These findings suggest muscle strength as a risk factor for incident cardiovascular disease and as a predictor of overall mortality [59]. In addition, regional muscle strength was shown as a predictor of medium-term mortality and hospitalization in older men and women [60].

2.2. Respiratory system

Pulmonary function also declines progressively with aging [61] due to fewer alveoli and capillaries or reduced diffusing capacity and increased residual volumes among other factors [62]. In addition, increased stiffness of chest wall combined with reduced respiratory muscle strength result in a shrunk forced expiratory volume [62]. These lung changes may, in turn, further contribute to loss in muscle strength and power as well as mobility. Further, the reverse has also been suggested, i.e., that the decline in muscle strength may lead to reduced pulmonary function, low physical performance, and mobility disability [63]. Although cross-sectional, a study in healthy older adults suggests that decline in mobility with aging may be due to a drop in both muscle strength and power and also mediated by decreases in spirometric pulmonary function [64]. In this sense, by limiting energy supply, lessened pulmonary function could result in impaired leg strength, contributing to the development of mobility disability [65]. Nevertheless, the observed association between mobility disability incidence, loss of ability to ambulate and pulmonary function in the elderly was relatively independent of respiratory muscle strength and leg strength. This suggests that physical activity and pulmonary function seem to contribute to the development of mobility disability through mechanisms other than the already known effects on muscle strength [66].

Findings regarding how frailty and exercise capacity were related to pulmonary function in community-dwelling disabled older women support the significance of respiratory function in physical performance. Further, the beneficial effects of pulmonary function on exercise capacity were only significant in the absence of frailty [67]. Along these lines, we may expect pulmonary/respiratory diseases to precipitate frailty and mobility disability. Supporting this idea, a higher frailty index was observed in a large sample of patients with chronic obstructive pulmonary disease (COPD) [68]. And indeed, a recent meta-analysis of observational studies concluded that older participants with COPD had a two-fold increased risk for frailty [69]. COPD patients exhibited lower physical function [70] and the risk for frailty with mobility disability increased in COPD patients as the disease grew in

severity [71]. In fact, COPD was revealed as a main risk factor for frailty in a large sample of middle-aged and older subjects [72].

Finally, frailty has been reported as an independent predictor of all-cause mortality in patients with interstitial lung disease referred for lung transplantation [73] as well as associated with incident and longer-duration hospitalization and poor quality of life in COPD patients [74]. In fact, it has been proposed that frailty is an independent risk factor for the development and progression of COPD and, in turn, evidence supports that COPD can lead to frailty [75]. In fact, longitudinal studies have reported that the association between frailty and COPD is, indeed, bidirectional [76].

2.3. Cardiovascular system

The incidence and severity of subclinical and clinical manifestations of cardiovascular diseases (CVD) increase steeply with advanced age [77,78] even in the absence of traditional risk factors [79]. That is, even after accounting for the higher prevalence of cardiovascular risk factors in older people, the aging process, by its own nature, independently worsens cardiovascular health [80]. The impact of the passing of time on structure and function of the cardiovascular system leads not only to cardiovascular events and strokes, but also to frailty, functional decline, and cognitive impairment [81]. Aging-related alterations involve the endothelium, vascular smooth muscle cells, as well as the extracellular matrix of vessel wall [82,83]. Intima-media thickening (IMT), increased arterial stiffness, and dilation of central elastic arteries are key aspects of age-associated changes in vasculature resulting in reduced ability to expand and contract in response to pressure variations [84]. Further, reduced thigh muscle cross-sectional area as an indicator of sarcopenia was associated with increased carotid IMT and pulse wave velocity (PWV) as a measure of arterial stiffness in middle-aged to elderly men. Conversely, thigh skeletal muscle cross-sectional area was reported as an independent determinant of PWV, suggesting that sarcopenia and atherosclerosis may interact with each other [85].

As it is known, increased arterial stiffness is related to advanced age [86]. And, it has been proposed to contribute to the association between sarcopenia and cognitive impairment [87]. Furthermore, cross-sectional studies in community-dwelling older adults confirmed that frailty was associated with arterial stiffness [88,89]. Based on data from a sample of patients in a Chinese Hospital, frailty was also shown to be associated with increased carotid IMT as well as with arterial stiffness measured as cardio-ankle vascular index (CAVI). Likewise, CAVI was higher in the frail group than in the pre-frail or robust groups and was inversely correlated with grip strength and walking speed [90].

Arterial stiffness is linked to endothelial dysfunction as suggested by the impairment of endothelial vasodilation that always precedes arterial stiffness [91]. Endothelial dysfunction, manifested by a reduction of the endothelium-dependent vasodilation, is associated with the aging process in both the micro- and the macrovasculature of animal models [92] and humans [82,93,94]. Endothelial dysfunction plays a key role in the onset and persistence of atherosclerosis, and as an independent predictor of cardiovascular events [95]. Endothelial function is related to physical performance as indicated by the significant relationship between brachial artery flow-mediated dilation (FMD) and physical function in elderly men [96]. Indeed, the impairment of endothelial vasodilation induced by insulin in older adults relates to the defective anabolism of muscle proteins driven by this hormone in skeletal muscle [97]. In addition, the levels of asymmetric dimethylarginine (ADMA), a marker of endothelial dysfunction, increase the risk of frailty in older adults free of atherosclerotic disease [98]. Moreover, frailty was associated with worse endothelial function and mortality in patients with chronic kidney disease [99].

Along similar lines, the role of vascular health in motor function is supported by longitudinal studies results reporting associations between elevated cardiovascular risk in early midlife and poor motor function later in life [100]. In addition, carotid IMT at baseline was

associated with lower isometric handgrip strength at follow-up in older men [101]. Also, cardiovascular risk scores at baseline in a cohort of CVD-free 45–69 year-olds were associated with future risk of incident frailty by the 10-year follow-up [102]. A recent study in 392 older participants reported that those with CVD were more likely to experience a rapid functional decline than their CVD-free counterparts [103].

Thus, poor cardiovascular function in the elderly likely contributes to the onset of frailty but the relationship between CVD and frailty is likely bidirectional [104] as frailty is an adverse prognostic factor in cardiac patients [105]. Frailty and pre-frailty were associated cross-sectionally with higher risk of CVD and longitudinal studies concluded that pre-frailty and frailty increased the risk for incident CVD in 23% and 70%, respectively [106]. In fact, data from 2,825 participants aged 70–79 and residing in the USA showed that moderate and severe frailty were associated with increased incidence of heart failure [107]. And, similarly, pre-frailty and frailty were associated with higher risk of CVD in Italian older people who enjoyed no limitations in activities of daily living [108]. Finally, frailty increased the risk for CVD development independently from early atherosclerosis markers [106]. Among specific frailty domains, exhaustion, low physical activity, slow gait speed, and weak grip strength have been associated with increased risk for incident CVD [109–111]. Recent work concludes that frailty and CVD share main risk factors as well as oxidative stress and inflammatory background [105,112,113]. Thus, physical exercise represents an efficacious strategy for improving both conditions [114]. This supports the stance that both conditions are bidirectionally related as they both also uniquely contribute to unsuccessful aging, while not eliminating the possibility of being separate manifestations of an underlying common physiological pathology.

2.4. Endocrine system/metabolic diseases

Sex hormones decline progressively with age among healthy, non-obese men starting in their 30s whereas the sex hormone binding globulin (SHBG) increases during their 50s and beyond [115]. The combination of these two changes leads to a steep decrease in free testosterone levels in aging men [116–118]. Decline in androgen levels has been postulated as a potential mechanism contributing to frailty. In Spanish men aged ≥ 65 years, lower free and total testosterone serum levels were associated with frailty [119] supporting previous findings [120–122]. A significant increase in the risk for frailty was detected in men with SHBG serum concentrations ≥ 66 nmol/L or with free testosterone levels < 243 pmol/L [123]. Moreover, prospective studies have shown that low levels of testosterone predict frailty onset or progression in men [120,122]. Although scarce, a handful of studies have also analysed the association of testosterone and frailty in women. In women aged 70–79 years of age, two or three deficiencies in hormonal levels of insulin-like growth factor 1 (IGF-1), free testosterone, or dihydroepiandrosterone sulphate (DHEAS) greatly increased the likelihood of being frail [124]. Older women presenting 4 or more Fried's criteria for frailty displayed very low levels of free testosterone, although this association appeared confined to obese women [119]. Despite the clear relationship between low androgen levels and frailty, data provided by testosterone supplementation studies in older adults are not consistent. A recent review concluded that whereas testosterone modestly improves lean muscle mass in older men regardless of frailty status, the hormone's effect on physical function is weak [125]. However, more recent findings suggest that testosterone supplementation may facilitate the molecular changes produced by exercise in skeletal muscle so as to actually enhance resistance training's benefit on physical function [126].

Diabetes mellitus (DM), predominantly type 2 diabetes, is one of the most prevalent chronic diseases in older adults [127]. There is a clear relationship between diabetes and frailty [128] and the relationship seems to be bidirectional [129]. In fact, frailty and sarcopenia are emerging as new complications leading to disability in addition to

traditional micro and macrovascular diseases [130]. In a cross-sectional study conducted in primary health care settings, older adults (65–74 years) with diabetes were more likely to perform poorly in physical tasks than their DM-free peers [131]. Longitudinal studies have reported that DM increases the risk for frailty in older adults (60 years or more) [132]. Multivariate analyses carried out in older diabetic participant data concluded that physical frailty was independently associated with a higher disability and mortality, suggesting that frailty in this population is an unfavorable and important prognostic factor [133,134]. The co-occurrence of diabetes and frailty in older people is not surprising since these two age-related conditions share common underlying pathophysiological mechanisms. These mechanisms involve imbalances in endocrine, neurohormonal, vascular, and muscular function among others. The conditions also share key risk factors including impaired insulin resistance, glucose dysregulation, physical inactivity, and obesity [19].

In addition to the associated comorbidities, diabetes directly impacts skeletal muscle thus contributing to mobility reduction in older individuals [28]. The association of diabetes with low gait speed is potentially mediated by impaired muscle function [135]. In fact, loss of muscle mass and/or strength is greater in long-lasting diabetes or higher HbA_{1c}, and the loss is attenuated by insulin sensitizers [28,136,137]. Muscle strength measured via handgrip test was inversely associated with fasting glucose, HbA_{1c}, fasting insulin as well as with insulin resistance as determined by homeostasis model assessment of insulin resistance (HOMA) score [138]. Longitudinal study results concluded that older patients with diabetes and HbA_{1c} level $\geq 8.5\%$ had a higher risk of low muscle quality and performance status than control non-diabetic peers [139].

In addition to diabetes, other related metabolic alterations have been proposed to have influence on physical function in the elderly. For instance, metabolic syndrome [140] has been linked to an increased risk of frailty [141–143], but not in all studies [144]. On the other hand, among adults over 50, frail ones were more likely to have metabolic syndrome than the non-frail [145]. In a USA population, metabolic syndrome was correlated with frailty index in younger (≤ 65) and older subjects (> 65), although the association was weaker in the latter. Frailty, but not metabolic syndrome, predicted mortality in both age groups [146], suggesting that the previously reported association of metabolic syndrome with mortality may have been influenced by the failure to adjust for frailty.

Insulin resistance seems to play a key role in the pathophysiological process underlying functional impairment related to diabetes in the elderly, even before the onset of diabetes. Supporting this, an inverse association was detected between quadriceps strength and insulin resistance in non-diabetic individuals 70 years and over [147]. Low insulin sensitivity has been associated with low lean muscle mass [148]. In fact, a positive association between HOMA-IR level and frailty in elderly adults has been recently reported whereas this association failed to reach significance in middle-aged participants. In this study, among the frailty components, weakness, exhaustion, and low physical activity were related to insulin resistance [149].

The direct impact of insulin resistance on skeletal muscle could explain the deterioration of physical function related to this condition [150]. In fact, altered muscle fiber type content and an increased accumulation of intramyocellular lipid droplets have been observed in muscle biopsies from older subjects with metabolic syndrome [151]. In this sense, non-diabetic insulin resistance exacerbates the decline in protein anabolic response in older adults and the decline only worsens in the presence of diabetes when glucose metabolism is further impaired [152].

Diabetes impacts vascular function in older adults. This is supported by the fact that heat-induced skin vasodilation was further impaired in the presence of type 2 diabetes in older subjects compared to their non-diabetic and younger counterparts [153], suggesting that, the impact of diabetes and aging on vascular function may be additive. Thus,

evidence from epidemiological and functional studies strongly suggests that the co-presence of older age and diabetes increases vascular impairment to a greater extent than either condition separately. Although the underlying mechanisms are not fully understood, inflammation has been pointed out as a key factor in the exacerbated vascular damage produced when older age and diabetes coexist [154].

Additionally, diabetes and insulin resistance may interfere with other systemic functions that influence the risk of frailty. Hormonal alterations may represent one of them. In this sense, reduced plasma levels of free and total testosterone have been observed in men with type 2 diabetes and the prevalence of testosterone deficiency syndrome in type 2 diabetic patients is estimated at around one third [155–159]. The hormonal impact of diabetes was suggested to be sex specific since lower levels of testosterone were confirmed in diabetic men but not women [160]. Interestingly, low testosterone levels are associated with insulin resistance in both diabetic and non-diabetic men [161–163]. In contrast, insulin resistance is associated with increased levels of testosterone in women [161,164]. However, in both men and women, circulating sex hormone binding globulin (SHBG) is reduced in the presence of diabetes, inversely related to insulin resistance and predicts glucose intolerance [160,162,164,165].

3. Age-Related signaling pathways involved in physical dysfunction and frailty and its modulation by physical exercise/activity

Physical activity is known to preserve or improve the function of multiple key systems affected by age, including the endocrine, respiratory, and cardiovascular systems as well as skeletal muscle. Understanding the pathways through which exercise impacts physical function is important as it might facilitate the development of new therapeutic strategies to improve performance in the aged population and to prevent and reverse frailty. Below we discuss the most common age-related signaling pathways involved in physical dysfunction and how they are modulated by exercise (Fig. 5).

3.1. Oxidative stress

The impact of oxidative stress on the functioning of different systems, tissues, and organs has been suggested as the main underlying link between aging and its associated chronic diseases and frailty [166]. In fact, both frailty and age-related chronic diseases were related to a common underlying oxidative damage [19].

Oxidative stress results from the imbalance between pro and antioxidant species. It is widely accepted that adequate efficiency of antioxidant response is compromised during aging [166]. The stimulation of transcription factor nuclear erythroid-2 like factor-2 (Nrf2)/antioxidant response element (ARE) pathway seems to play a prominent role in response to oxidative insult in order to induce antioxidant defense. Studies in rodents demonstrated that aging is associated with decreased expression of Nrf2 in skeletal muscle which is related to frailty phenotype in these animals [167]. In fact, Nrf2 deficiency exacerbates age-related unfavorable outcomes regarding loss of muscle mass and physical function together with increased oxidative stress and mitochondrial dysfunction [167–169]. Based on this evidence, it has been postulated that the defect in the Nrf2-mediated signaling during aging contributes to manifestation of chronic age-related diseases including frailty [19]. The observed association between frailty phenotype, reduced systemic mRNA expression of Nrf2, and three of its target genes (heme oxygenase-2, thioredoxin reductase-1 and superoxide dismutase-2) in community-dwelling older adults supports this hypothesis [170].

Despite their well-known deleterious role, ROS are key mediators in exercising muscle exerting an adaptive response that involves transcription of redox-sensitive factors which, in turn, promote the increase in cytoprotective proteins such as catalase, superoxide dismutases, and

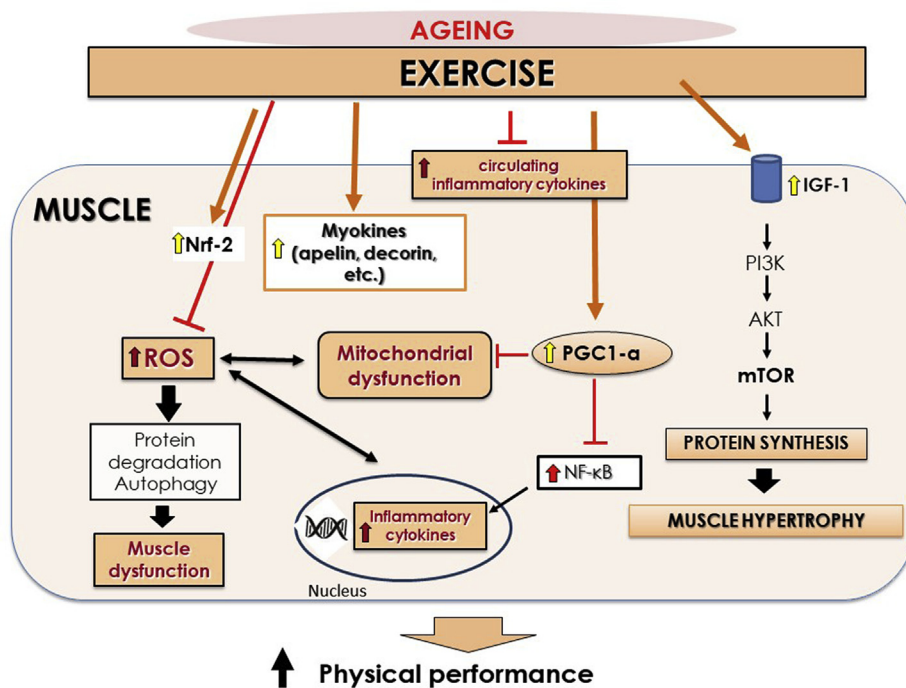


Fig. 5. Aging process is associated with increased reactive oxygen species (ROS) and inflammation resulting in muscle dysfunction. Decreased levels of insulin-like growth factor (IGF-1) are related to aging with the subsequent diminished protein synthesis and muscle growth via phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway. Exercise may exert potent anti-inflammatory and anti-oxidative stress (i.e., through nuclear erythroid-2 like factor-2 (Nrf-2) activation) effects and consequently improve muscle function. In addition, exercise increases protein synthesis via activation of IGF-1 pathway and target myokines reducing protein degradation. An increased signaling of the transcription factor peroxisome proliferator-activated receptor γ coactivator-1 α (PGC-1 α) is also induced by exercise, improving mitochondrial function and reducing inflammation mediated by nuclear factor κ B (NF- κ B).

heat shock proteins that prevent oxidative damage. This response to ROS generation is severely diminished in aged muscle [171].

Although previous studies failed to demonstrate a reduction of oxidative stress with exercise in the elderly [172] despite improvement in their overall health condition [173], anti-oxidative effects of exercise training are widely accepted. But not all types of exercise produce the same effects. Single bouts of exercise exceeding certain intensity and duration have been shown to transiently increase ROS from the mitochondria and other oxidases which may actually harm the cell [174]. In contrast, chronic exercise showed benefits by attenuating age-related oxidative stress in different organs including skeletal muscle [175], and arteries [176] in animal models. Furthermore, muscle biopsies from lifelong trained older subjects showed decreased oxidative stress and increased catalase expression when compared to the untrained group [174]. In fact, increased antioxidant status has been closely related to age-associated skeletal muscle changes improvement [177].

Compared to a sedentary group, trained elderly presented lower plasmatic concentrations of oxidized LDL (marker of oxidative stress) and decreased expression of genes involved in oxidant production evaluated in peripheral blood mononuclear cells [178]. A recent study observed how 12-week exercise training produced a reduction in plasmatic levels of protein carbonylation in older subjects with COPD. Moreover, protein carbonylation was associated with variations in muscle size and pennation angle as well as with exercise-induced structural and functional adaptations [179]. Furthermore, Mota and collaborators reported the effectiveness of a combined exercise program in reducing oxidative stress including DNA damage and increased antioxidant capacity in women over 40, regardless of age, suggesting that physical exercise may help mitigate the aging processes associated with oxidative stress [180]. Supporting this work, Cobley and colleagues reported an attenuation of age-related macromolecules damage and an increase in HSP72 and catalase in muscle biopsies from lifelong trained individuals [177].

An increase in Nrf2 produced by exercise in the aged was proposed as one of the different mechanisms by which healthy lifestyle and dietary habits mediate the increase in longevity [23]. For instance, Nrf2 is proposed to be necessary for redox adaptations to exercise [181] and as one of mediators of physical activity-promoted protection against ROS-induced skeletal muscle damage [182]. Studies with knockout

mic for Nrf2 supported the role of this factor in mediating exercise-induced antioxidant and functional actions in skeletal muscle [183,184].

Nrf2 activation in response to exercise is not limited to skeletal muscle level but also it occurs at the systemic level. In fact, exercise-induced Nrf2-signaling in blood mononuclear cells has been demonstrated to be impaired in older men [185]. Exercise also induces activation of Nrf2 in the cardiovascular system [186]. This is important since Nrf2 down-regulation seems to be related to age-related vascular dysfunction that improves after Nrf2 activation [187].

3.2. Inflammation

Low-grade chronic inflammation is one of the traits of the aging process. Substantial evidence shows that aging is characterized by a general increase in circulating levels and cell capability to produce pro-inflammatory cytokines (e.g. interleukin IL-6, tumor necrosis factor alpha (TNF- α), and C-reactive protein (CRP)). An increase in nuclear factor κ B (NF- κ B) signaling and a reduction in anti-inflammatory cytokines (e.g. interleukin 10, adiponectin, transforming growth factor- β) may also characterize the aging process [188,189]. Chronic inflammation, in turn, plays a role in the development of age-related diseases [112]. Moreover, elevated levels of pro-inflammatory cytokines correlate with increased risk of morbidity and mortality among the elderly, whether frail or not [23]. It is worth noting that several processes trigger these inflammatory pathways, including age-associated redox balance, senescence, and impaired autophagy [190].

Substantial evidence supports the relationship between chronic inflammation and physical performance in elderly subjects. Elevated levels of different cytokines such as IL-6, TNF- α and CRP as well as white blood cells (WBC) increase have been associated with poor function and mobility status [191,192]. A recent population-based cross-sectional study found an inverse and independent relationship between serum CRP levels in old males and handgrip strength and physical performance [193]. Likewise, abundant studies point to the association between IL-6 and frailty [194].

Again, how older people exercise matters. Acute bouts of exercise induce an inflammatory response which elevate pro-inflammatory cytokine levels which cause transient damage to contracting skeletal

muscles [195]. Regular exercise, however, decreases the IL-6 and CRP levels according to a recent meta-analysis [196]. Additionally, increased levels of physical activity were also associated with higher levels of the anti-inflammatory mediators adiponectin and interleukin 10 (IL10) in addition to the reduction of pro-inflammatory cytokines [195].

Reduction in the expression of toll-like-receptor (TLR) on monocytes is one of the potential mechanisms through which physical activity brings about anti-inflammatory effects. Stewart and colleagues (2005) found that 10–12 weeks of moderate exercise lowered TLR4 expression and pro-inflammatory biomarkers in previously sedentary older participants to levels similar to those observed in young individuals [197]. This evidence suggests that inflammation in older subjects is reversible and, with the right intervention, it may be preventable [198].

It is worth noting that the effect of physical activity on inflammatory response varies by type, intensity, and frequency of the exercise as well as on participant's characteristics [195]. Resistance exercise appears to decrease TNF- α expression in aged skeletal muscle which, in turn, may attenuate age-associated muscle changes [174]. Furthermore, older diabetic patients saw a reduction in their CRP concentrations and an increase in adiponectin levels after 16 weeks of resistance training [199]. A recent study has provided evidence that aerobic exercise is more appropriate in modulating the immune system and inflammatory markers among the elderly population than resistance exercise [200]. Whereas there is overwhelming evidence pointing to the anti-inflammatory effect that exercise has on older people through its influence on cytokine levels, some studies have failed to reach such favourable conclusion [201]. In neither frail nor prefrail older adults did prolonged progressive resistance exercise training affect IL-6, IL-8 and TNF- α circulating levels. Moreover, the higher the levels of these markers the lower the strength gains were during resistance exercise intervention [202].

It has been proposed that age-related inflammation of adipose tissue is a key factor in skeletal muscle inflammation and muscle dysfunction [203]. As aforementioned, insulin resistance is a condition associated with physical impairment in the elderly. In fact, the relationship between insulin resistance and frailty could be mediated by inflammatory processes as inflammation downregulates IGF-1 which affects muscular regeneration [113]. In addition, inflammation causes insulin resistance via the TNF receptor superfamily member 1A and the TLR-induced activation of Janus kinase which, in turn, interferes with insulin signaling. Concurrently, insulin resistance causes inflammation via central obesity (adipocytes release the C-C motif chemokine 2 (CCL2)) and via M1 macrophages tissue accumulation [113,204].

3.3. Autophagy

Autophagy is one of the multiple pathways by which cellular content is degraded. Autophagy plays a key role in maintaining skeletal muscle homeostasis through the removal of damaged cell components [205]. Thus, autophagy-deficient mice mimic several age-related characteristics including loss of muscle mass and quality [206] suggesting the main role of this process is protecting against aged-related cellular impairment. Evidence suggests that aging alters the autophagy process present in skeletal muscle, thus, contributing to sarcopenia [207]. There are two main markers of this important process. One, lipidated microtubule-associated protein 1 light chain 3 (LC3) II is often used as a marker of the number of autophagosomes; and two, elevated LC3 II/LC3I protein ratio in combination with decreased cargo protein Sequestosome-1 (p62) levels may indicate increased autophagy [205]. An increase, decrease, and non-change in LC3II/LC3I protein ratio have been observed in aged skeletal muscle of various species [208]. Recently, Aas and collaborators observed higher levels of LC3II, which may indicate increased levels of phagosomes, in older participants, across frailty status, compared to young participants, suggesting an age-related process. On the other hand, they found higher levels of LC3I,

which may represent an attenuated phagosome formation, in frail old compared to young individuals. Furthermore, LC3I negatively correlated with specific strength. The correlations observed between specific strength and some markers of autophagy indicates a possible link between these two factors [206].

Exercise impacts on the autophagy implicated in skeletal muscle aging. Park and colleagues showed that activating autophagy through physical activity increases muscle functioning and improves the sarcopenic phenotype [209]. This could be related with the fact that induction of chronic contractile activities in skeletal muscle cells recovers LC3II levels and autophagy deficiency through decreasing oxidative stress, resulting in improvement of mitochondrial function [210]. In this sense, long term (34 weeks) voluntary resistance wheel exercise initiated in middle-aged mice (15 month-olds) has been shown to increase markers of mitochondrial density and activity and to increase LC3II/I ratios. This was related to causing soleus hypertrophy and to preventing sarcopenia in the hindlimb muscles of physically active aged mice when compared to sedentary controls [211]. Meanwhile, in human skeletal muscle, Dethlefsen and collaborators showed that age and training status only modestly affected autophagic and apoptotic markers. In this sense, a trend of higher LC3I, and LC3II levels were observed in both trained and untrained elderly men [208]. Nevertheless, endurance exercise training has been shown to increase the LC3II/LC3I ratio in skeletal muscle of aged rats [212] while lifelong endurance exercise training seems to prevent the ratio's age-related change in triceps muscle [213] and in humans' vastus lateralis [214]. These findings suggest that autophagy regulation is part of the metabolic adaptation to exercise training.

In addition to chronic exercise, acute exercise also activates autophagy and increases insulin sensitivity in skeletal muscle of older mice [215]. However, recent studies indicate that exercise-activated autophagy in skeletal muscle may depend on its intensity and duration [209]. Therefore, evidence relating autophagy and exercise is inconsistent and requires further study.

3.4. Mitochondrial dysfunction

Mitochondrial dysfunction, including alterations in proteostasis, biogenesis, dynamics, and mitophagy, is a key characteristic of aging [216]. In fact, impaired mitochondrial function and biogenesis, when observed in aged skeletal muscle, contributes to sarcopenia, poor physical performance, and chronic fatigue [217,218]. Not surprisingly, mitochondrial dysfunction seems to be a determinant factor in the association of frailty with other age-related diseases [219]. Probably due to the dysfunction's association to the highly prevalent age-related sedentarism which, in turn, is closely related to frailty and poor physical performance [220].

Mitochondria are not only a source of, but also a target of, oxidative stress resulting in mitochondrial dysfunction; thus, leading to a vicious cycle. Recent work identified alleles in mitochondrial DNA associated with unfavorable frailty and grip strength outcomes supporting the clinical relevance of mitochondrial DNA alterations [23].

Skeletal muscles activate different redox-sensitive pathways as an adaptive response to oxidative stress generated during contractile activity. In this activity, NF- κ B, MAPK, and the peroxisome proliferator-activated receptor γ coactivator-1 α (PGC-1 α), seem to be the most relevant to exercise physiology. PGC-1 α is considered the master regulator of mitochondrial integrity, function, and biogenesis. Reduced PGC-1 α in addition to an age-related lack of response mediated by this factor has been previously reported [19,221]. In addition, and if we take into account the implication of defective PGC-1 α signaling in sarcopenia and age-related skeletal muscle alterations, PGC-1 α has the potential of being a significant factor in the evolution of frailty phenotype [19].

Moreira and colleagues reviewed several studies reporting that chronic endurance exercise, regardless of time and intensity, induces

PGC-1 α gene expression in the skeletal muscle in animal and older human models [222]. Halling and collaborators provided evidence using mice that physical activity protects against age-related mitochondrial fragmentation in skeletal muscle by curbing mitochondrial fission protein expression in a PGC-1 α dependent manner [213]. These findings support the important contribution of PGC-1 α to the beneficial effects of exercise training at advanced age by maintaining mitochondrial metabolic and antioxidant capacity [223].

As discussed above, Nrf2 activation is key for adaptive antioxidant defense in response to exercise. In addition to its effects on oxidative damage, exercise-induced Nrf2 activation may exert beneficial effects on muscle performance by improving mitochondrial biogenesis and function [167–169,224].

On the other hand, central to the maintenance of a healthy mitochondrial pool is the removal of dysfunctional organelles via mitophagy. Despite scarce data on how mitophagy is impacted by growing older and chronic exercise [225], mitophagy dysregulation has been denoted as a major pathogenic mechanism in muscle wasting [226]. In fact, reduced protein levels of LC3 II and Atg7 have been detected in muscle biopsies of older individuals [227]. Therefore, exercise-induced mitophagy might benefit aged muscle by preventing the accumulation of damaged mitochondria. Supporting this, 6-month weight loss in combination with a moderate intensity exercise program was reported to increase mRNA expression of LC3II, Atg, and lysosome-associated membrane protein 2 (LAMP-2) in the vastus lateralis of elderly overweight women [228]. Furthermore, lifelong exercise may preserve the expression of LC3II and Atg at the same levels as those observed in young controls [228].

3.5. IGF1/mTOR

As we age, insulin/IGF-1 signaling is impaired, mainly due to insulin resistance and lowered IGF-1 levels, with the subsequent diminished protein synthesis and muscle growth via phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway [23]. Previous work has reported an association between IGF-1 and frailty. Doi and colleagues concluded that lower serum IGF-1 levels were independently related to frailty in older adults [229]. Further, IGF-1 levels were lower in individuals with frail/low relative appendicular skeletal muscle mass (RASM) compared to their frail/normal RASM peers. IGF-1 levels were significantly associated with frail/low RASM status for the overall cohort [230].

Insulin-like growth factor cell signaling pathway, involving PI3K, AKT and mTOR, is crucial for post-exercise protein synthesis increase [221]. mTOR is one of the major pathways modulated by exercise, although different data indicated that the outcome varies depending on the type of training [231]. For instance, strength training activates IGF-1 and the mTOR pathway is stimulated resulting in muscle protein synthesis through mRNA translation and ribosomal biogenesis. The impact of aerobic exercise varies by age, however. In young animals, with a lower cell energy state, AMPK is activated, mTOR is inhibited, and PGC-1 α is activated leading to mitochondrial biogenesis [232]. Among old animals, mitochondrial biogenesis activation by aerobic exercise is somehow inhibited [221].

In addition, studies involving resistance type of exercise have usually reported a weaker anabolic protein response in older individuals when compared to younger ones as a consequence of mTORC1 signalling pathway dysregulation. This may be indicative of the presence of higher levels of cellular stress markers in older individuals which, in turn, may impact the post-exercise remodeling responses [221].

It is worth underscoring that regular exercise augments skeletal muscle mass by increasing glucose levels. Higher glucose levels boost insulin action resulting in improved insulin resistance [233]. Furthermore, a recent study reported that a 12-week combined anaerobic and aerobic exercise program may improve insulin resistance, IGF-1,

growth hormone (GH), and DHEA-S levels in elderly Korean women [234].

3.6. Myokines

Myokines are molecules, cytokines or signaling peptides (e.g., IL-6, IGF-1, irisin, myostatin, IL-15, fibroblast growth factor 21) expressed, synthesized, and released by skeletal myocytes in response to muscle contractions with pluripotent effects [235]. The expression of some of these myokines may vary with age in rodents and humans. Some such as apelin [236] may decline, some may remain unchanged such as myostatin, and still others may increase such as GDF-11 (a member of transforming growth factor TGF- β signaling pathway) [237].

Moreover, myokines seem to affect multiple processes associated with physical frailty, including muscle wasting, dynapenia, and slowness [238].

A recent review has reported that the benefits of exercise include stimulating a healthy anti-inflammatory environment, mainly via the release of muscle-derived myokines, and reducing age-related loss of muscle mass and function [239]. In humans, an increase in systemic concentration of decorin has been reported after acute and chronic exercise [240]. This myokine seems to play a role in inactivating myostatin, a known negative regulator of muscle mass, resulting in decreased muscle protein degradation [241]. The level of circulating irisin increased and presented a positive correlation with both grip and leg strength after an exercise program [242]. Apelin is another exercise-induced myokine reported to be involved in neutralizing age-associated muscle wasting [236]. Muscle wasting is offset by inducing mitochondriogenesis, fostering muscle's regenerative capacity, and mitigating muscle-related inflammation [237].

It is worth mentioning that myokines are likely to play an important role in whole body homeostasis. Thus, the shifts in their production/synthesis/downstream signaling may play a role in the onset of certain metabolic, cardiovascular, and kidney diseases among others [238].

This multisystemic effect, also attributable to the other mentioned signaling pathways, may contribute to the positive impact of physical activity on frailty, especially taking into account that this frailty results from a multisystemic dysfunction (Fig. 6).

4. Exercise training interventions

Several types of exercise programs have been described [243]. Every kind of intervention has its own characteristics and expected effects on skeletal muscle and function, as well as on other body systems.

4.1. Physical exercise

Physical activity is defined as any body movement produced by the skeletal system that increases energy expenditure. Physical exercise is physical activity carried out with a structured frequency and whose objective is to maintain or improve some component of an individual's physical fitness (muscular strength, flexibility, balance or cardiovascular endurance) [243]. Specificity is the fundamental principle of physical exercise. Hence, in order to generate muscular, cardiorespiratory, and central system adaptations, an exercise program that works on all these components should be proposed. When several adaptations are needed, as in the case of frail/prefrail people, multi-component exercise programs have been proposed as the most effective option [244,245].

The effectiveness of all these programs has been largely established (Table 1), although the ideal composition of the physical exercise program remains elusive [255]. Exercise training must be prescribed as a treatment for age-related frailty [256] and, like any treatment, must be adjusted to the right dose. Physical exercise prescribers must increase (or decrease) the dose based on individual progress. Prescribers

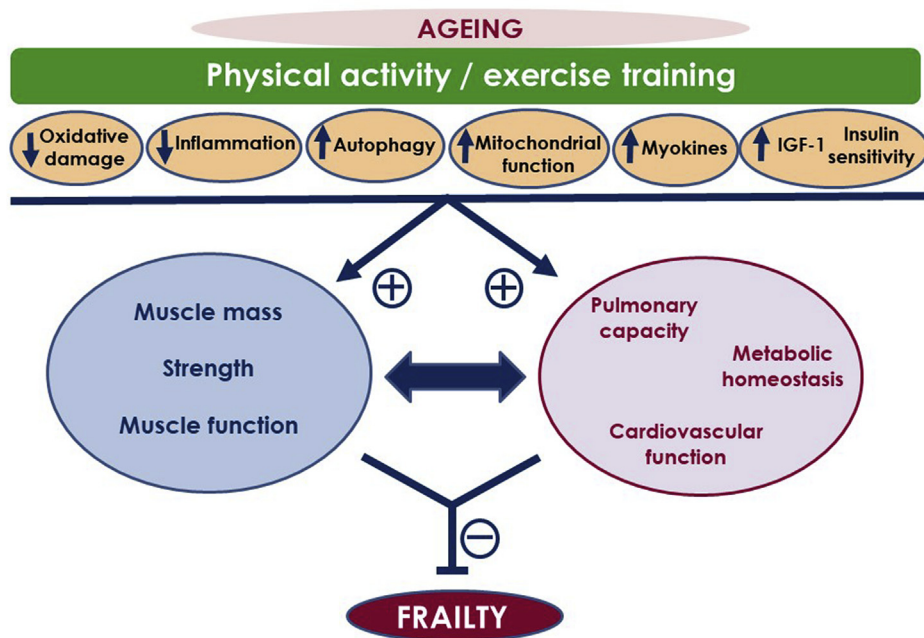


Fig. 6. Physical activity/exercise training may influence the outcome of the aging process by modulating key signaling pathways. Exercising results in reduced age-related oxidative damage, reduced chronic inflammation, increased autophagy, improved mitochondrial function, improved myokine profile, augmented insulin-like growth factor-1 (IGF-1) signaling, and insulin sensitivity. These actions promote beneficial effects on skeletal muscle (muscle mass, strength, and function) but also at systemic level, inducing improvements in function of cardiovascular, respiratory and metabolic systems. Exercise-induced improvements in muscle function as well as systemic benefits and age-related chronic diseases alleviation are all related to the improvements in physical function and frailty improvement by exercise/physical activity.

should combine the main variables in training (duration, type, intensity and frequency) until they find the optimal dose for each individual. The goal should be to establish an evidence-based and feasible exercise protocol to be implemented in the clinic.

4.2. Aerobic exercise

Aerobic capacity, i.e., the heart and lungs ability to oxygenate muscles, has been strongly associated with mortality, CVD, mobility limitations, and disability [58]. Aerobic capacity is usually measured via VO_2 maximum or peak. After the third decade of age, this capacity progressively declines, decreasing the ability to perform activities of daily living (ADLs). One of the most notable effects of endurance training is on increasing VO_2 peak, an important determinant of frailty in older adults [257]. Moreover, as the muscle adapts to endurance exercise training, its oxidative capacity increases resulting in higher fatigue resistance or increased muscle endurance [246].

Several ways of assessing cardiopulmonary condition are currently available. Based on exercise gas exchange variables, cardiopulmonary exercise testing (CPET) is the best evaluation tool for determining exercise intolerance, or dyspnea on exercise, and estimating the cardiorespiratory fitness. Despite being limited by the setting and by the expensive equipment required, CPET is most commonly used for disease management such as heart failure and pulmonary hypertension. Further, it has potential diagnostic utility for older adults with decline in exercise levels [258].

Two of the conventional submaximal exercise tests commonly used in elderly as a measure of walking speed and mobility performance are the 6-min walking test and the 400 m walking test. These tests only require a long corridor (≥ 30 m recommended) and a stopwatch. Additionally, the placement of chairs along the corridor and having a trained professional walk closely behind the patient are suggested. In addition, the 400 m test has been shown as a prognostic factor and a predictor for CVD, mobility limitation, and mobility disability in older persons reporting no walking difficulties [58]. Additional, valid measures of health outcomes using shorter distances have been established. A well-validated protocol entails a 4 m course from a standing start [259]. A gait speed of at least 1.4 m/s indicates patients are likely to be able to perform their ADLs independently, whereas a gait speed of < 0.8 m/s suggests patients are likely to be frail, to be at increased risk of

falls, and to be dependent regarding their ADLs and their Instrumental Activities of Daily Living (IADLs) [260].

Guidelines from the American College of Sports Medicine and the American Heart Association for older adults recommend a minimum of 150 min per week of moderate intensity aerobic training (30 min on five out of seven days per week) or a minimum of 60 min (20 min on three days per week) of vigorous activity [261]. Although frail individuals may not be able to meet this recommendation, modest increases in activity and strengthening exercise could impact positively in the progression of functional improvement [246,262].

Many activities have been proposed for increasing aerobic capacity such as brisk walking, jogging, water aerobics, swimming, dancing, or bicycle riding. In addition to these classical approaches, a recent paper has shown benefits after implementing a High Interval Intensity Training- HIIT program [252]. Among them, walking is the easiest, cheapest, most feasible, most relevant to ADLs, and the easiest to be assessed in the clinic. Although there are different approaches according to the functional status of the person [253,263,264] there are not standardized and generally accepted rules about the prescription of aerobic exercise to frail people.

4.3. Strength exercise

Muscle strength is the force or tension that a muscle or muscle group generates [265]. The extent of muscle strength loss with age, inactivity, injury, and immobilization depends on impaired neuromuscular activation and reduced muscle volumen [266]. Strength workout seems to be the key element in preventing sarcopenia and falls, while keeping functional capacity [249,267], also in older people [246].

There are some well-validated techniques to measure muscle strength. Handgrip strength (on dominant arm) is the most common, and it is used in research and clinical settings. The most common dynamometer used for this test is JAMAR Hydraulic Hand Dynamometer. Test should be repeated ideally twice, recording the best one [268].

In order to measure intensity (percentage of the maximal strength that an individual can develop), the one-repetition maximum (1-RM) is commonly used. It is defined as the maximal weight an individual can lift for just one repetition with correct technique, and it is considered the gold standard for assessing muscle strength [269]. Depending on the intensity, strength training should be prescribed every other day,

Table 1
Study findings of the effect of physical exercise interventions on physical function in older people across frailty status.

Author, year	Sample	Intervention	Main findings
Fiatarone et al., 1994 [246]	100 older adults Frail 72-98 year-olds Nursing home	10 weeks MCI (3 types: ET, multnutrient supplementation, or both (group B))	<ul style="list-style-type: none"> ● ET improved muscle strength ● All training methods improved gait speed and muscle mass and both declined in non-exercisers ● Stair climbers power improve vs non exercisers ● The group B gained weight compared with ET or multnutrient group ● Improved SPPB and 400 m test vs control
Pahor et al., 2006 [247]	424 older adults SPPB \leq 9 70-89 year-olds Community dwellers	24 weeks MCI (aerobic, strength, balance and flexibility)	<ul style="list-style-type: none"> ● Intervention improved SPPB vs control ● Intervention significantly decreased frailty at 12 months but not at 3
Cameron et al., 2013 [248]	216 older adults Frail (Fried phenotype) \geq 70 year-olds Community dwellers	12 months multifactorial individually according the Fried criteria met: If weight loss, a dietician evaluated nutritional intake If exhaustion and Geriatric Depression Scale score was high, study team considered referral to a psychologist or psychiatrist If weakness, slowness or low energy expenditure, patient received 10 home-based physiotherapy sessions	<ul style="list-style-type: none"> ● Intervention improved TUG with single and dual tasks, rise from a chair, balance performance, and reduced incidence of falls. ● Intervention enhanced muscle power and strength
Cadore et al., 2014 [249]	24 older adults Frail and prefrail (Fried phenotype) \geq 90 year-olds Nursing home	12 weeks MCI (muscle power training, balance and gait retrain)	<ul style="list-style-type: none"> ● Structured, moderate-intensity physical activity program conducted in a centre (twice/wk) and at home (3-4 times/wk): aerobic, resistance, and flexibility training activities. ● Or a health education program: workshops on topics relevant to older adults and upper extremity stretching exercises ● Reduced major mobility disability over 2.6 years among older adults at risk for disability vs health education program
Pahor et al., 2014 [21]	818 older adults 70 - 89 year-olds Community-dwellers	12 weeks. Three groups: one MCI (Warm-up, strength training, balance training and cool-down), MCI plus nutritional program (cooking class) (MCI-NP); and control	<ul style="list-style-type: none"> ● MCI improve handgrip strength, but effect was not maintained at 6-month postintervention ● MCI-NP and control did not obtained significant changes in measures of physical performance. However, handgrip strength declined postintervention and follow-up in the MCI-NP group ● Reverses frailty and improves functional measurements: Barthel, Lawton and Brody, Tinetti, Short Physical Performance Battery and physical performance ● Improves cognitive, emotional, and social networking determinations: Mini-Mental State Examination, geriatric depression scale from Yesavage, EuroQol quality-of-life scale ● Decreases the number of visits to primary care physician ● Significant improvement in frailty biomarkers.
Kwon et al., 2015 [250]	89 older adults Prefrail (Fried criteria, although considered frail if met 2 criteria at the time of enrolment) 65-91 year-olds Community-dwellers	12 weeks. Three groups: one MCI (Warm-up, strength training, balance training and cool-down), MCI plus nutritional program (cooking class) (MCI-NP); and control	<ul style="list-style-type: none"> ● MCI (proprioception, aerobic, strength, and stretching exercises for 65 min, 5 days per week, 24 weeks). ● Control group
Tarazona-Santabalbina et al., 2016 [251]	100 frail subjects (Fried phenotype) \geq 70 year-olds Community-dwellers	<ul style="list-style-type: none"> ● Six weeks MCI (Power training and HIIT) ● Usual care 	<ul style="list-style-type: none"> ● Improves cognitive, emotional, and social networking determinations: Mini-Mental State Examination, geriatric depression scale from Yesavage, EuroQol quality-of-life scale ● Decreases the number of visits to primary care physician ● Significant improvement in frailty biomarkers.
Losa-Reyna et al., 2019 [252]	20 frail and prefrail (Fried phenotype) 77.2-95.8 year-olds Community-dwellers	<ul style="list-style-type: none"> ● Six weeks MCI (Power training and HIIT) ● Usual care 	<ul style="list-style-type: none"> ● Reduction Frailty Phenotype ● Improvements in SPPB, muscle power, muscle strength and aerobic capacity vs control group
Martínez-Velilla et al., 2019 [253]	370 older adults > 75 year-olds Acute care hospitalization	<ul style="list-style-type: none"> ● In-hospital MCI included individualized moderate-intensity resistance, balance, and walking exercises (2 daily sessions) ● Usual care 	<ul style="list-style-type: none"> ● Increased the SPPB scale and Barthel Index score over the usual-care group ● Reversed functional decline ● Significant intervention benefits at the cognitive level over the usual-care group
Rodríguez-Mañas et al. et al., 2019 [22]	964 prefrail and frail older adults (Fried phenotype) with type 2 diabetes > 70 year-olds Community-dwellers	<ul style="list-style-type: none"> ● Multimodal intervention individualized and progressive resistance exercise programme for 16 weeks plus a nutritional educational program over seven sessions plus Investigator-standardized training to ensure optimal diabetes care ● Usual care 	<ul style="list-style-type: none"> ● After 12 months: Improvement in SPPB scores vs usual care ● Cost-effective improvement in the functional status of older frail and prefrail participants with type 2 diabetes mellitus. Vs usual care
Yu et al., 2019 [254]	127 prefrail subjects (FRAIL scale) \geq 50 year-olds Community- dwellers	<ul style="list-style-type: none"> ● 12-week MCI (resistance and aerobic exercises, cognitive training, board game activities) ● Wait-list control group 	<ul style="list-style-type: none"> ● Reduction in the combined frailty score ● Improvements in muscle endurance, balance, verbal fluency, attention and memory, executive function, and self-rated health vs control group

ET: Exercise Training; HIIT: High Interval Intensity Training; MCI: Multicomponent Intervention; MCI-NP: Multicomponent Intervention plus Nutritional Program; SPPB: Short Physical Performance Battery; TUG: Timed Up and Go.

especially in the initial workout stages [270]. Simple instructions should be provided, and both haptic support and mirror techniques are recommended [271].

4.4. Power exercise

Musculoskeletal power can be defined as the product of the force of a muscular contraction and its velocity. After the age of 50, around 3% of muscle power is lost every year, three times faster than strength [272]. Leg power is highly related to physical performance in older people [273].

Muscle power can be measured in any exercise or movement. Mostly common muscle lower exercises, leg press and knee extension, show good reliability and validity [274]. The 5 times sit-to-stand (5STS) test is an easy and inexpensive procedure in which only a chair and a stopwatch are required. It has shown to be a valid, clinically relevant tool [275].

Power training intensity should range from 30% to 60% of 1-RM load because maximal power output is maximized at these intensities [276]. Participants should perform concentric (shortening) phase exercises as fast as possible.

Power training should be prioritized in elderly, because it improves gait speed, chair stand test and stair climb time [270]. In a recent meta-analysis, high speed training resulted in improvements in the Short Physical Performance Battery (SPPB), although not in other functional capacity tools [270]. Furthermore, lower training volumes have been reported to be associated with greater improvements in muscle power [277].

4.5. Flexibility exercise

Flexibility is the range of motion (ROM) of one or several joints. Flexibility is scarcely measured in studies, and no scale has achieved wide acceptance. Probably, measuring flexibility with a goniometer on each specific joint could be the best option to assess ROM changes. A stretching or flexibility program is aimed at greater ROM by rising both static and dynamic stretching tolerance [278]. Static stretching refers to the ability to maintain the position at the end of the ROM. Dynamic stretching refers to achieving, on a repeated gradual transition on any part of the body, a progressive increase in ROM [279]. Dynamic stretching can be included in warm-up [266], whereas static stretching exercises could be performed at the end, as part of the cool-down phase [278].

4.6. Balance exercise

Neuromuscular systems, sensory systems (i.e., vestibular, visual, somatosensory) and cognitive systems (i.e., cerebellum, hippocampus, prefrontal and parietal cortices) have an important role in balance. With aging, all these systems deteriorate, increasing the risk of falling [280]. Inter-joint coordination and the appropriate timing of muscle action is also affected.

Berg Balance test is probably the most common test to evaluate balance in the elderly, assessing risk for falls in older community-dwelling adults through direct observation of their performance [281]. However, this test is time-consuming and balance assessment by SPPB is much faster, representing a more convenient tool for clinical practice.

There is evidence showing that balance and functional exercises reduce the rate of falls by 24% and by 13% the number of older people who experience one or more falls. Moreover, multi-component exercise programs (balance and functional exercises plus resistance exercises) reduce the rate of falls by 34% and by 22% the number of people experiencing one or more falls [282]. Further, supervised balance exercise programs seem to get better results than unsupervised ones [283]. Balance exercises are recommended three days per week, with at least two of them being supervised. Both dynamic and static exercises should

be performed [283]. Patients with poor scores in the progressive Romberg test of the SPPB could benefit from a higher frequency of balance training [284].

There are many exercises to improve balance depending on which system (sensory, cognitive, or musculoskeletal system) needs to be worked on. They include single leg stances, semi-tandem and tandem stance, toe walking, heel walking, tandem gait, walking on a balance board, and eye-hand or eye-leg coordination. The possibility of making each of them with open or closed eyes, joining the arms to the body or opening them, doing them on unstable surfaces or adding cognitive components such as specific orders, music or dual-task exercise, makes it almost impossible to monitor the workload. The program should include static vs. dynamic task, changes in the base of support, variations in the center of gravity height, and distinct standing surfaces [280]. Exercise difficulty should progressively increase involving both motor and cognitive tasks (dual- and multi-task activities) [280].

4.7. Non-physical training exercises

Recently Marusic and Grosprêtre reviewed one of the proposed tools, the non-physical training exercises, to improve balance and strength in older people, including those who are frail. These exercises include activities such as motor imagery (MI) and action observation (AO) [285,286]. These tools have been gaining relevance because normal aging is also associated with a progressive reduction in central and peripheral neural function. MI stands for the mental simulation of an action without any corresponding motor output, but still causing neuronal activation [286]. Meanwhile, AO, a tool grounded in basic neuroscience and the mirror neuron system [287], has been proposed to intensify neural activation induced by mental practice [286]. These types of interventions are deemed safe and efficient and do not add additional neuromuscular fatigue when incorporated into any type of intervention, something relevant in frail people [286]. Although the results are very promising, their effectiveness is still awaiting supporting evidence.

4.8. Adherence

The best physical exercise is the one that is actually carried out. Adherence rates to exercise programs are usually suboptimal, although comparisons across studies are often hampered due to differences in reporting [288]. Adherence may be improved by following certain tips. Before starting the exercise program, patients must be informed about the possible risks and benefits of the exercise program. A clear description of the program may increase motivation and adherence [289]. In addition, physical exercise professionals must inform about the importance of physical exercise in physical functioning, well-being, and quality of life [290], and attend to patient preferences and acceptance [291]. It is also desirable to create a friendly and familiar training atmosphere with the patients and; finally, the proper execution of the exercises must be closely monitored [271].

Other barriers to overcome are socioeconomic factors. Participation in exercise programs may be reduced by lack of transportation, fixed incomes, or inclement weather [292]. Thus, although supervised exercise programs seem to have better results in terms of strength and balance [283], home exercises [293] or video games-based interventions [294] could be a good option for some patients. Notwithstanding, as the impact of social isolation on frailty is well established, group exercise enjoys the additional benefit of socialization [295].

4.9. Adverse events

In contrast to the usual risks associated with poly-pharmacy, physical exercise administration is safe, relatively free of potential unwanted side effects [296], and adverse events are rare [297]. The use of a multidisciplinary team (e.g., geriatricians, nurses, physiotherapists)

seems to be the best option in order to avoid unnecessary risks, especially regarding the most vulnerable participants.

4.10. Adapting exercise intervention to individual functional status

4.10.1. Robust subjects

Older people who perform more than 180 min of weekly exercise report better health-related quality of life [298]. A substantial increase in physical activity level regardless of the baseline level (i.e., from sedentarism to moderate activity or from moderate to vigorous activity) has been associated with a reduction in sarcopenia prevalence and better performance of muscle mass and function [299]. More specifically, strength training seems fundamental, since decline in strength levels in older adults compromises overall function and it is predictive of future functional decline and higher incidence of frailty, disability, and mortality [58,300].

4.10.2. Prefrail older adults

The population of prefrail adults is one of the main targets of exercise interventions since it includes between 35% and 50% of individuals over 65 [108,301] and it is the subpopulation most likely to benefit from an exercise program [302]. Again, strength training is key since muscle weakness seems to be the most prevalent of the Fried components of frailty among the prefrail [303,304]. Kwon et al. reported that with just one weekly training, prefrail women could improve their strength. However, one day a week was not enough to achieve improvements in physical function, and any improvements in strength were lost three months after the end of the intervention [250]. In support of more frequent training, the MID-FRAIL study, which included pre-frail older people with type 2 diabetes mellitus participating in a multimodal intervention (detailed description of the study is provided below), reported improvements in functioning (as assessed by SPPB) among those participating in a strength training program twice weekly for 16 weeks [22].

4.10.3. Frail patients

Several training programs in different care settings (ambulatory or in-hospital) have been designed for frail people. A well-designed multicomponent exercise program showed improvements in gait speed, balance, SPPB functioning scores, ADL performance, as well as in frailty status [251]. The program was more intensive than most. It included a high training frequency (5 days per week) and relatively long sessions (65 min each). The intervention included strength exercises with elastic bands, stretching, and aerobic exercises including walking, arm movements and stair climbing. Attendance of at least 50% of the programmed sessions was associated with a substantially higher likelihood of reversing frailty to the point of robustness [251]. There is also evidence of improvements in leg strength and in SPPB functioning score obtained with a two-day/week supervised lower and upper body strength training program. Further, greater gains in muscle mass were obtained in the group receiving protein supplements [305,306].

Results from the “Sarcopenia and Physical Frailty IN older people: multi-component

Treatment strategies (SPRINTT)” study are expected to clarify the association between physical exercise and physical frailty and their relationship with sarcopenia. This randomized controlled trial follows 1500 community dwelling older persons aged 70 years and older with sarcopenia and physical function impairment (SPPB \leq 9) for up to 36 months. The efficacy of a MultiComponent Intervention (MCI), based on long-term planned exercise program and dietary guidance /intervention for preventing mobility disability is tested in comparison with a Healthy Aging Lifestyle Education (HALE) [307].

Among the many comorbidities present in frail and prefrail individuals, one of the most common is diabetes. In the MID-Frail study, 964 frail and prefrail elderly with diabetes were included according to the Fried phenotype. In this study, the effect of a three-pronged

intervention, including a resistance exercise program, a nutritional and educational program, and a standardized across sites researcher-enhanced training for best practices in diabetes care, was compared with a usual care group. The physical exercise intervention was a supervised individualized resistance exercise program consisting of a 2-week pre-training and learning phase followed by a 16-week program with participants undergoing two 45-min exercise sessions per week. Selected exercises were leg presses and bilateral knee extensions carried out in two to three sets of 8–10 repetitions each with a load equivalent to 40–80% of 1-RM. The intervention not only improved the functional capacity of the treatment group compared to the usual care group but also it proved to be cost-efficient with average savings of 428.02 euros per participant per year [22].

A recent systematic review found strength muscle improvements in frail older adults with very different protocols [308]. Training frequencies ranged from 1 to 6 times per week, including from 1 to 3 exercise series, and series including from 6 to 15 repetitions. Intensity was controlled by the rate of perceived effort (RPE) or by the percentage of 1-RM (from 30 to 100%). The review reported several findings. The main ones being that strength exercise, either performed in isolation or in combination with other training modalities, did improve muscle mass, strength and power, and/or functional capacity (not all studies saw improvements in all aspects). It is worth mentioning that using RPE to control exercise intensity was associated with no muscle strength improvement, suggesting that RPE underestimates exercise-related effort in this population of individuals.

4.10.4. Hospitalized older adults

Being immobilized, a usual condition in institutionalized and hospitalized older people [309], reduces muscle mass by 0.5% and muscle strength by 0.3–4.2% per day [310]. These losses often result in a significant deterioration in functional status with the corresponding decline in quality of life [311].

Improving the functional capacity of hospitalized oldest old patients through an MCI has proven feasible [253]. Due to the high levels of sedentarism these patients present, high frequency interventions (i.e., 2 daily exercise sessions for 5–7 consecutive days) seem to have better results than lower intensity interventions. The first session of the day was supervised, lasted about 20 min, and included balance, gait retraining, and resistance exercise. The second one was unsupervised and consisted of strength exercises using 0.5–1.0 kg anklets and a handgrip ball. This intervention improved SPPB score, Barthel Index, and cognition [253].

Different strategies have been proposed to successfully improve strength in these patients [312]. Nevertheless, resistance training seems to be the best exercise to improve strength and other outcomes, such as muscle mass, neural impulse, or mitigated bone loss. The effects of resistance training could be optimized if combined with vibration (general or local), blood flow restriction, and especially with neuromuscular electrical stimulation [312,313]. Restriction of blood flow and vibration can be combined with aerobic training and with low intensity strength training (< 20%), having special relevance in situations where high intensity exercise is not possible.

4.11. From research to clinical setting

Due to the heterogeneity of the population of older adults, there is a lack of consensus regarding a gold standard measure of functional capacity. This, combined with the differences among exercise programs, makes the translating of results from research settings to clinical practice difficult to say the least.

Numerous scales and tools have been tested as measures for physical capabilities of older adults and to detect clinically significant changes. Subjective scales are important to epidemiologic and qualitative research, as well as for learning what patients feel or think about their household or recreational activity functional level.

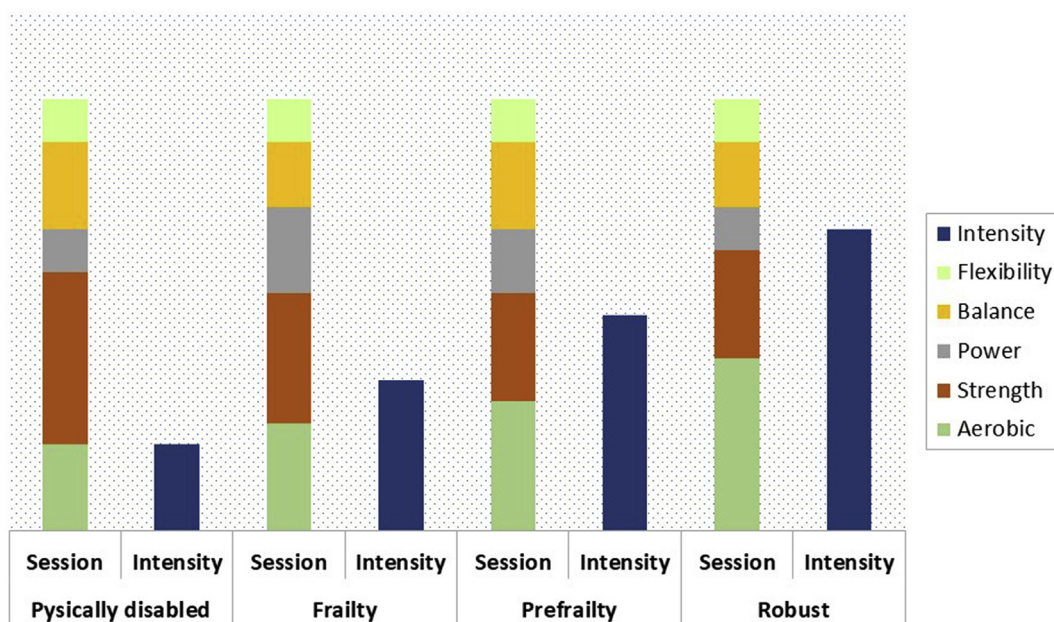


Fig. 7. Distribution of the type of exercises in a standard training session according to patient frailty status. Intensity should generally increase as the frailty status improves, although High Interval Intensity Training-HIIT can be used also in frail patients.

However, objective scales are more sensitive to changes, and can be standardized and reproduced. For instance, gait speed is a key element in the physical independence of a person and, thus, frailty, and, consequently, it has been repeatedly evaluated in different clinical settings.

Another test used and validated to evaluate physical function in older adults is the SPPB [314]. In addition to assessing gait speed at the individual's usual pace, this test measures balance (using the Romberg progressive test) and strength in lower limbs (with the 5STS test). The SPPB has been correlated with ADLs loss [315] and it is a good tool to identify patients who may benefit from an exercise intervention [302].

The prescription of different physical exercise programs in frail and prefrail patients based on the baseline physical performance of the patient is becoming a well-established strategy. Although the main evidence comes from the SPPB-based prescription, other instruments to assess frailty status, like the Frailty Trait Scale (FTS) [316] or its short-form FTS5 [317], could be theoretically used for the same purpose [248].

In the LIFE study, the prescription of physical activity-based interventions depending upon the SPPB score improved subsequent health outcomes [21,247,314]. Similarly, exercise prescription based on functional capacity as revealed by SPPB score could be optimal for using in physical exercise programs such as Vivifrail [263].

Using this approach may improve the prescription of physical exercise programs, thus optimizing their effects in the following ways (Fig. 7):

- 1 Emphasizing strength interventions could be useful in those patients who have low knee strength, low grip strength, and poor 5STS as well as people with higher scores in the Brachial/Ankle Index (BAI) which could be compatible with peripheral artery disease [318].
- 2 Emphasizing power interventions for patients with low gait speed, poor 5STS and balance test scores.
- 3 Emphasizing balance intervention for patients with low Romberg progressive test scores.
- 4 Verbal fluency could be improved with dual tasks and strength training [249] and multicomponent exercise programs [254,319].
- 5 Emphasizing aerobic training in patients with sedentary behavior, low gait speed, or low physical condition. It could be also recommended in patients with higher BAI scores [320].

Additional research is needed to further contribute to our knowledge about the optimal dose of individually fitted exercise programs by frailty status. In fact, not prescribing exercise programs to older populations may be considered unethical, in light of the substantial evidence showing health benefits [321]. Finally, evidence-based effective physical exercise intervention protocols should be translated to clinical practice.

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Declaration of competing interest

No Conflicts Of Interest.

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Toledo Study of Healthy Ageing

To answer the questions in the following chapters, data from the Toledo Study of Healthy Aging (TSHA) were used. TSHA is a prospective Spanish cohort study initiated in 2006 (2006-2009; wave 1) and consisted of 2488 (75.2 mean age, 56.1% women) participants aged ≥ 65 years living in the province of Toledo, Spain[213]. This study, which comprised 24% of the older living in the province of Toledo, aimed at studying determinants and consequences of frailty and aging, their social, clinical, pathophysiological, and genetic determinants, as well as their impact on the health care system and on different adverse events in institutionalized (1.9% of the sample) and community-dwelling older people. Participants signed an informed consent form when recruitment. The study conformed to the ethical standards defined in the 1964 Declaration of Helsinki and it was approved by the Clinical Research Ethics Committee of the Toledo Hospital. Baseline information on socio-demographic data, health status, lifestyle, social support, morbidity, among others were collected. In addition, home visits were performed in order to collect fasting blood samples and perform physical examinations and different clinical tests.

New waves of the previously mentioned data were collected from each subject after a mean follow-up of 5 years (2011-2013; wave 2) and of 3 years (2015-2017; wave 3). To avoid the classical risk of attrition affecting the cohorts of older people, TSHA is an open cohort, which allows to refill the participants lost due to death or lost in the follow-up. This also indicates that each wave can be used as a validation cohort under some circumstances. Moreover, in each one of the waves some new determinations have been added to the dataset, raising the opportunity to address different research questions fitted to the changing hot topics in the field. This is the case of body composition that was measured through appropriate methods in the second wave.

Chapter 2: Associations between frailty trajectories
and frailty status and adverse outcomes in community-
dwelling older adults

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Associations between frailty trajectories and frailty status and adverse outcomes in community-dwelling older adults

Alejandro Álvarez-Bustos¹, Jose Antonio Carnicero-Carreño^{1,2}, Juan Luis Sanchez-Sanchez³, Francisco Javier Garcia-Garcia^{1,4}, Cristina Alonso-Bouzón^{1,5} & Leocadio Rodríguez-Mañás^{1,5*} 

¹Biomedical Research Center Network for Frailty and Healthy Ageing (CIBERFES), Institute of Health Carlos III, Madrid, Spain; ²Biomedical Research Foundation, Getafe University Hospital, Getafe, Spain; ³Gerontopole of Toulouse, Institute of Ageing, Toulouse University Hospital (CHU Toulouse), Toulouse, France; ⁴Geriatrics Department, Virgen del Valle Hospital, Toledo, Spain; ⁵Geriatrics Department, Getafe University Hospital, Getafe, Spain

Abstract

Background The association between frailty and adverse outcomes has been clearly defined. Frailty is associated with age, but different frailty evolution patterns might determine the incidence of adverse outcomes at older ages. So far, few observational studies have examined how distinct frailty trajectories could be associated with differences in the risk of adverse events and assessing whether frailty trajectories could define risk of death, hospitalization, worsening, and incident disability better than one-off assessment. Our hypothesis is that prospective increases in frailty levels are associated with higher risk of adverse events compared with subjects that prospectively decreased frailty levels.

Methods Participants' data were taken from the Toledo Study of Healthy Ageing. Frailty was evaluated using the Frailty Trait Scale 5 (FTS5), being 0 the lower (*the most robust*) and 50 the highest (*the frailest*) score. FTS5 scores at baseline and follow-up (median 5.04 years) were used to construct frailty trajectories according to group-based trajectory modelling (GBTM). Multivariate Cox proportional hazard and logistic regression models were used to explore associations between frailty status and trajectory membership and the adverse outcomes. Deaths were ascertained through the Spanish National Death Index. Disability was evaluated through the Katz Index. Hospitalization was defined as first admission to Toledo Hospital.

Results Nine hundred and seventy-five older adults (mean age 73.14 ± 4.69 ; 43.38% men) were included. GBTM identified five FTS5 trajectories: *worsening from non-frailty* (WNF), *improving to non-frailty* (INF), *developing frailty* (DF), *remaining frail* (RF), and *increasing frailty* (IF). Subjects belonging to trajectories of increasing frailty scores or showing consistently higher frailty levels presented with an increased risk of mortality {DF [hazard ratio (HR), 95% confidence interval (CI)] = 2.01 [1.21–3.32]; RF = 1.92 [1.18–3.12]; IF = 2.67 [1.48–4.81]}, incident [DF (HR, 95% CI) = 2.06 (1.11–3.82); RF = 2.29 (1.30–4.03); IF = 3.55 (1.37–9.24)], and worsening disability [DF (HR, 95% CI) = 2.11 (1.19–3.76); RF = 2.14 (1.26–3.64); IF = 2.21 (1.06–4.62)], compared with subjects prospectively showing decreases in frailty levels or maintaining low FTS5 scores. A secondary result was a significant dose–response relationship between baseline FTS5 score and adverse events.

Conclusions Belonging to trajectories of prospectively increasing/consistently high frailty scores over time are associated with an increased risk of adverse outcomes compared with maintaining low or reducing frailty scores. Our results support the dynamic nature of frailty and the potential benefit of interventions aimed at reducing its levels on relevant and burdensome adverse outcomes.

Keywords Frailty; Mortality; Disability; Older adults; Trajectory modelling

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*Correspondence to: Leocadio Rodríguez Mañas, Geriatrics Department, Getafe University Hospital, Ctra de Toledo, 28905 Getafe, Spain.
Email: leocadio.rodriguez@salud.madrid.org

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Background

Frailty is defined as an age-associated, biological syndrome characterized by decreased physiological reserves, which puts an individual at risk when facing minor stressors. Because of its powerful association with adverse events (i.e. disability, mortality, and hospitalization)¹ and its high prevalence in older adults,² frailty has been placed in the geriatric medicine spotlight.¹

Frailty is dynamic in nature and potentially reversible.^{3,4} However, to date, only a limited number of observational studies have examined how changes in frailty status (i.e. trajectories of frailty) can predict usual adverse events. The categorical structure of the classical tools for assessing the frailty status⁵ may partially account for the short number of studies assessing such relationship. In fact, most of the previous researches have not considered frailty as a continuum^{4,6} or are limited by their analytical approach, ignoring the variability or reversibility in frailty score trajectories.^{7,8} Nevertheless, our group has recently developed the so-named Frailty Trait Scale 5 (FTS5),⁸ a Short Form of the 12 items one⁷ that allows the continuous evaluation of frailty levels, potentially overcoming several of previous frailty assessment pitfalls. This instrument refines risk profiling of the individual and outperforms the predictive ability of adverse events (i.e. mortality, hospitalization, and disability)⁸ even better than classical frailty tools, as the two most commonly used tools,⁹ the Frailty Phenotype⁵ and Frailty Index.¹⁰

The aim of this study is to explore the existence of different frailty trajectories and to investigate their associations with adverse outcomes (disability, hospitalization, and mortality) in a representative sample of older adults. Our hypothesis is that prospective decreasing frailty levels along ageing are associated with a lower risk of adverse events, compared with developing or maintaining higher frailty levels. A secondary objective is to compare cross-sectionally and longitudinally assessed frailty levels in terms of predictive ability.

Methods

This is a prospective analysis of the Toledo Study of Healthy Ageing (TSHA), a population-based longitudinal study whose main aim is to explore the prevalence, determinants, and impact of frailty in a Spanish cohort of older adults (>65 years).¹¹

In the present analysis, we included subjects with frailty and covariates data at TSHA Waves 1 (2006–2009) and 2 (2011–2013) and outcomes data at Wave 3 (2015–2017) or time-censoring, depending on the outcome of interest. Wave 2 occurred 5.04 (range 2.32–6.84) median years after the first wave. Wave 3 visit was performed 2.99 (range 2–5.4) median years after the Wave 2.

TSHA protocol was approved by the Clinical Research Ethics Committee of Toledo Hospital Complex, which was conformed according to the ethical standards defined in the 1964 Declaration of Helsinki. As detailed elsewhere previously,¹¹ participants signed an informed consent form prior to inclusion.

Frailty Trait Scale 5

Frailty was assessed through the FTS5⁸ that evaluates five core aspects of frailty:

- Physical activity was determined using the Physical Activity Scale for the Elderly scale.
- Gait speed was defined using the 3 m walking test at their usual pace, according to the standard protocol. The best time of two performances was chosen. At least, 1 min of resting was given between attempts.
- Hand grip strength was measured using JAMAR Hydraulic Hand Dynamometer (Sammons Preston Rolyan, Bolingbrook, IL). The best peak strength of three performances was selected and gathered using international standard procedures. Between performances, at least 1 min of resting was permitted.
- Body mass index was measured according to the standard procedure (weight/height²).
- Progressive Romberg test was established according to the standing balance feet together, semi-tandem, and tandem position.

Each domain score ranges between 0 and 10, being 0 the best score and 10 the worst. FTS5 items are summed up to obtain a final score between 0 and 50, being 0 the lowest and 50 the highest frailty score. FTS5 scoring process is displayed in Supporting Information, *Appendix S1*.

Adverse outcomes

Mortality

Vital status and death dates were ascertained through the Spanish National Death Index (Ministry of Health, Consumer Affairs and Social Welfare). Participants were followed-up to March 2019 or death. Median follow-up for mortality was 6.76 (range 0.26–7.50) years.

Hospitalization

Hospitalization was defined as the first admission according to the records of the Toledo Hospital Complex. Participants' hospitalizations were followed-up to December 2016 with a median follow-up of 4.18 (range 0.02–5.25) years.

Incident or worsening disability

Basic activities of daily living were evaluated by the Katz Index.¹² Transitions of a score of 6 to 5 or less in the Katz Index at follow-up were considered as incident disability. Worsening disability was defined as a loss of 1 point or more during the same time-period. Median follow-up for incident and worsening disability was 2.99 (range 2–5.4) years.

Covariates

Covariates were selected according to previous research and biological plausibility for confounding effects. Age, gender, and educational level (no school, primary school incomplete, and primary school complete or superior) were registered during visits. Comorbidities were measured using the Charlson Index score.¹³ The number of prescription and non-prescription drugs within the Anatomical Therapeutic Chemical Classification System taken by the participant was calculated. Polypharmacy was defined as the use of five or more drugs per day. Cognitive status was evaluated using the Mini-Mental State Examination.¹⁴ Covariates data were assessed at Wave 2 visit.

Trajectory modelling

We used GBTM to identify distinct patterns of evolution in frailty levels according to the baseline FTS5 score and changes in the FTS5 score between Waves 1 and 2 visits. This mixture analysis uses semi-parametric empirical models and tries to identify relatively homogeneous clusters of participants following similar longitudinal patterns of evolution and estimate their shape and direction parameters within a continuous distribution. GBTM assumes that the sample is composed of distinct subpopulations that are not identifiable based on measured characteristics *ex ante*.^{15,16}

We compared models defining two with 10 trajectory groups to find the optimal number of trajectories, based on values from the Bayesian Information Criterion (BIC). BIC is an index used in Bayesian statistics to choose between different models. Two times the change in the BIC between models greater than 10 was used as indicative of better fit in order to compare more complex—with a greater number of trajectories—or more parsimonious—with a lower number of trajectories—models.¹⁷ Every subject was assigned to a trajectory depending on their FTS5 score and changes in FTS5 score. The reliability of the final model classification was evaluated using mean posterior probability of membership, which represents their probability of belonging to the group they were assigned to by previous grouping based on their individual features. Trajectories mean posterior probability of membership indicates its internal consistency. A higher value indicates a better classification quality.¹⁵ At last, we checked the number of subjects within each trajectory to confirm

adequate sample size for analysing the ensuing risk of adverse outcomes.

Statistical analysis

Descriptive statistics were shown as mean (standard deviation) and frequency (%) for continuous and categorical variables, respectively. Descriptive features of subjects in the different frailty trajectories were compared through the analysis of variance test for continuous variables and χ^2 tests for categorical variables.

Cox proportional hazard regression models were used to explore associations between frailty trajectories and time-censored adverse outcomes (mortality and hospitalization), and logistic regressions were used for incident and worsening disability.

We further explored associations between final FTS5 scores in Wave 2 and adverse events. We studied adverse events risks according to the FTS5 score as the change of one point (continuous) and categorized into five categories: ≤ 10 , 11–15, 16–20, 21–25, and > 25 .

We used the following set of models: Model 1 was the raw model. Model 2 was adjusted by age and gender. In Model 3, we added the MMSE. In Model 4, we added the Charlson Index, polypharmacy, and Katz Index. Finally, we estimated Model 5 including the educational level.

All analyses were performed using the Statistical Package R Version 3.6.1 for Windows (Vienna, Austria). Statistical significance was set at P value < 0.05 .

Results

Participant baseline characteristics are shown in *Table 1*, and 975 subjects (mean age 73.14 ± 4.69 ; 43.38% men) were included.

Frailty Trait Scale 5 trajectories and adverse outcomes

The GBTM yielded a five-frailty trajectory model as the best fit to the data: *worsening from non-frailty* (WNF) (226, 23.17%), *improving to non-frailty* (INF) (353, 36.20%), *developing frailty* (DF) (127, 13.03%), *remaining frail* (203, 20.82%), and *increasing frailty* (IF) (66, 6.76%) (*Figure 1*). Mean posterior probabilities of membership, an index of quality classification, ranged from 0.74 (± 0.14) to 0.77 (± 0.18) indicating a moderate fit for this model.

In the fully adjusted models, when comparing with WNF, subjects pertaining to trajectories showing both an increase and maintenance in frailty scores showed an increased risk for developing adverse outcomes compared with those

Table 1 Demographic characteristics of the sample according to the FTS5 trajectory

Variable	All	WNF	INF	DF	RF	IF	P value
N (%)	975	226 (23.17)	353 (36.20)	127 (13.03)	203 (20.82)	66 (6.76)	
Age, mean (SD)	73.14 (4.69)	71.20 (3.52)	72.48 (4.50)	73.72 (4.75)	75.12 (4.92)	76.05 (4.64)	<0.001
Gender, men (%)	423 (43.38)	139 (61.50)	169 (47.88)	55 (43.31)	50 (24.63)	10 (15.15)	<0.001
FTS5 basal, mean (SD)	18.08 (6.79)	9.44 (2.48)	19.01 (4.34)	16.02 (2.06)	24.67 (4.23)	26.39 (5.12)	<0.001
Change in FTS5 per year, mean (SD)	-0.01 (1.56)	0.80 (1.34)	-1.23 (0.81)	1.61 (1.80)	-0.25 (0.82)	1.37 (0.86)	<0.001
Dependent according Katz Index score ≤ 5, n (%)	124 (12.72)	11 (4.87)	38 (10.76)	12 (9.45)	41 (20.20)	22 (33.33)	<0.001
MMSE, mean (SD)	24.44 (4.39)	26.02 (3.34)	24.68 (4.40)	24.51 (3.81)	22.85 (4.72)	22.22 (5.27)	<0.001
Charlson Index, mean (SD)	0.94 (1.43)	0.78 (1.28)	0.83 (1.37)	1.27 (1.60)	1.00 (1.45)	1.29 (1.64)	0.003
Educational level							
No school, n (%)	647 (66.70)	113 (50.22)	251 (71.71)	91 (71.65)	139 (68.81)	53 (80.30)	<0.001
Primary school incomplete, n (%)	162 (16.70)	54 (24.00)	36 (10.29)	24 (18.90)	37 (18.32)	11 (16.67)	<0.001
Primary school complete or superior, n (%)	161 (16.60)	58 (25.78)	63 (18.00)	12 (9.45)	26 (12.87)	2 (3.03)	<0.001
Number of drugs per day, mean (SD)	4.06 (2.72)	3.40 (2.59)	3.46 (2.55)	4.72 (2.61)	4.84 (2.62)	5.88 (2.97)	<0.001
Polypharmacy, n (%)	391 (40.10)	78 (34.51)	104 (29.46)	61 (48.03)	104 (51.23)	44 (66.67)	<0.001
Death, n (%)	211 (21.64)	31 (13.72)	61 (17.28)	38 (29.92)	56 (27.59)	25 (37.88)	<0.001
Hospitalization, n (%)	393 (40.31)	83 (36.73)	124 (35.13)	48 (37.80)	100 (49.26)	38 (57.58)	0.007
Incident disability, n (%)	183 (29.66)	31 (18.90)	64 (26.23)	25 (33.33)	50 (44.64)	13 (59.09)	<0.001
Worsening disability, n (%)	204 (26.56)	31 (16.76)	69 (23.71)	29 (29.90)	56 (37.33)	19 (42.22)	<0.001

DF, developing frailty; FTS5: Frailty Trait Scale 5; IF, increasing frailty; INF, improving to non-frailty; MMSE, Mini-Mental State Examination; RF, remaining frail; WNF, worsening from non-frailty.

In bold: $P < 0.05$. Mean (SD): continuous variables. N, %: categorical variable.

showing a decreasing evolution, except for hospitalization. In this latter outcome, only those maintaining or increasing their frailty score, but not those who developed it during

the time of the trajectory, DF, showed an increased risk (Table 2). By opposite, improving the frailty score according to FTS5—INF—was associated with a low risk for developing

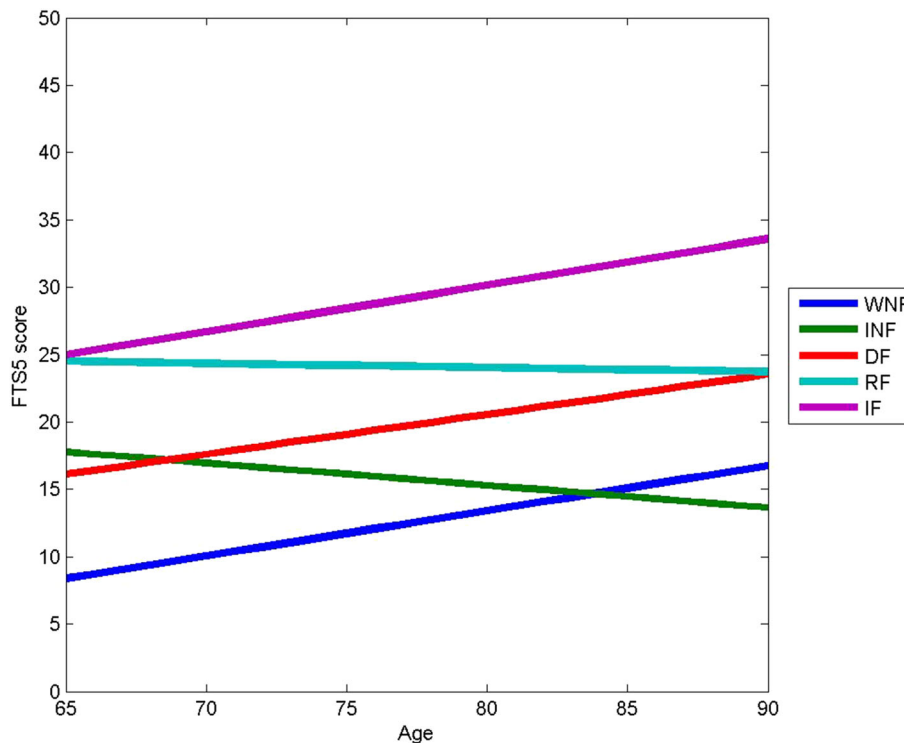


Figure 1 Trajectories according Waves 1 and 2 FTS5 score and changes in FTS5 score. DF, developing frailty; FTS5, Frailty Trait Scale 5; IF, increasing frailty; INF, improving to non-frailty; RF, remaining frail; WNF, worsening from non-frailty.

Table 2 Multivariate regression models showing the association between FTSS trajectories on different adverse events

Reference (WFN)	Model 1		Model 2		Model 3		Model 4		Model 5	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Death										
INF	1.28 (0.83, 1.97)	0.267	1.13 (0.73, 1.75)	0.587	1.12 (0.72, 1.74)	0.606	1.08 (0.69, 1.68)	0.735	1.11 (0.71, 1.73)	0.654
DF	2.42 (1.51, 3.90)	<0.001	2.04 (1.24, 3.33)	0.005	2.01 (1.23, 3.29)	0.006	1.94 (1.18, 3.19)	0.009	2.01 (1.21, 3.32)	0.007
RF	2.25 (1.45, 3.49)	<0.001	1.99 (1.24, 3.20)	0.004	1.95 (1.21, 3.14)	0.006	1.88 (1.16, 3.05)	0.010	1.92 (1.18, 3.12)	0.008
IF	3.18 (1.88, 5.38)	<0.001	2.86 (1.62, 5.04)	<0.001	2.76 (1.55, 4.89)	<0.001	2.55 (1.42, 4.58)	0.002	2.67 (1.48, 4.81)	0.001
Hospitalization										
INF	0.94 (0.73, 1.22)	0.663	0.95 (0.73, 1.23)	0.680	0.94 (0.72, 1.22)	0.657	0.95 (0.73, 1.24)	0.720	0.94 (0.72, 1.22)	0.637
DF	1.12 (0.81, 1.56)	0.496	1.11 (0.79, 1.55)	0.553	1.10 (0.79, 1.54)	0.576	1.06 (0.75, 1.49)	0.743	1.04 (0.74, 1.47)	0.801
RF	1.57 (1.20, 2.06)	<0.001	1.65 (1.23, 2.22)	<0.001	1.63 (1.21, 2.19)	0.001	1.61 (1.19, 2.16)	0.002	1.58 (1.17, 2.14)	0.003
IF	1.92 (1.35, 2.75)	<0.001	2.03 (1.38, 2.98)	<0.001	1.98 (1.34, 2.92)	<0.001	1.92 (1.29, 2.85)	0.001	1.89 (1.27, 2.82)	0.002
Worsening disability										
INF	1.60 (1.03, 2.50)	0.038	1.41 (0.90, 2.22)	0.138	1.40 (0.89, 2.20)	0.149	1.38 (0.87, 2.18)	0.173	1.53 (0.96, 2.45)	0.075
DF	2.42 (1.41, 4.15)	0.001	1.94 (1.11, 3.39)	0.020	1.93 (1.10, 3.37)	0.021	1.87 (1.06, 3.29)	0.030	2.11 (1.19, 3.76)	0.011
RF	3.06 (1.90, 4.94)	<0.001	2.27 (1.35, 3.80)	0.002	2.18 (1.30, 3.67)	0.003	2.01 (1.18, 3.40)	0.010	2.14 (1.26, 3.64)	0.005
IF	3.81 (1.97, 7.40)	<0.001	2.75 (1.36, 5.54)	0.005	2.60 (1.28, 5.27)	0.008	1.96 (0.95, 4.06)	0.070	2.21 (1.06, 4.62)	0.035
Incident disability										
INF	1.58 (1.00, 2.50)	0.050	1.43 (0.90, 2.28)	0.130	1.41 (0.88, 2.24)	0.152	1.40 (0.87, 2.25)	0.163	1.50 (0.92, 2.43)	0.103
DF	2.35 (1.31, 4.19)	0.004	1.96 (1.09, 3.56)	0.026	1.92 (1.06, 3.48)	0.032	1.87 (1.02, 3.43)	0.043	2.06 (1.11, 3.82)	0.021
RF	3.51 (2.11, 5.83)	<0.001	2.50 (1.45, 4.34)	0.001	2.40 (1.38, 4.17)	0.002	2.20 (1.25, 3.87)	0.006	2.29 (1.30, 4.03)	0.004
IF	6.51 (2.70, 15.68)	<0.001	4.49 (1.80, 11.19)	0.001	4.19 (1.67, 10.51)	0.002	3.22 (1.25, 8.32)	0.015	3.55 (1.37, 9.24)	0.009

95% CI, 95% confidence interval; DF, developing frailty; FTSS, Frailty Trait Scale 5; HR, hazard ratio; IF, increasing frailty; INF, improving to non-frailty; OR, odds ratio; RF, remaining frail; WNF, worsening from non-frailty.
 In bold: P value < 0.05. Model 1: raw model. Model 2: Model 1 plus age and gender. Model 3: Model 2 plus MMSE. Model 4: Model 3 plus Charlson Index, Polypharmacy, and Katz Index. Model 5: Model 4 plus educational level.

any of the adverse outcomes, similar to the reference risk, *WNF*, which denoted the risk of people that remained robust along the follow-up. We did not find any particular additional risk in any of the categories of high risk, not allowing to ascribe a particular higher risk to any of the three trajectories with a poor prognosis.

Intermediate trajectories comparison and adverse outcomes

To study if similar baseline scores but with different evolution were associated with different risk, we repeated the analysis taking as reference each different trajectory.

When comparing with *INF*, subjects who were grouped in the *DF* had an increased risk of mortality of 1.81 [95% confidence interval (CI): 1.20–2.75] in the fully adjusted model, although not for the other adverse events. *MF* and *IF* trajectories had also a significant higher risk for death and hospitalization when *INF* was used as the reference category.

When *DF* was the reference, we found an increased risk for hospitalization for those subjects if belonging to *MF* (hazard ratio = 1.51; 95% CI = 1.10–2.08) or *IF* (HR = 1.81; 95% CI = 1.21–2.72).

Cross-sectionally assessed frailty and adverse outcomes

When we cross-sectionally assessed the association between frailty through FTS5 scores and the adverse outcomes, FTS5 showed a continuously increasing risk for developing any of the adverse outcomes (participant baseline characteristics according FTS5 score are shown in *Table S1*). This finding was consistent irrespective of the study wave at which the FTS5 score was selected as the exposure. When we split the score in FTS5 in five categories, we found a significant increased risk of death, incident, and worsening disability beyond a $FTS5 \geq 20$, compared with $FTS5 \leq 10$. In the case of hospitalization, the incremental risk was significant for values higher than 10, compared with 10 or lower, even after adjusting for potential confounders (*Table 3*).

Discussion

This work expands previous evidence linking frailty over time to adverse outcomes incidence in a population of community-dwelling older adults. Frailty is a continuum physiological construct that should be evaluated as a continuous identity, getting a proportional dose–effect relationship when risks adverse outcomes are associated with increasingly high FTS5 categories. Our results point to a dose–response association between frailty and an increased risk of death,

hospitalization and disability progression, with significant increases even for values well below the proposed FTS5 score thresholds for frailty.⁸ However, although frailty burden tended to increase with age,² there could be variability in the rate of progression. According to our results, trajectories clearly show that reversing or improving frailty scores might be beneficial, obtaining the same risk than subjects with the lowest frailty scores over time. Our work does so by employing a novel methodological approach that overcomes important limitations of previous research. We identified five distinct trajectories of frailty, which supports the dynamic nature of this construct. Increasing frailty trajectories or those who maintained higher frailty scores over time had higher risk of death, hospitalization, and incident or worsening disability, than those who remained non-frail.

In fact, we have identified a trajectory in which those subjects with moderate frailty could reduce their frailty levels, what indicates that middle frailty burden could be reduced in community-dwelling older adults as it has been shown in other studies.¹⁸ On the other hand, unexpectedly, we have not identified any trajectory in which those subjects with high frailty load reduced their frailty levels. This could confirm that high frailty load might be hard, but not impossible, to revert and probably point towards the need of tailored interventions to avoid frailty progression that may reduce the risk of developing adverse events. To do so, the early and accurate detection of frailty remains a need.^{19,20} The clinical relevance of this finding supports assessing frailty levels to determine older adults health status and contributes to previous research indicating that the reduction of frailty load might be effective in lowering the burden of late-life adverse outcomes.

FTS5 includes objective functional measures (such as walking speed, grip strength, or balance test) and capture longitudinal frailty changes. These scales have been widely used in geriatric medicine to assess older adults' functional status. Sensitivity and positive predictive value of FTS5 rising score could permit recognize and stratify patients, supported by clinical judgement, with a reliable predictor of death or at risk of another adverse outcome (disability, first disability, or hospitalization) according to their frailty trajectory. Even including relevant cofounders, frailty trajectories have showed different adverse events risks according to frailty dynamics.

The Fried frailty phenotype⁵ is largely the most frailty used tool.⁹ It is based on the presence or absence of five domains to determine frailty (weight loss, gait speed, handgrip strength, physical activity, and fatigue) and identifies a very high (frail) and moderate (pre-frail) risk groups against adverse events.⁵ Nevertheless, this tool is a categorical instrument, limiting, hence, the construction of different trajectories. Another commonly used tool is the Frailty Index (FI).¹⁰ FI defines the amount of individual frailty based on the accumulation of deficits getting a proportion of physical, mental, and cognitive deficits present in an individual.^{10,21}

Table 3 Multivariate regression models showing the association between FTSS score (continuous or categorized) at Wave 2 on different adverse events

Death	Model 1		Model 2		Model 3		Model 4		Model 5	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
FTSS change in 1 point (continuous)	1.05 (1.03, 1.07)	<0.001	1.05 (1.03, 1.07)	<0.001	1.05 (1.03, 1.07)	<0.001	1.05 (1.02, 1.07)	<0.001	1.05 (1.03, 1.07)	<0.001
	1.00	—	1.00	—	1.00	—	1.00	—	1.00	—
	1.49 (0.90, 2.46)	0.121	1.25 (0.75, 2.08)	0.389	1.25 (0.75, 2.09)	0.389	1.22 (0.73, 2.04)	0.442	1.24 (0.74, 2.08)	0.404
	1.57 (0.94, 2.63)	0.084	1.45 (0.86, 2.45)	0.164	1.43 (0.84, 2.42)	0.184	1.44 (0.85, 2.44)	0.177	1.45 (0.85, 2.45)	0.172
	2.39 (1.46, 3.92)	0.001	2.10 (1.24, 3.56)	0.006	2.08 (1.22, 3.53)	0.007	2.01 (1.18, 3.43)	0.011	2.04 (1.20, 3.50)	0.009
FTSS > 25	3.13 (1.92, 5.11)	<0.001	2.95 (1.71, 5.08)	<0.001	2.86 (1.65, 4.95)	<0.001	2.77 (1.58, 4.84)	<0.001	2.87 (1.64, 5.04)	<0.001
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Hospitalization	1.03 (1.02, 1.05)	<0.001	1.04 (1.03, 1.06)	<0.001	1.04 (1.03, 1.05)	<0.001	1.04 (1.02, 1.05)	<0.001	1.04 (1.02, 1.05)	<0.001
	1.00	—	1.00	—	1.00	—	1.00	—	1.00	—
	1.54 (1.13, 2.11)	0.007	1.58 (1.15, 2.17)	0.005	1.58 (1.15, 2.17)	0.005	1.56 (1.13, 2.14)	0.007	1.55 (1.13, 2.14)	0.007
	1.48 (1.07, 2.06)	0.018	1.60 (1.15, 2.24)	0.006	1.58 (1.13, 2.22)	0.007	1.54 (1.10, 2.16)	0.012	1.54 (1.10, 2.16)	0.013
	2.10 (1.53, 2.88)	<0.001	2.34 (1.66, 3.29)	<0.001	2.32 (1.64, 3.27)	<0.001	2.23 (1.58, 3.16)	<0.001	2.23 (1.58, 3.16)	<0.001
Worsening disability	2.28 (1.64, 3.17)	<0.001	2.66 (1.85, 3.84)	<0.001	2.60 (1.79, 3.76)	<0.001	2.47 (1.69, 3.60)	<0.001	2.46 (1.69, 3.59)	<0.001
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
FTSS change in 1 point (continuous)	1.06 (1.04, 1.08)	<0.001	1.05 (1.02, 1.07)	<0.001	1.05 (1.02, 1.07)	<0.001	1.04 (1.01, 1.06)	0.004	1.04 (1.01, 1.06)	0.003
	1.00	—	1.00	—	1.00	—	1.00	—	1.00	—
	1.50 (0.90, 2.51)	0.124	1.21 (0.71, 2.06)	0.482	1.22 (0.71, 2.07)	0.470	1.20 (0.70, 2.05)	0.511	1.22 (0.71, 2.10)	0.464
	1.59 (0.93, 2.70)	0.090	1.28 (0.73, 2.22)	0.387	1.23 (0.71, 2.15)	0.457	1.12 (0.64, 1.97)	0.690	1.12 (0.64, 1.98)	0.692
	3.02 (1.78, 5.11)	<0.001	2.14 (1.21, 3.80)	0.009	2.10 (1.18, 3.74)	0.011	1.96 (1.09, 3.52)	0.025	1.98 (1.10, 3.58)	0.023
Incident disability	3.35 (1.93, 5.83)	<0.001	2.29 (1.23, 4.25)	0.009	2.15 (1.15, 4.01)	0.016	1.73 (0.91, 3.30)	0.095	1.81 (0.95, 3.46)	0.073
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
FTSS change in 1 point (continuous)	1.09 (1.06, 1.12)	<0.001	1.07 (1.04, 1.11)	<0.001	1.07 (1.04, 1.10)	<0.001	1.06 (1.03, 1.10)	<0.001	1.07 (1.03, 1.10)	<0.001
	1.00	—	1.00	—	1.00	—	1.00	—	1.00	—
	1.50 (0.88, 2.55)	0.134	1.23 (0.71, 2.12)	0.467	1.23 (0.71, 2.13)	0.458	1.24 (0.71, 2.15)	0.455	1.25 (0.72, 2.18)	0.434
	1.79 (1.04, 3.11)	0.037	1.48 (0.84, 2.61)	0.179	1.42 (0.80, 2.53)	0.228	1.33 (0.74, 2.39)	0.333	1.32 (0.73, 2.36)	0.355
	3.46 (1.99, 6.01)	<0.001	2.49 (1.37, 4.54)	0.003	2.44 (1.34, 4.45)	0.004	2.33 (1.26, 4.30)	0.007	2.36 (1.27, 4.37)	0.006
FTSS > 25	5.16 (2.74, 9.73)	<0.001	3.46 (1.72, 6.95)	0.001	3.19 (1.57, 6.48)	0.001	2.71 (1.31, 5.64)	0.007	2.80 (1.34, 5.83)	0.006

95% CI, 95% confidence interval; FTSS, Frailty Trait Scale 5; HR, hazard ratio; OR, odds ratio. In bold: P value < 0.05. Model 1: raw model. Model 2: Model 1 plus age and gender. Model 3: Model 2 plus MMSE. Model 4: Model 3 plus Charlson Index, Polypharmacy, and Katz Index. Model 5: Model 4 plus educational level.

FI has been shown to predict death equally well or better than the Fried phenotype²¹ and some studies have studied frailty trajectories according to the FI.^{22,23} However, FI is subject to measurement error due to self-reported health data, having a number of changeable items, which difficult its comparison, and would not allow for capturing improvements in frailty because the data on which it is based are mostly on long-term or irreversible deficits.²⁴ These two tools are supposed to measure the same construct, but using different domains and approaches. Because of that, some authors have raised the possibility that they can complement each other.²⁵ Notwithstanding, FTS5 may capture this construct with a better accuracy.⁸ However, although FTS5 is a recent and promising scale, it should be validated in other cohorts.

Regarding the GBTM algorithm classification quality, the mean posterior probability of membership to each group is greater than 0.70, which is taken as a consistent indication that the modelled trajectories group individuals with similar patterns of change according to the outcome variable and discriminate between individuals with dissimilar patterns of change in a specific variable over time.²⁶

Our findings regarding FTS5 trajectories and adverse events cannot be directly compared with previous studies due to the novelty of the scale and the identification of subgroups using GBTM. Although GBTM has been used by previous studies in order to explore the longitudinal evolution of subtypes²⁷ and factors related to frailty,²⁸ as physical activity,²⁹ we have only identified one study which used this method to explore frailty evolution with adverse outcomes.³⁰ This latter study examined patterns of cognition and frailty in 690 community-dwelling older adults and found that longitudinal declines in cognition had twice higher rates of hospitalization. According to disability, those with declines in cognition had higher rates of mobility disability, instrumental activities of daily living, but the dose–response association was especially accentuated for activities of daily living disability.³⁰

Disablement process is not linear and could fluctuate in cycles of deterioration and recovery short time periods, and these fluctuations could be higher in late life.²² Nevertheless, although disabled rates increase with ageing,³⁰ their evolution could depend on intraindividual variability in mobility limitation.³¹ This finding supports frailty as a multidimensional measurement of health status and a sign of a loss of homeostasis with overall system vulnerability to estimate adverse event risk and an opportunity to anticipate disability.^{1,5,8} Our results show that those trajectories of physical and functional decline are more likely to lead to disability or to a progress in their disability levels. Only those subjects who had moderate frailty scores and improved them (*improving to non-frailty*) have no statistically significant differences with respect to the reference trajectory. However, to date, no study has studied FTS5 fluctuations in shorter time intervals as a prognostic value to disability or mortality.

Frailty evolution has been previously associated with death. Buchman *et al.* analysed trajectories in a continuous frailty scale using gait speed, grip strength, body composition, and fatigue and found that baseline frailty and annual change in frailty were independently associated with mortality in a similar way of using a categorical frailty measure after adjustment for confounders. This approach reached also statistically results when the authors studied instrumental and basic activities of daily living incident disability, obtaining similar results to ours.³² Rapid or moderate increases compared with those with stable frailty,³³ or those with higher fluctuations²² in Frailty Index scores, were associated with higher mortality. Moreover, a 12 year follow-up study from the Canadian National Population Health Survey showed that the less frail individuals at baseline showed a healthier profile at follow-up, whereas frailer participants were more likely to die and utilized more healthcare services during the same period,³⁴ consistent with clinical experience and frailty constructs.³⁵

Improvements in medicine jointly to other socio-economic facts have led to an extended lifespan but in many cases, accompanied by chronic health problems and disabilities associated with ageing.³⁵ According to some studies, current population cohorts are not only ageing, but they may also be frailer, especially in low-income individuals.³⁶ The surveillance of frailty status is paramount to predict older adults' future health³⁵ and public health burden and must be a priority for public health policies.³⁷ Our findings might support studies that indicate that the increase in life expectancy is associated with greater levels of frailty, leading to disability what may lead to greater costs for medical care, social services, and long-term care.³⁸

Strengths and limitations

This study has many strengths, including the large population included, the excellent ascertainment of adverse events, and the inclusion of relevant confounders that might distort the associations.

We used GBTM, a novel powerful statistical tool to group subjects into patterns of evolution over age or time of a variable of interest according to the baseline score, magnitude, and direction of the change without using *ad hoc*, *ex ante* classification rules.^{15,16} Nevertheless, it is inherently limited at capturing individual variability and may lead to overgrouping.¹⁶ Because only two measurements were available to assess trajectories, the results should be interpreted with caution because the existing evidence suggests that studies with two time points cannot measure within-person change³⁹ but instead changes in terms of rank-order in the levels of a variable. Confirmation of our results in studies with more time points is therefore warranted.

Our study used two frailty assessments that were 5.04 years apart on average. Therefore, when clustering individuals, we could have failed at differentiating between rapid changes in frailty attending to an increasing individual vulnerability before death and more progressive changes related to ageing process. More frequent assessment might assist in reducing this bias.

Furthermore, discrepancies between how frailty is conceptualized, and the lack of a gold standard definition or tool limits our results extrapolation.

Future directions

Although works of frailty trajectories are a growing research area, more prospective works are necessary to confirm these results, analysing drivers and predicting trends in frailty states and ways to prevent and modify increases in frailty prevalence.

Older adults' health improvements and policies to promote them will potentially reduce costs incurred by an aged population. In not doing so, medical care, social services, and long-term care may lead to greater costs.³⁸ The better knowledge we have on how frailty changes over time, the better we could prevent it with rehabilitation, physical exercise, or nutritional programmes. Individualized programmes for older adults according to their frailty status are paramount in the clinical setting, especially in terms of functional outcomes.⁴⁰ In this regard and in the absence of a pharmacological approach for frailty, physical exercise has arisen as the unique contrasted alternative, with growing evidence in frail community dwellers, what have led some experts to question whether not prescribing it might be unethical.⁴¹ Nevertheless, more research focusing on the intensity, timing of exercise and identification of the population who might benefit the most from those interventions are still necessary.

Conclusions

Our results support frailty as a continuum physiological construct with a proportional dose–effect relationship against adverse outcomes. Our study contributes to expand the notion of frailty dynamic nature and points towards the association of its load reduction and reduced risk of adverse events such as mortality, hospitalization, and disability. We

suggest that interventions tailored to the individual frailty status might positively impact the economic and public health burden of frailty.

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Conflict of interest

Nothing to declare.

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Demographic characteristics of the sample according to the FTS5 score.

Appendix S1. Frailty Trait Scale 5 (FTS5) score.

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Chapter 3: Role of sarcopenia in the frailty transitions
in older adults: a population-based cohort study

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Role of sarcopenia in the frailty transitions in older adults: a population-based cohort study

Alejandro Álvarez-Bustos¹, Jose Antonio Carnicero-Carreño^{1,2}, Betty Davies³, Francisco Javier Garcia-Garcia^{1,4}, Fernando Rodríguez-Artalejo^{5,6}, Leocadio Rodríguez-Mañas^{1,3*}  & Cristina Alonso-Bouzón^{1,3}

¹CIBER of Frailty and Healthy Ageing, CIBERFES, Instituto de Salud Carlos III, Madrid, Spain; ²Biomedical Research Foundation, Getafe University Hospital, Carretera de Toledo, Madrid, Spain; ³Geriatrics Department, Getafe University Hospital, Carretera de Toledo, Madrid, Spain; ⁴Virgen del Valle Hospital, Carretera de Cobisa, Toledo, Spain; ⁵Department of Preventive Medicine and Public Health, Universidad Autónoma de Madrid/IdiPaz, Madrid, Spain; ⁶CIBER of Epidemiology and Public Health CIBERESP, Instituto de Salud Carlos III, Madrid, Spain

Abstract

Background Frailty and sarcopenia are age-associated syndromes that have been associated with the risk of several adverse events, mainly functional decline and death, that usually coexist. However, the potential role of one of them (sarcopenia) in modulating some of those adverse events associated to the other one (frailty) has not been explored. The aim of this work is to assess the role of sarcopenia within the frailty transitions and mortality in older people.

Methods Data from the Toledo Study of Healthy Aging (TSHA) were used. TSHA is a cohort of community-dwelling older adults ≥ 65 . Frailty was assessed according with the Frailty Phenotype (FP) and the Frailty Trait Scale-5 (FTS5) at baseline and at follow-up. Basal sarcopenia status was measured with the standardized Foundation for the National Institutes of Health criteria. Fisher's exact test and logistic regression model were used to determine if sarcopenia modified the transition of frailty states (median follow-up of 2.99 years) and Cox proportional hazard model was used for assessing mortality.

Results There were 1538 participants (74.73 ± 5.73 ; 45.51% men) included. Transitions from robustness to prefrailty and frailty according to FP were more frequent in sarcopenic than in non-sarcopenic participants (32.37% vs. 15.18%, $P \leq 0.001$; 5.76% vs. 1.12%; $P \leq 0.001$, respectively) and from prefrailty-to-frailty (12.68% vs. 4.27%; $P = 0.0026$). Improvement from prefrail-to-robust and remaining robust was more frequent in non-sarcopenic participants (52.56% vs. 33.80%, $P \leq 0.001$; 80.18% vs 61.15%, $P \leq 0.001$, respectively). When classified by FTS5, this was also the case for the transition from non-frail-to-frail (25.91% vs. 4.47%, $P \leq 0.001$) and for remaining stable as non-frail (91.25% vs. 70.98%, $P \leq 0.001$). Sarcopenia was associated with an increased risk of progression from robustness-to-prefrailty [odds ratio (OR) 2.34 (95% confidence interval, CI) (1.51, 3.63); $P \leq 0.001$], from prefrailty-to-frailty [OR (95% CI) 2.50 (1.08, 5.79); $P = 0.033$] (FP), and from non-frail-to-frail [OR(95% CI) 4.73 (2.94, 7.62); P -value ≤ 0.001]. Sarcopenia does not seem to modify the risk of death associated with a poor frailty status (hazard ratios (HR, 95%) $P > 0.05$).

Conclusions Transitions within frailty status, but not the risk of death associated to frailty, are modulated by the presence of sarcopenia.

Keywords Frailty; Sarcopenia; Transitions; Death; Aging

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*Correspondence to: Leocadio Rodríguez-Mañas, Geriatrics Department, Getafe University Hospital, Carretera de Toledo, km 12,500, 28905 Getafe, Madrid, Spain. Email: leocadio.rodriguez@salud.madrid.org

Introduction

In old age, pathways leading to disability could be accelerated by certain conditions as frailty and sarcopenia.^{1–3} Frailty is an age-associated, biological syndrome characterized by decreased biological reserves and is associated with adverse outcomes (i.e. disability, institutionalization, death, and hospitalization).⁴ In 2006, Gill and colleagues proved that frailty is a dynamic state that changes over time, mainly impairing, but also improving.⁵ These results, confirmed in other longitudinal studies^{6–8} and in a recent meta-analysis,⁹ opened an ample opportunity for the prevention of frailty and its consequences.⁵ Moreover, some studies have suggested that different factors influence the frailty transitions (such as older age, previous diseases,^{8,10} physical activity and mobility levels,⁶ socio-economic and clinical factors,^{6,11} vitamin D levels,¹¹ or hospitalizations⁸). A better knowledge of these factors and how they could modulate the frailty transitions would help to both refine the prognosis of frailty but also to develop effective strategies for the prevention and restoration of frailty, improving the quality of life of older people.⁴

Sarcopenia, the loss of lean muscle mass and muscle strength and/or function,² has been proposed as the biological substrate of frailty.¹² Although frailty and sarcopenia could coexist and have been related as states of increased vulnerability due to degradation on multiple systems^{2,13–15} and physical function impairment,¹⁶ both entities have been clearly distinguished.¹⁷

We previously described that only a minority of people with sarcopenia has frailty and, by opposite, that between a third and a quarter of frail people do not have sarcopenia, suggesting an association between sarcopenia and frailty beyond the simple coexistence of the two entities.¹⁷ More recently, another group, using data from the Hertfordshire cohort study have reported similar findings in a cross-sectional study.¹⁸ This fact opens the possibility of different risks for the outcomes depending upon the coexistence of sarcopenia in frail patients, raising the chance of the existence of different clinical phenotypes,¹⁷ but to date, no study has addressed this hypothesis.

Methods

Participant's data were taken from the Toledo Study of Healthy Aging (TSHA). This study was conformed according to the ethical standards defined in the 1964 Declaration of Helsinki and approved by the Clinical Research Ethics Committee of the Toledo Hospital, Spain. Participants signed an informed consent form previous to recruitment.

As detailed elsewhere previously,¹⁹ TSHA is a longitudinal cohort aimed at studying different aging phenotypes through

socio-demographic, clinical and genetical variables and its relationship with physical and neuropsychological assessments and lifestyle components, such as physical activity, diet, tobacco, and alcohol consumption. TSHA was designed to study frailty prevalence and its underlying causes in rural and urban community-dwelling older adults aged 65 years or older. Subjects from the cohort were selected by a two-stage random sampling of the municipal census of the province of Toledo. Sampling was conducted within census sections in six strata according to sex, age and town-size groups, recruiting 24% of the population aged 65 and older in the Toledo province.

For the purposes of the current study, data from basal (2011–2013) and follow-up (2014–2017; median time of 2.99 years, range 2.0–5.4) face-to-face visits were analysed.

Study variables

Frailty status was assessed according to two established criteria: the Frailty Phenotype¹ and the Frailty Trait Scale 5 (FTS5)²⁰ at baseline and at follow-up.

Frailty status

Fried scale

Frailty Phenotype (FP) was assessed according to its five criteria fitted to Spanish population²¹:

1. Weight loss: defined as self-reported unintentional weight loss of ≥ 4.5 kg in the last year.
2. Exhaustion: was measured by self-report using two questions: ('How many days during the last week have you felt that anything you did was a big effort?' and 'How many times during the last week have you felt that you could not keep on doing things?'). The criterion was met when participant answered at a score of 2 or higher (0–4).
3. Weakness: handgrip strength was measured using JAMAR Hydraulic Hand Dynamometer (Sammons Preston Rolyan, Bolingbrook, IL). Best peak strength of three performances was selected and gathered using international standard procedures.²² Between performances, at least 1 min of resting was permitted. Results was adjusted for sex and body mass index. Low grip strength ≤ 20 th percentile.
4. Slowness: was defined using the 3 m walking test at their usual pace, according to the standard protocol. Best time of two performances was chosen. Cut-offs were adjusted by sex and height.
5. Low physical activity: defined as being in the lowest quintile using the Physical Activity Scale for the Elderly (PASE) scale,²³ stratified by gender.

The stages of frailty were defined as robust or not frail in those whose score was 0. A score of 1 or 2 indicated that someone is pre-frail. People were considered frail when they

met three or more domains. Differences in the cut-off points of the frailty criteria in the TSHA according to Fried's originals are shown in Supporting Information S1.

Frailty Trait Scale 5 (FTS5)

FTS5²⁰ is a recent tool developed and validated in the TSHA. It seems to improve the accuracy of the Frailty Phenotype to predict adverse events (death, hospitalization, incident frailty, and disability)²⁰ in older adults even better than classical frailty tools, as the two most used tool²⁴: the Frailty Phenotype¹ and the Frailty Index.²⁵ In addition, it allows continuous assessment of frailty levels, being sensitive to small changes that have been shown to be related to the risk of different adverse events such as disability, hospitalization and mortality, potentially overcoming several of the pitfalls of previous frailty assessment.²⁶ It is composed by five domains [gait speed, grip strength, physical activity, body mass index (BMI), and balance].

Gait speed, handgrip strength, and physical activity were performed, as has been detailed previously, and scored according to the rules of this scale (Supporting Information S2).

BMI was estimated as body weight in kg (adjusted to the nearest 0.1) divided by height in meter squared. Height was measured using a stadiometer at head level to the nearest centimetre.

Balance was evaluated using the progressive Romberg test.²⁷ This battery test consists of testing the balance ability of the participant in three position (side-by-side, semi-tandem and full-tandem position), each one more challenging than previous and with the goal of maintaining balance for at least 10 s.

FTS5 score ranges from 0 to 50, being 0 the lowest frailty score and 50 the highest. Each of the five domains scores from 0 to 10. Scores to 25.25 or higher were considered as frail and lower as no frail.

Sarcopenia

Sarcopenia was measured at baseline and defined according to the Foundation for the National Institutes of Health (FNIH), fitted to the cut-off points of our population (standardized FNIH [sFNIH]).¹⁷ An individual was qualified as sarcopenic if he or she had a low muscle mass, in addition to a low gait speed and a grip strength below the cut-off points.

Muscle mass was determined using dual-energy X-ray absorptiometry (DEXA) (Hologic, Serie Discovery QDR, Bedford, MA, USA). DEXA scans were analysed using the software Physician's Viewer (apex System Software, version 3.1.2: Bedford, USA).

BMI-adjusted by appendicular lean mass (BMI/ALM), derived as the sum of the muscle mass of the arms and legs was finally determined. According to sFNIH diagnosis

algorithm, low muscle mass was present in men and women when ALM/BMI is below 0.65 and 0.54, respectively.

Gait speed and handgrip strength measurement methodology has been explained previously. Gait speed cut-off point was <0.8 m/s and handgrip strength cut-off points were <25.51 kg for men and <19.19 kg for women.

Mortality

Vital status was ascertained by the Spanish National Death Index (Ministry of Health, Consumer Affairs and Social Welfare), hospital records, and phone contact during the study follow-up. Mortality follow-up time was right censored at 4 years. Median follow-up time was 2.64 years (range from 0.60 to 4.00).

Co-morbidity

Charlson index²⁸ was used to assess co-morbidity.

Nutritional status

Mini-Nutritional Assessment²⁹ was used to assess nutritional status. Participants were categorized according to their score as well-nourished (≥ 24), at risk of malnutrition (17–23.5), or undernourished (<17). Due to the small number of undernourished subjects we merged this category with at-risk of malnutrition in the same category.

Cognitive status

The Mini-Mental State Examination³⁰ was used to evaluate the cognitive status. Participants were classified into two categories (normal cognitive status and cognitive impairment) according to their cut-off point based on their educational level adjusted to the Spanish population.³¹

Statistical analysis

Characteristics of the subjects at baseline were stratified according to frailty status and presence, or absence, of sarcopenia.

Descriptive statistics were shown as mean (standard deviation, SD) and number (*N*, %). Differences between sarcopenic and non-sarcopenic were tested using Mann-Whitney and χ^2 test.

We used Fisher exact test to assess if transitions between frailty status were modified by the presence of sarcopenia.

The association between sarcopenia and basal frailty status with the outcomes were assessed using Cox proportional hazard model for death and logistic regression model for improvement, maintenance and worsening in frailty category: robust, prefrail and frail in FP; and no frail and frail in FTS5. We used two models. Model 1 was the univariate model. Then, we adjusted by age, gender and Charlson index (Model 2). Additionally, in a sensitivity analysis, we included to Model 2 cognitive or nutritional status as confounders.

Analyses were performed using the Statistical Package R version 3.6.1 for Windows (Vienna, Austria). Statistical significance was set at P -value <0.05 .

Results

Study population

There were 1538 participants (700 men) included in the analysis, with a mean age of 74.73 (5.73 SD) years old. Three hundred forty-eight met criteria of sarcopenia according to the sFNIH. Participant's characteristics are shown in *Table 1*. Sarcopenia rates were statistically higher in individuals with frailty. While 77.64% (FTS5) and 56.82% (FP) of subjects with frailty were sarcopenic, only 16.19% (FTS5) and 15.02% (FP) of non-frail participants met sarcopenic criteria. Moreover, frailty rates within the sarcopenic individuals were statistically higher than in non-sarcopenic individuals (Supporting Information S3). The status of the participants was successfully assessed along the follow-up in 1349 subjects (87.71%). Participants lost for the follow-up did not show any difference in their baseline characteristics regarding age (P -value 0.904), gender (P -value 0.348), Charlson index (P -value 0.792), frailty (FP: P -value 0.718; FTS5: P -value 0.775), and sarcopenia (P -value 0.331) data.

Frailty transitions

Transitions in frailty status and mortality according to the presence or absence of sarcopenia at baseline are included in *Table 2*. Subjects who met sarcopenia criteria showed a higher probability to impair their frailty status, disregarding the tool used to assess their condition. When FP was used, people with sarcopenia showed a higher percentage of transitions from robust to prefrail (32.37% vs. 15.18%; $P \leq 0.001$) and frail (5.76% vs. 1.13%; $P \leq 0.001$) and from prefrail to frail (12.68% vs. 4.27%; $P = 0.003$). When FTS5 was used, the percentage of those progressing from non-frail to frail achieved the figure of 25.91% in those with sarcopenia, while it was 4.47% in those non-sarcopenic ($P \leq 0.001$). When we looked to those remaining in the same frailty status, we again observed the same trend. Those without sarcopenia had the highest probability of remaining robust than their sarcopenic counterparts (FP: 80.18% vs. 61.15%, $P \leq 0.001$; FTS5: 91.25% vs. 70.98%, $P \leq 0.001$).

Although most of these spontaneous transitions were toward a worse state of frailty (Figure 1), some individuals improved, especially those who did not meet the criteria for sarcopenia. In this line, a lower number of prefrail sarcopenic persons (according to the FP) improved in their frailty status (29.27% vs. 45.22%; $P \leq 0.001$).

Risk of worsening, maintenance or improving within the same frailty status at baseline according to the presence or

Table 1 Characteristics of the participants

	All	Frailty Phenotype				FTS5		P-value
		Robust Fried	Prefrail Fried	Frail Fried	Frail	No frail	Frail	
N (%)	1,538	1,058 (68.79)	436 (28.35)	44 (2.86)	1,377 (89.53)	161 (10.47)		
Age (SD)	74.73 (5.73)	73.55 (5.19)	76.99 (6.01)	80.70 (4.95)	74.18 (5.48)	79.42 (5.74)		<0.001
Gender, male (%)	700 (45.51)	477 (45.09)	200 (45.87)	23 (52.27)	661 (48.00)	39 (24.22)		<0.001
Charlson index (SD)	1.18 (1.59)	1.01 (1.42)	1.52 (1.83)	1.89 (2.27)	1.13 (1.55)	1.65 (1.86)		<0.001
Sarcopenia (%)	348 (22.62)	159 (15.02)	164 (37.61)	25 (56.82)	223 (16.19)	125 (77.64)		<0.001
Cognitive impairment or dementia (%)	241 (15.98)	132 (12.67)	89 (20.99)	20 (47.62)	184 (13.58)	57 (37.25)		<0.001
At-risk of malnutrition and malnourished (%)	368 (24.93)	154 (15.13)	182 (43.75)	32 (76.19)	282 (21.36)	86 (55.13)		<0.001

Data are expressed as mean (SD) and frequency (%). In bold: P -value < 0.05 . N, number of the sample; FTS5, Frailty Trait Scale 5; SD, standard deviation.

Table 2 Number and rates of transition in frailty status and mortality according to the presence or absence of sarcopenia

Fried phenotype		Follow-up group						
Basal frailty state	Basal sarcopenia state	Robust	Prefrail	Frail	<i>P</i> -value	Death	<i>P</i> -value	Total
From robust	No sarcopenic to (%)	639 (80.17)	121 (15.18)	9 (01.12)	<0.001	28 (03.51)	0.13	797
	Sarcopenic to (%)	85 (61.15)	45 (32.37)	8 (05.76)		1 (00.72)		139
From prefrail	No sarcopenic to (%)	123 (52.56)	85 (36.32)	10 (04.27)	<0.001	16 (06.84)	0.13	234
	Sarcopenic to (%)	48 (33.80)	59 (41.55)	18 (12.68)		17 (11.97)		142
From frail	No sarcopenic to (%)	2 (11.11)	9 (50.00)	2 (11.11)	0.32	5 (27.78)	0.89	18
	Sarcopenic to (%)	3 (15.79)	7 (36.84)	4 (21.05)		5 (26.32)		19

FTS5		Follow-up group					
Basal frailty state	Basal sarcopenia state	No frail	Frail	<i>P</i> -value	Death	<i>P</i> -value	Total
From no frail	No sarcopenic	939 (91.25)	46 (04.47)	<0.001	44 (04.28)	0.53	1,029
	Sarcopenic	137 (70.98)	50 (25.91)		6 (03.11)		193
From frail	No sarcopenic	8 (27.59)	14 (48.28)	1.00	7 (24.14)	0.63	29
	Sarcopenic	32 (30.19)	56 (52.83)		18 (16.98)		106

Data are shown as number and percentage. In bold: *p*-value <0.05. Percentage adds up to 100 horizontally. FTS5: Frailty Trait Scale 5.

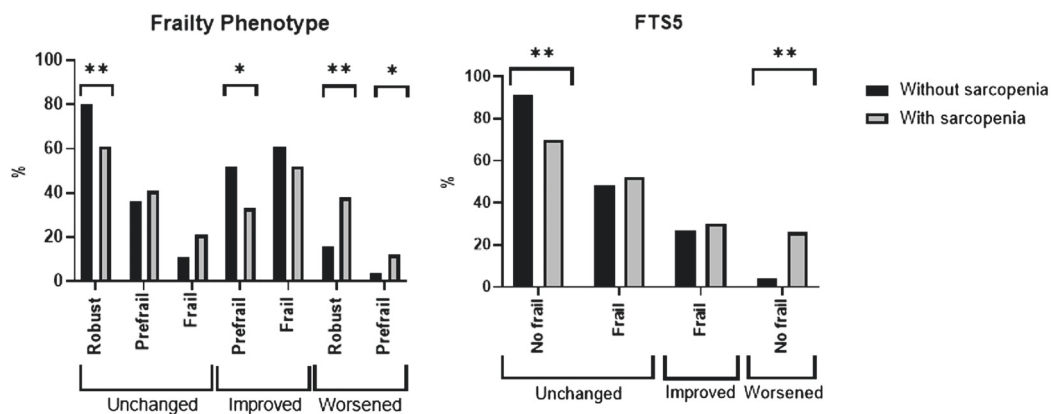


Figure 1 Rates of transitions in frailty status, assessed by FP and FTS5, according to the presence of sarcopenia. FP, frailty phenotype; FTS5, Frailty Trait Scale 5. **P* < 0.005; ***P* < 0.001. Columns without symbol means non-significant difference *P* ≥ 0.05.

absence of sarcopenia is shown in *Table 3*. Sarcopenic subjects were significantly more likely to worsen in their frailty status (FP: robust OR (95% CI) 2.34 (1.51; 3.63). *P*-value < 0.001, prefrail OR (95% CI) 2.50 (1.08; 5.79), *P*-value = 0.033; FTS5 non-frail OR (95% CI) 4.73 (2.94; 7.62), *P*-value < 0.001). Robust non-sarcopenic subjects were significantly more likely to maintain their robustness regardless of the tool used. According to the FP, prefrail individuals with sarcopenia were more likely to maintain their prefrailty status or worsening while those without sarcopenia improved in their frailty status twice as much.

In frail participants, people without sarcopenia had a higher possibility of improving frailty [FP: OR (95% CI) 2.96 (0.41; 21.20); FTS5: OR 1.50 (0.48; 4.73)] and those with sarcopenia of maintaining their frail condition [FP: OR 2.51 (0.37; 17.13); FTS5: OR 1.31 (0.47; 3.63)]. In no case, these increases in risk achieved statistical significance. Sensitivity analysis models adding cognitive and nutritional status are shown in the Supporting Information S4.

Mortality

Even though frailty was associated to a higher mortality (FP: robust 2.74%; prefrail 7.57%; frail 22.73%, *P* < 0.001; FTS5: no frail 3.63%; frail 15.53%, *P* < 0.001), there were no significant differences in mortality between sarcopenics and non-sarcopenics within the same frailty status (*Table 2*). According to this finding, there were no statistically significant differences in the risk of mortality between sarcopenic and non-sarcopenic older adults within the same frailty category (*Table 4*), as expected. These findings were not modified when nutritional and cognitive status were added to the model (Supporting Information S5).

Discussion

This study directly addresses the relationship between sarcopenia and frailty regarding the prognosis of frailty. We show

Table 3 Risk of worsening, maintenance, and improvement in frailty status according to the presence or absence of sarcopenia

Frailty tool	Basal frailty state	Basal sarcopenia state	Worsening						Staying the same						Improving					
			Model 1		Model 2		Model 1		Model 2		Model 1		Model 2		Model 1		Model 2			
			OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value		
Frailty Phenotype	Robust	No Sarcopenic	1	<0.001	1	<0.001	3.06 (2.07; 4.53)	<0.001	2.48 (1.63; 3.75)	<0.001	NA	<0.001	NA	<0.001	NA	<0.001	NA	<0.001		
		Sarcopenic	3.06 (2.07; 4.53)		2.34 (1.51; 3.63)		1		1		1		1		1		1			
	Prefrail	No Sarcopenic	1	0.002	1	0.033	1	0.14	1	0.018	2.09 (1.24; 3.52)	0.001	2.09 (1.24; 3.52)	0.001	2.09 (1.24; 3.52)	0.001	2.09 (1.24; 3.52)	0.001		
		Sarcopenic	3.50 (1.56; 7.85)		2.50 (1.08; 5.79)		1.40 (0.90; 2.18)	0.42	1.77 (1.10; 2.83)	0.35	2.20 (0.33; 14.73)	0.42	2.20 (0.33; 14.73)	0.42	2.20 (0.33; 14.73)	0.42	2.96 (0.41; 21.20)	0.28		
Frail	No Sarcopenic	NA		NA		2.20 (0.33; 14.73)		2.51 (0.37; 17.13)		2.20 (0.33; 14.73)		2.20 (0.33; 14.73)		2.20 (0.33; 14.73)		2.96 (0.41; 21.20)				
	Sarcopenic	NA		NA		7.45 (4.80; 11.55)	<0.001	5.29 (3.30; 8.46)	<0.001	1		1		1		1				
Frailty Trait Scale 5	No frail	No Sarcopenic	1	<0.001	1	<0.001	1	1.00	1	0.61	1	1.00	1	1.00	1	1.00	1	0.49		
		Sarcopenic	7.45 (4.80; 11.55)		4.73 (2.94; 7.62)		1		1		1		1		1		1			
	Frail	No Sarcopenic	NA		NA		1.00 (0.38; 2.64)		1.31 (0.47; 3.63)		1.00 (0.38; 2.64)		1.00 (0.38; 2.64)		1.00 (0.38; 2.64)		1.50 (0.48; 4.73)			
		Sarcopenic	NA		NA		1		1		1		1		1		1			

In bold: P-value <0.05. NA, not applicable. Model 1: univariate regression model. Model 2: adjusted by age and gender and Charlson index. OR, odds ratio; LL, lower limit; UL, upper limit. LL and UL were calculated according to 95% confidence interval.

Table 4 Risk of death within the same frailty status according to the presence or absence of sarcopenia

Frailty tool	Basal frailty state	Basal sarcopenia state	Model 1		Model 2	
			OR (95% CI)	P-value	OR (95% CI)	P-value
Frailty phenotype	Robust	No Sarcopenic to (%)	3.39 (0.82; 14.07)	0.09	3.00 (0.71; 12.69)	0.14
		Sarcopenic to (%)	1		1	
	Prefrail	No Sarcopenic to (%)	0.67 (0.37; 1.20)	0.18	0.71 (0.38; 1.30)	0.26
		Sarcopenic to (%)	1		1	
	Frail	No Sarcopenic to (%)	2.29 (0.75; 7.00)	0.15	1.50 (0.48; 4.63)	0.48
		Sarcopenic to (%)	1		1	
Frailty Trait Scale 5	No frail	No Sarcopenic to (%)	1.72 (0.79; 3.76)	0.17	1.73 (0.78; 3.87)	0.18
		Sarcopenic to (%)	1		1	
	Frail	No Sarcopenic to (%)	1.42 (0.63; 3.20)	0.40	0.99 (0.43; 2.27)	0.98
		Sarcopenic to (%)	1		1	

In bold: P -value < 0.05 . NA, not applicable. Model 1: univariate regression model. Model 2: adjusted by age and gender. OR, odds ratio; LL, lower limit; UL, upper limit. LL and UL were calculated according to 95% confidence interval.

that sarcopenia seems to be a modulator of transitions in the frailty status: sarcopenic individuals had more than two-fold the risk of non-sarcopenics of worsen across the frailty continuum. In this continuum, sarcopenia was an independent predictor of frailty but not in mortality. These findings reinforce the hypothesis of the existence of different frailty phenotypes in which sarcopenia could be one of the major risk factors of developing functional decline along the frailty spectrum, with a less relevant role, if any, in the mortality associated to frailty.

One of the strengths of this study is the large community-based population used. Moreover, frailty tools and sarcopenia diagnosis criteria used in this study have been standardized and adjusted to the study population prior to this analysis, showing a better predictive ability.^{17,21} Furthermore, muscle mass has been determined by DEXA, which is considered the gold standard in assessing body composition. Finally, and to avoid biases linked to the tool used, frailty has been evaluated by using two different tools without detecting relevant differences in the findings depending upon the tool, thus reinforcing the strengths of the results. On the other hand, our study presents a reliable ascertainment of mortality. Using the Spanish National Death Index ensures that all the deaths occurring in the cohort are registered.

Some weaknesses can be found in our study, but they do not seem to significantly bias the results and/or the conclusions. Although grip strength and gait speed are used to assess both frailty and sarcopenia, a fact that could explain some of the overlapping between the two entities, the cut-off points used for qualifying the participants as sarcopenic or frail are different, being higher for sarcopenia.

Another limitation regards the low prevalence of frailty when FP is used. This prevalence is lower to the one found in the whole TSHA cohort and is probably explained by the lower number of frail subjects who attended to the DEXA examination. The consequence of this low power is a decrease in the ability to detect some differences, making non-significative some of our findings. In our study, this potential source of bias could account for the outcomes in frail

subjects, a category only met by 44 individuals at baseline when using the frailty phenotype. The lack of significant differences impacts both changes in frailty status and the risk of death. Regarding death, although there is an increase in the percentage of deaths as the frailty status worsen from robust to prefrailty and frailty, there is no differences inside each category of frailty. Having measured frailty by two different tools makes this unlikely, taking into account that the amount of people qualified as frail using FTSS is not so low ($n = 161$) and the number of events is high enough to make our results stable. The findings in our study are quite consistent and do not change depending upon the method of assessing frailty.

It must be highlighted that the design of our study suffers from a ceiling effect for those who are frail. As we are only assessing the frailty status, but not disability, this makes impossible for those who are frail to impair their functional condition toward disability.

Although sarcopenia is usually mentioned as a key factor in frailty and has been proposed as a biomarker to confirm frailty,¹⁷ its role in the transitions of the frailty status has been broadly neglected. In fact, we have not found studies addressing the issue of how the presence of sarcopenia can influence the changes in the frailty status along the time in terms of worsening, improving or maintenance of that status. However, in a study assessing the role of muscle mass, by the determination of the Phase Angle, in the transition of frailty, they found a direct relationship between muscle mass and the improvement in the frailty status,³² a finding supporting our results.

Although frailty generally increases with age, there is high variability between subjects, and not necessarily should increase over time.^{9,26} According to the FP, a 57% of total participants remain in their basal frailty status. These results are similar to those found in other studies^{5,7} or meta-analysis.⁹ Moreover, among those who started being prefrail, 23% improved in their frailty status and 18.2% worsened, with twice the risk of improvement in those prefrail subjects without sarcopenia, and twice the risk of worsening in sarcopenic

ones. This higher prevalence of improvement in those who started being prefrail was found by Lee and colleagues after 2 years of follow-up.⁸ They showed that 23.4 and 26.6% of the prefrail men and women, respectively, improved in their frailty status; and 11.1 and 6.6% worsened.

Also, as we assessed subject at 3 years, there may be transitions in frailty status that we are not capturing because of the time between visits. Several studies in the literature have assessed the transitions in the frailty status, with separate times of observation and controversial results, not allowing to establish what is the best time to reassess it.^{6,33,34}

Unanswered questions

According to our results, it seems that the presence of sarcopenia influences the spontaneous transition of frailty over time, suggesting the existence of different clinical phenotypes (sarcopenic vs. non-sarcopenic) with different prognosis within the framework of frailty.¹⁷ The existence of some other phenotypes of frailty with different origin and course has been proposed by other authors recently.^{35–37} These different phenotypes raise the need of studying the different pathogenic pathways leading to each of them, but also the need of doing further research for identifying risk^{8,11} and protective¹¹ factors, and looking for different diagnostic and therapeutic approaches according to these different phenotypes, with the final aim of providing a most personalized and accurate clinical framework for prevention, detection, and intervention of frailty,³⁸ thus contributing to healthy aging.

Conclusions

These results show sarcopenia as a modulator of frailty suggesting the existence of two different clinical phenotypes of frailty (with and without sarcopenia) associated to different prognosis. This raises the need of assessing sarcopenia as a second step after diagnosing frailty in the daily clinical management of this condition.

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Conflict of interest

Authors have no conflict of interest to declare.

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Chapter 4: Healthcare cost expenditures associated to frailty and sarcopenia

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RESEARCH

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Healthcare cost expenditures associated to frailty and sarcopenia

Alejandro Álvarez-Bustos¹ , Beatriz Rodríguez-Sánchez² , Jose A. Carnicero-Carreño^{1,3} ,
Walter Sepúlveda-Loyola^{4,5} , Francisco J. Garcia-Garcia^{1,6} and Leocadio Rodríguez-Mañas^{1,7*}

Abstract

Objectives: Frailty and sarcopenia have been related with adverse events, including hospitalization. However, its combined effect with hospitalization-related outcomes, including costs, has not been previously investigated. Our purpose was to explore how frailty, sarcopenia and its interaction could impact on healthcare expenditures.

Methods: 1358 community-dwelling older adults from the Toledo Study of Healthy Ageing (TSHA) were included. Sarcopenia was measured using the Foundation for the National Institutes of Health criteria fitted to our cohort. Frailty was defined according to Frailty Trait Scale 5 (FTS5) and the Frailty Index fitted to the cut-off points of TSHA population. Hospitalization costs were taken from hospital records and costs were attributed according to Diagnostic-Related Groups, using as the cost base year 2015. Two-part regression models were used to analyze the relationship between frailty and sarcopenia and hospital admission, number of hospitalizations, length of stay and hospitalization costs.

Results: Sarcopenia was associated only with the probability of being admitted to hospital. Frailty was also associated with higher hospital use, regardless of the frailty tool used, but in addition increased hospital admission costs at follow-up by 23.72% per year and by 19.73% in the full model compared with non-frail individuals. The presence of sarcopenia did not increase the costs of frailty but, by opposite, frailty significantly increased the costs in people with sarcopenia, reaching by 46–56%/patient/year at follow-up. Older adults with frailty and sarcopenia had a higher risk of hospitalization, disregarding the tool used to assess frailty, and higher hospitalization costs (FTS5) in the full model, at the cross-sectional and at the follow-up level.

Conclusions: Frailty is associated with increased hospitalization costs and accounts for the potential effects of sarcopenia.

Keywords: Frailty, Sarcopenia, Hospital admission, Healthcare costs, Ageing

Introduction

Healthcare systems are suffering an increasing burden in terms of a heavier demand due to chronic health diseases accompanying the ageing of the population. Since 1980, people aged 65 years and older has almost tripled, and prospective studies expected these population to double

by 2050 [1]. Although healthcare expenditures (HCE) increase as people age, age itself is considered a distraction from the true drivers of spending [2, 3], like physical debilitating conditions [4]. This is also true for those who are not heavily disabled: older adults with moderate functional limitations are expected to live for longer periods of time and with greater use of medical care than most older adults with disabilities, increasing in an exponential way as their frailty status worsen [5].

Frailty and sarcopenia, two highly prevalent conditions in older people, are characterized by physical function

*Correspondence: leocadio.rodriguez@salud.madrid.org

⁷ Geriatrics Department, Hospital Universitario de Getafe, Getafe University Hospital, Ctra de Toledo km 12,500, 28905 Getafe, Spain
Full list of author information is available at the end of the article



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impairment with a high potential risk of disability [6, 7]. Frailty is defined as an age-associated, biological syndrome characterized by decreased biological reserves of the individual, increasing the risk of adverse events when facing minor stressors [7]. On the other hand, sarcopenia is defined as a loss of lean mass, strength and/or function usually associated with ageing [8]. These entities are closely related to chronic disease, a high prevalence of polypharmacy [9, 10] and adverse events, such as falls and poor quality of life [11–13]. In addition, it has been proposed that older people with frailty or sarcopenia are more likely to be hospitalized, augmenting health service costs [4, 14–16]. Furthermore, frailty and sarcopenia could be reverted [17–20], and the cost associated to them avoidable, thus preventing imminent future society demands.

Frailty and sarcopenia have been related between them [21], could coexist, but are two different conditions [22]. In addition, the lack of a universal gold standard for frailty assessment has allowed a wide spectrum of frailty assessment tools that focus on different characteristics of subjects with a poor agreement between them [23–25]. The Frailty Index is one of the most used frailty tools inside the “cumulative deficit” approach to frailty. It is constructed through a long checklist of symptoms, signs, diseases, disabilities, laboratory, radiographic or electrocardiographic abnormalities and social characteristics [26, 27] and even health utilization [28]. The Frailty Trait Scale 5 (FTS5) is an instrument stemming from the frailty phenotype conceptual framework [13] with a predictive ability of adverse events in community-dwelling older adults that could improve the FI one and aiming to overcome some of its drawbacks [29]. It includes objective functional measures, and it has proven to be highly dynamic and sensitive to changes with different risks of adverse events as mortality, hospitalization and disability associated to its score [30]. Although there are some studies that have already supported the increasing economic burden of frailty and sarcopenia in terms of healthcare costs in older populations [4, 31–34], to the best of our knowledge, there is no study that has analyzed the economic impact of these two prevalent conditions separately and their interaction on costs related to hospitalizations in older adults. This gap in the literature has motivated the purpose of this study, motivating the purpose of our research.

Methods

Participant data were taken from the Toledo Study of Healthy Ageing (TSHA). TSHA is a longitudinal cohort that was designed to analyze different models of frailty and ageing and to measure the impact that frailty, comorbidity and disability may have on health system

by assessing rural and urban community dwelling older adults aged 65 years or older [35]. TSHA was performed in concordance with the Helsinki Declaration of 1975 and was approved by the Clinical Research Ethics Committee of the Toledo Hospital in Spain. Participants signed an informed consent form. Visits were performed in the second wave of the study (basal visit) between 2011 and 2013 and the outcomes were collected during the third wave (until December 2015).

Measures of frailty

Frailty was measured using Frailty Index (FI) and Frailty Trait Scale 5 (FTS5).

Frailty Index: characterizes frailty as an accumulation of deficits. It is based on the ratio between deficits present in the individual and the total measured deficits [36]. Subjects were considered frail if the score was ≥ 0.275 . The TSHA FI was built following Searle et al., using 40 items with scores of 0 to 1 [37]. TSHA FI scoring tool is displayed in the Supplementary Information Table S1.

Frailty Trait Scale 5 [29]: a Short Form of the 12 items one [38] is a continuous scale that monitor frailty status in a range between 0 to 50. Each domain score range between 0 to 10. Subjects were considered as frail if their score were > 25 and no frail ≤ 25 [29]:

- Physical Activity: defined using the PASE scale [39].
- Gait speed: was defined using the 3-m walking test at their usual pace, according to the standard protocol. Best time of two performances was chosen.
- Hand grip strength: was measured using JAMAR Hydraulic Hand Dynamometer (Sammons Preston Rolyan, Bolingbrook, IL). Best peak strength of three performances was selected and gathered using international standard procedures [40]. Between performances, at least 1 min of resting was permitted.
- Body Mass Index: was measured according to the standard recommendation (weight/height²).
- Balance test: was established according to the standing balance feet together, semi-tandem, and tandem position (progressive Romberg balance test) [41].

FTS5 scoring tool is displayed in the Supplementary Information Table S2.

Sarcopenia

Sarcopenia was measured at baseline and was calculated according to the Foundation for the National Institutes of Health (FNIH), but fitted to the cut-points of our population (standardized FNIH [sFNIH]) [22]. According to this definition, sarcopenia is present when the low grip strength, low muscle mass and low gait speed criteria are met.

Muscle mass was determined using Dual-Energy X-ray Absorptiometry (DEXA) (Hologic, Serie Discovery QDR, Bedford, MA, USA). DXA scans were analyzed using the software Physician's Viewer (apex System Software, version 3.1.2: Bedford, USA). BMI- adjusted by Appendicular Lean Mass (ALM/BMI), derived as the sum of the muscle mass of the arms and legs, it was used as marker of low lean mass. According to sFNIH diagnosis algorithm, low muscle mass was considered in men and women when ALM/BMI is below 0.65 and 0.54 respectively.

Gait speed and handgrip strength measurement methodologies were explained above. Gait speed cut-off point was <0.8 m/s and handgrip strength cut-off points were <25.51 kg for men and <19.19 kg for women.

Hospitalization

Hospitalization after recruitment was defined as first admission and was registered reviewing the records of Toledo Hospital Complex. Participants' hospitalizations were followed-up to December 2015 with a median of 167 weeks (36.43 weeks SD).

Hospitalization is composed of four measures: having been admitted to hospital which takes value 1 if the respondent has been hospitalized in the previous 12 months and 0 otherwise, number of hospitalizations per year, average length of stay in days per year and hospitalization costs in euros per year. In order to estimate hospitalization costs, we used data from each survey respondent at baseline and during the follow-up period from hospital clinical records and we subsequently estimated the costs per person and per year in €. The unit costs per each Diagnostic Related Group (DRG), which were obtained from national data sources, were multiplied by the number of hospital admissions for each DRG. All costs were updated, if applicable, and expressed in 2015 euros.

Covariates

Age and gender were self-reported. Comorbidities were ascertained by the Charlson Index Score [42]. Polypharmacy was defined as the intake of ≥ 5 drugs/day [43]. All covariates were measured at the baseline visit (between 2011 and 2013).

Study variable and statistical analysis

Given the substantial proportion of zeros within the number and costs of hospital admission, as well as the length of stay, which led to a skewed distribution of the data, two-part regression models will be run for such outcomes, which assume a first part for modelling the probability of being admitted to hospital and a second part on the positive continuous outcome only on those who have been admitted to hospital.

Two-part models combine a model for the binary response variable, which would take value 1 if the individual has been admitted to hospital at least once and 0 if no hospitalizations, and a model for the outcome variable that is conditioned on the binary response [44], conditional on having been admitted to hospital.

The first stage of the two-part model was performed as a traditional logit regression model, in which the estimated coefficients capture the effects on the log-odds-ratio [45].

The second stage involves a Generalized Linear Model (GLM) with a gamma distribution in case of hospitalization costs with a log link and a zero-truncated Poisson distribution for the number of hospitalizations and length of stay, in days.¹ GLM models have frequently been used for healthcare costs analysis recently, given the skewed distribution of costs [47]. GLMs are empirical transformations of the classical ordinary least square (OLS) regression model, which specify the conditional mean function directly. Specifically, GLMs do not require transformation scales, but a response distribution of one of the exponential family of distributions (normal, Poisson, gamma, binomial, inverse Gaussian), which relates the mean of the response to a scale on which the model effects combine additively [48]. As previously stated, according to the Modified Park Test, the chosen family was the Gamma distribution for modelling total hospitalization costs and the Poisson distribution for the other two continuous outcomes in our analysis [49].

Several regression models have been run. The first regression model only includes one of the main variables of interest (sarcopenia or frailty). In a second regression model, age and its square, and gender have been included. Model three adds to Model two the other variable of interest (sarcopenia or frailty, as applicable). Model four adds the comorbidity severity of individuals according to the Charlson Index, which is medium-low if the Charlson Index score is 1 or 2; and high if the Charlson Index score is three or higher. Moreover, polypharmacy is also included if the daily number of drugs the subject is taking is 5 or more. We also perform the likelihood ratio test in order to detect overfitting after the inclusion of new variables in the nested models.

Two assessments will be made regarding the association between frailty and sarcopenia and hospitalization outcomes: the first analysis will entail the associations within the same wave (outcome and main variables of

¹ Since the number of hospital admissions and the average length of stay do not allow for zero-count data, a zero-truncated regression model was run for the second part of the two-part model for these outcomes. The data are truncated because there are no observations on individuals who stayed for zero days nor for negative values [46]. Additionally, we used robust standard errors for the parameter estimates.

Table 1 Characteristics of the sample, at baseline

Variable	Frailty Index			FTS5			Sarcopenia		
	Frail	No frail	p-value	Frail	No frail	p-value	With sarcopenia	Without sarcopenia	p-value
N (%)	83 (6.11)	1275 (93.89)		141 (10.38)	1217 (89.62)		303 (22.31)	1055 (77.69)	
Age (SD)	81.72 (5.65)	74.73 (5.89)	< 0.001***	79.48 (5.76)	74.02 (5.47)	< 0.001***	77.53 (5.52)	73.74 (5.52)	< 0.001***
Gender, female, n (%)	936 (68.90)	718 (52.85)	< 0.001***	1021 (75.18)	693 (51.03)	< 0.001***	1116 (82.18)	615 (45.31)	< 0.001***
Sarcopenia yes, n (%)	867 (63.86)	266 (19.61)	< 0.001***	1088 (80.14)	212 (15.61)	< 0.001***	–	–	–
Charlson Index (SD)	2.25 (2.30)	1.08 (1.46)	< 0.001***	1.76 (1.93)	1.11 (1.54)	< 0.001***	1.57 (1.90)	1.06 (1.48)	< 0.001***
Drugs, mean (SD)	7.25 (3.40)	4.74 (2.86)	< 0.001***	6.95 (2.86)	4.56 (2.77)	< 0.001***	6.18 (2.97)	4.42 (2.73)	< 0.001***
Polypharmacy, n (%)	168 (80.38%)	731 (49.59%)	< 0.001***	112 (79.43%)	581 (47.74%)	< 0.001***	303 (69.97%)	1055 (45.59%)	< 0.001***
Hospitalization yes, n (%)	370 (27.27)	117 (8.62)	< 0.001***	221 (16.31)	108 (7.97)	0.001***	166 (12.21)	107 (7.88)	0.019*

Mean (SD): continuous variables. N, %: categorical variable

FTS5 Frailty Trait Scale 5

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$

interest measured in wave 2), whereas the second analysis will consider outcomes at follow-up, wave 3, and the independent variables evaluated in wave 2. The sample size will be reduced at follow-up assessment from 1358 individuals to 1349 older adults due to mortality, during the hospital admission ($n = 9$).

Results

Participants’ characteristics classified depending on frailty status according to different frailty tools and sarcopenia are shown in Table 1. Prevalence of frailty are 12.42% (FI) and 10.38% (FTS5). In our sample, 22.31% were diagnosed with sarcopenia.

Regardless of the tool used to assess frailty, in the bivariate analyses frail individuals seem to be older, more likely to have sarcopenia, and to be in worse health status (higher Charlson index value). Moreover, they seem to be more prone towards polypharmacy. Older adults with sarcopenia presented similar characteristics to those with frailty.

Table 2 reports the differences in hospitalization-related outcomes, showing a higher number of hospital admissions, longer stays, and higher hospitalization costs among older adults with frailty and with sarcopenia, compared to their counterparts.

Results from the regression analyses

Table 3 shows that sarcopenia, when it is the only independent variable, is associated with an increased risk of being admitted to hospital both at the cross-sectional level (OR 1.56) and at follow-up (OR 1.47). However, it

is not significantly related to the other hospital-related outcomes. Such associations were observed in the second regression model, when age and gender were considered (OR 1.48 in the cross-sectional analysis and OR 1.76 at follow-up), but only remained at follow-up when frailty entered the analysis (Model 3). In the fourth regression model, sarcopenia was only significantly associated with higher odds of being admitted to hospital at follow-up (OR 1.46) when frailty is evaluated by the Frailty Index.

As it is shown in the Table 4, in the raw model, frailty was cross-sectionally associated with higher risk of hospitalization, mean length of stay (the log-count of average length of stay increases by 0.74 and 0.53 days in case of being frail according to the FI and the FTS5, respectively, compared to non-frail older adults), disregarding the tools used, and with an increase in hospital costs by 22.85%² when FTS-5 was used to assess the condition, but not when FI was used. In the fully adjusted model, only FI showed a significantly higher risk of hospitalization. When the association in the follow-up was estimated, frailty was associated with almost all the outcomes. Frailty was associated with an increase in costs, ranging from an increase by 13.98% (FTS-5, Model 2) to a maximum increase by 38.69% (FI, Model 1). When fully adjusted, some of the figures and associations changed. When we assessed the relationship between frailty and

² The coefficients on hospitalization costs in the text do not match the coefficients reported in the tables, due to the corresponding exponential transformation associated with the log-link. For example, the 22.85% comes from the calculation of $\exp.(0.2058307) - 1$.

Table 2 Summary statistics on hospitalization-related outcomes, at baseline

Variable	Frailty according to the Frailty Index		Frailty according to the FTS5		Sarcopenia	
	Frail	No frail	Frail	No frail	With sarcopenia	Without sarcopenia
Number of hospitalizations						
P25	0	0	0	0	0	0
P50	0	0	0	0	0	0
P75	1	0	1	0	0	0
P95	3	1	2	1	2	1
Average length per hospital admission						
P25	0	0	0	0	0	0
P50	0	0	0	0	0	0
P75	7.75	0	0.25	0	0	0
P95	29.50	7.50	18.25	6.50	10.50	6
Accumulated costs of hospital admission, 2015€						
P25	0	0	0	0	0	0
P50	0	0	0	0	0	0
P75	1279.36	0	517.51	0	0	0
P95	4782.86	2058.84	2323.29	1939.79	2264.69	1884.10

FTS5 Frailty Trait Scale 5

the outcomes in the long-term, we observed an association between frailty and the probability of being admitted to hospital (FTS5), the number of hospital admissions (FTS5 and FI) and length of hospitalization (FI, which increased the log count of average length of stay by 0.611 days). The increase in costs was only significant for the FTS5, which were higher by 19.73% among frail individuals than the non-frail. The differences in the significant associations between frailty and hospital admission and sarcopenia and hospital admission observed before were confirmed in Table 5, when the different combinations of sarcopenia and frailty status entered the analysis. Older adults with sarcopenia but without frailty showed a significantly higher probability of hospitalization at follow-up regardless of the tool used in Models 2 and 3, but not for the other outcomes either cross-sectional or longitudinal. On the other hand, older adults with frailty but without sarcopenia were significantly more likely to have most of the hospitalization-related outcomes in the raw model, especially when frailty was assessed by the Frailty Index, although only the length of hospital stay was significantly longer in the fully adjusted cross-sectionally model, and number and length of hospitalization for the FI at follow-up. However, older adults that have frailty and sarcopenia presented a significant association with the likelihood of being admitted to hospital, both at the cross-sectional and the follow-up levels, regardless of the frailty tool when the interaction was the only variable. In the fully adjusted model, both tools showed significant association with the probability of being admitted to

hospital, in both cross-sectional and longitudinal analysis, but only FTS5 showed higher hospitalization costs, which increased by 11.18 and 4.74% among frail individuals with sarcopenia against the reference category, at the cross-sectional and at follow-up level, respectively.³ Additionally, we assessed the likelihood ratio test for each regression model in order to estimate if the sequence of models suffer from overfitting (Table 6).

Moreover, when performing the analyses only on frail older adults (Supplementary Information Table S4), presence of sarcopenia significantly reduced length of hospitalization in the FI cross-sectional raw model but does not significantly modify any other outcome. This result would confirm the limited significance of sarcopenia as a determinant of hospital use. In case of running the analyses on older adults with sarcopenia (Supplementary Information Table S5), frailty is, in fact, significantly associated with higher hospital use, especially at follow-up, when in the full model (adjusted for age, gender, comorbidity severity and polypharmacy), being frail was associated with more number of hospitalization (FTS5), higher length of stay (FI) and hospital admission costs, which increased by 55.63% per year when the FI was used

³ When the interaction between frailty and sarcopenia was included in addition to each of these terms individually, the results showed that none of the interactions between frailty and sarcopenia were statistically significant, but for its interaction in the full model when assessing hospitalization costs and frailty was measured through the FTS5 (Table S3, Supplementary Material).

Table 3 Results on the association between sarcopenia and the hospitalization-related outcomes, both at the cross-sectional level and at follow up

	Cross-sectional analysis		At follow-up	
	Sarcopenia if frailty is measured via the Frailty Index	Sarcopenia if frailty is measured via the FTSS	Sarcopenia if frailty is measured via the Frailty Index	Sarcopenia if frailty is measured via the FTSS
Model 1				
OR on the probability of being admitted to hospital	1.557** (1.141–2.106)		1.469** (1.133–1.982)	
Coeff on number of hospital admissions	0.221 (– 0.358–0.799)		0.009 (– 0.366–0.384)	
Coeff on length of hospitalization	0.162 (– 0.221–0.545)		– 0.037 (– 0.343–0.269)	
Coeff on hospitalization costs	– 0.032 (– 0.320–0.255)		– 0.063 (– 0.295–0.168)	
Model 2				
OR on the probability of being admitted to hospital	1.481* (1.034–2.104)		1.760*** (1.283–2.456)	
Coeff on number of hospital admissions	0.513 (– 0.271–1.298)		– 0.011 (– 0.484–0.463)	
Coeff on length of hospitalization	0.159 (– 0.307–0.626)		– 0.140 (– 0.531–0.250)	
Coeff on hospitalization costs	0.055 (– 0.248–0.359)		– 0.051 (– 0.303–0.202)	
Model 3				
OR on the probability of being admitted to hospital	1.318 (0.909–1.895)	1.456 (0.991–2.134)	1.629** (1.177–2.301)	1.477* (1.028–2.132)
Coeff on number of hospital admissions	0.484 (– 0.387–1.355)	0.387 (– 0.507–1.281)	– 0.142 (– 0.669–0.385)	– 0.231 (– 0.642–0.180)
Coeff on length of hospitalization	– 0.033 (– 0.565–0.498)	– 0.096 (– 0.599–0.406)	– 0.298 (– 0.726–0.129)	– 0.244 (– 0.705–0.216)
Coeff on hospitalization costs	0.025 (– 0.282–0.333)	0.122 (– 0.227–0.471)	– 0.093 (– 0.359–0.172)	– 0.129 (– 0.374–0.116)
Model 4				
OR on the probability of being admitted to hospital	1.197 (0.824–1.726)	1.318 (0.897–1.934)	1.463* (1.059–2.074)	1.348 (0.941–1.944)
Coeff on number of hospital admissions	0.357 (– 0.404–1.117)	0.264 (– 0.533–1.061)	– 0.180 (– 0.654–0.293)	– 0.270 (– 0.637–0.097)
Coeff on length of hospitalization	– 0.092 (– 0.558–0.374)	– 0.151 (– 0.585–0.283)	– 0.035 (– 0.747–0.045)	– 0.318 (– 0.735–0.099)
Coeff on hospitalization costs	0.013 (– 0.283–0.309)	0.091 (– 0.241–0.423)	– 0.126 (– 0.373–0.122)	– 0.164 (– 0.403–0.075)

95% confidence intervals in parentheses, *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$

Model 1 includes sarcopenia as the only independent variable. Model 2 enters sociodemographic characteristics (age and its square and gender) in addition to sarcopenia. Model 3 adds to Model 2 the frailty status, measured by the Frailty Index or the Frailty Trait Score. Models 4 adds the comorbidity severity of individual according to the Charlson Index, which is medium-low if the Charlson Index score is 1 or 2; and high if the Charlson Index score is three or higher. Moreover, polypharmacy is also included if the daily number of drugs the subject is taking is 5 or more

and by 45.50% in case of the FTSS, compared with non-frail individuals.

Discussion

To our knowledge, this is the first study to demonstrate in community-dwelling older adults the costs of hospitalization to frailty and sarcopenia taking into account their interaction.

While sarcopenia increases only the likelihood of being hospitalised, frailty was also related to other outcomes such as an increase in the number of hospitalizations, in hospital stay and in healthcare costs. In addition, the interaction of having frailty and

sarcopenia had an increased likelihood of hospitalization at both cross-sectional and follow-up, and increased length of stay and hospital-related costs (FTSS) at follow-up. Further segmentation of the sample revealed that could be frailty and not sarcopenia what increased healthcare expenditures. Among older adults with sarcopenia, the presence of frailty, even when adjusted for potential confounders such age, gender, polypharmacy or comorbidity, increased both the number of admissions and hospital stay and exponentially increased costs. In this line, it has been reported that those older adults with sarcopenia have two-fold risk for hospitalization and a significative higher hospital stays that those without sarcopenia, increasing in

Table 4 Results on the association between frailty and the hospitalization-related outcomes, both at the cross-sectional level and at-follow up

	Cross-sectional analysis		At follow-up	
	Frailty measured with the Frailty Index	Frailty measured with the FTSS	Frailty measured with the Frailty Index	Frailty measured with the FTSS
Model 1				
OR on the probability of being admitted to hospital	3.611*** (2.666–4.899)	1.586* (1.045–2.361)	2.687*** (1.990–3.609)	2.127*** (1.505–3.110)
Coeff on number of hospital admissions	0.366 (–0.092–0.824)	0.397 (–0.247–1.039)	0.535*** (0.306–0.764)	0.327* (0.104–0.757)
Coeff on length of hospitalization	0.739*** (0.417–1.061)	0.526* (0.094–0.959)	0.626*** (0.349–0.902)	0.183* (0.062–0.360)
Coeff on hospitalization costs	0.104 (–0.121–0.330)	0.206* (0.075–0.487)	0.212* (0.040–0.385)	0.064 (–0.239–0.367)
Model 2				
OR on the probability of being admitted to hospital	2.797*** (2.000–3.923)	1.283* (1.003–1.996)	2.337*** (1.677–3.221)	2.086*** (1.420–3.181)
Coeff on number of hospital admissions	0.558 (–0.081–1.196)	0.515 (–0.178–1.209)	0.628*** (0.342–0.914)	0.397* (0.084–0.877)
Coeff on length of hospitalization	0.845** (0.349–1.344)	0.498* (0.039–0.958)	0.724** (0.303–1.145)	0.155 (–0.241–0.551)
Coeff on hospitalization costs	0.168 (–0.062–0.398)	0.112* (0.039–0.185)	0.327** (0.142–0.512)	0.131* (0.013–0.249)
Model 3				
OR on the probability of being admitted to hospital	2.172** (1.296–3.666)	1.054 (0.643–1.697)	1.766* (1.065–2.876)	1.701* (1.102–2.716)
Coeff on number of hospital admissions	0.127 (–0.717–0.972)	0.301 (–0.470–1.073)	0.616** (0.189–1.043)	0.518* (0.069–0.966)
Coeff on length of hospitalization	0.719** (0.183–1.256)	0.555* (0.068–1.042)	0.761** (0.291–1.231)	0.274 (–0.202–0.750)
Coeff on hospitalization costs	0.179 (–0.214–0.572)	0.186 (–0.143–0.229)	0.278* (0.003–0.553)	0.201* (0.115–0.287)
Model 4				
OR on the probability of being admitted to hospital	1.801* (1.070–3.046)	0.937 (0.569–1.523)	1.445 (0.870–2.360)	1.481* (1.014–2.403)
Coeff on number of hospital admissions	–0.101 (–0.819–0.617)	0.183 (–0.516–0.882)	0.509* (0.075–0.944)	0.473* (0.066–0.881)
Coeff on length of hospitalization	0.450 (–0.016–0.916)	0.357 (–0.075–0.789)	0.611** (0.200–1.023)	0.220 (–0.210–0.650)
Coeff on hospitalization costs	0.008 (–0.342–0.359)	0.212 (–0.113–0.538)	0.227 (–0.060–0.514)	0.181* (0.012–0.350)

95% confidence intervals in parentheses. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$

Model 1 includes frailty status, measured by the Frailty Index or the Frailty Trait Score, as the only independent variable. Model 2 enters sociodemographic characteristics (age and its square and gender) in addition to frailty. Model 3 adds to Model 2 sarcopenia. Models 4 adds the comorbidity severity of individual according to the Charlson Index, which is medium-low if the Charlson Index score is 1 or 2; and high if the Charlson Index score is three or higher. Moreover, polypharmacy is also included if the daily number of drugs the subject is taking is 5 or more

\$375 the cost per person and had an annual marginal increase of \$2315 [34], but in that study frailty was not assessed. However, our results might indicate that probably the frailty construct, and not the presence of sarcopenia, is what increases health economic costs in the medium/long term but more studies showing the combination of these entities are needed.

Traditionally, the allocation of healthcare resources has been made based on chronic conditions profiles. However, such approach might have been wrongly understood

[13], since more recent existing evidence has pointed towards a greater burden of disability and dependency, as well as their previous stages [50]. Functional decline explains health care utilization with chronic conditions and disability [4] and hospitalization represents a major driver of total HCE [32, 51] and long-term care expenditure [52]. According to these new burdensome conditions, health economic resources should be destined to policies or interventions in which greatest health patient benefits can be obtained [32] contributing with valuable

Table 5 Results on the association between the frailty and sarcopenia status and the hospitalization-related outcomes, both at the cross-sectional level and at-follow up

	Cross-sectional analysis		At follow-up	
	Frailty measured with the Frailty Index	Frailty measured with the FTSS	Frailty measured with the Frailty Index	Frailty measured with the FTSS
Model 1				
Non-frail # without sarcopenia	Ref.	Ref.	Ref.	Ref.
Non-frail # with sarcopenia				
OR on the probability of being admitted to hospital	1.295 (0.908–1.828)	1.388 (0.949–2.030)	1.357 (0.991–1.871)	1.293 (0.916–1.827)
Coeff on number of hospital admissions	0.258 (–0.443–0.959)	0.101 (–0.683–0.884)	–0.095 (–0.618–0.429)	–0.335 (–0.728–0.059)
Coeff on length of hospitalization	0.264 (–0.185–0.713)	0.007 (–0.452–0.466)	–0.125 (–0.487–0.238)	–0.122 (–0.527–0.282)
Coeff on hospitalization costs	–0.005 (–0.327–0.317)	0.043 (–0.341–0.427)	–0.096 (–0.377–0.185)	–0.177 (–0.429–0.075)
Frail # without sarcopenia				
OR on the probability of being admitted to hospital	2.926** (1.367–6.262)	1.334 (0.533–3.339)	2.771** (1.333–5.760)	3.175** (1.492–6.754)
Coeff on number of hospital admissions	0.391 (–0.694–1.477)	0.467 (–0.311–1.245)	0.733** (0.241–1.226)	0.165 (–0.561–0.891)
Coeff on length of hospitalization	1.302*** (0.745–1.859)	0.891** (0.261–1.521)	0.985** (0.371–1.599)	0.337 (–0.510–1.184)
Coeff on hospitalization costs	0.380 (–0.240–1.001)	0.362* (0.070–0.795)	0.259 (–0.207–0.726)	–0.045 (–0.579–0.490)
Frail # with sarcopenia				
OR on the probability of being admitted to hospital	3.316*** (1.854–5.931)	1.768* (1.113–2.740)	2.621*** (1.485–4.624)	2.025*** (1.376–3.116)
Coeff on number of hospital admissions	0.232 (–0.568–1.031)	0.406 (–0.343–1.154)	0.443* (0.052–0.834)	0.307 (–0.194–0.807)
Coeff on length of hospitalization	0.424 (–0.146–0.994)	0.436 (–0.080–0.951)	0.458* (0.038–0.878)	0.101 (–0.287–0.488)
Coeff on hospitalization costs	–0.005 (–0.505–0.496)	0.169* (0.144–0.194)	0.093 (–0.218–0.403)	0.057 (–0.296–0.411)
Model 2				
Non-frail # without sarcopenia	Ref.	Ref.	Ref.	Ref.
Non-frail # with sarcopenia				
OR on the probability of being admitted to hospital	1.324 (0.895–1.941)	1.427 (0.943–2.162)	1.681** (1.200–2.411)	1.640* (1.119–2.395)
Coeff on number of hospital admissions	0.567 (–0.340–1.474)	0.401 (–0.579–1.380)	–0.100 (–0.737–0.536)	–0.340 (–0.795–0.115)
Coeff on length of hospitalization	0.314 (–0.229–0.857)	0.034 (–0.479–0.547)	–0.203 (–0.661–0.255)	–0.211 (–0.691–0.269)
Coeff on hospitalization costs	0.078 (–0.248–0.405)	0.111 (–0.271–0.493)	–0.085 (–0.374–0.203)	–0.158 (–0.425–0.109)
Frail # without sarcopenia				
OR on the probability of being admitted to hospital	2.216 (0.994–4.945)	0.940 (0.361–2.448)	2.109 (0.977–4.545)	2.785* (1.187–6.540)
Coeff on number of hospital admissions	0.416 (–0.823–1.655)	0.363 (–0.778–1.504)	0.687* (0.135–1.240)	0.321 (–0.410–1.053)
Coeff on length of hospitalization	1.256*** (0.716–1.796)	0.945** (0.380–1.510)	0.918** (0.250–1.585)	0.349 (–0.538–1.235)
Coeff on hospitalization costs	0.379 (–0.205–0.962)	0.258* (0.131–0.385)	0.312 (–0.139–0.763)	0.100 (–0.410–0.610)
Frail # with sarcopenia				
OR on the probability of being admitted to hospital	2.837*** (1.501–5.370)	1.561 (0.933–2.553)	2.638** (1.428–4.847)	2.305*** (1.495–3.726)
Coeff on number of hospital admissions	0.518 (–0.389–1.424)	0.682 (–0.196–1.559)	0.437* (0.014–0.860)	0.316 (–0.275–0.906)
Coeff on length of hospitalization	0.428 (–0.202–1.057)	0.400 (–0.189–0.990)	0.371 (–0.102–0.843)	0.014 (–0.428–0.456)
Coeff on hospitalization costs	0.114 (–0.390–0.618)	0.054* (0.001–0.107)	0.167 (–0.154–0.488)	0.091 (–0.271–0.452)
Model 3				
Non-frail # without sarcopenia	Ref.	Ref.	Ref.	Ref.
Non-frail # with sarcopenia				
OR on the probability of being admitted to hospital	1.170 (0.786–1.729)	1.252 (0.820–1.911)	1.483* (1.057–2.144)	1.469* (1.002–2.149)
Coeff on number of hospital admissions	0.401 (–0.437–1.240)	0.255 (–0.664–1.174)	–0.163 (–0.747–0.421)	–0.466 (–0.903–0.029)

Table 5 (continued)

	Cross-sectional analysis		At follow-up	
	Frailty measured with the Frailty Index	Frailty measured with the FTSS	Frailty measured with the Frailty Index	Frailty measured with the FTSS
Coeff on length of hospitalization	0.156 (− 0.368–0.680)	− 0.096 (− 0.597–0.405)	− 0.295 (− 0.741–0.150)	− 0.381 (− 0.867–0.105)
Coeff on hospitalization costs	0.057 (− 0.261–0.376)	0.073 (− 0.287–0.433)	− 0.131 (− 0.398–0.135)	− 0.219 (− 0.486–0.048)
<i>Frail # without sarcopenia</i>				
OR on the probability of being admitted to hospital	1.628 (0.730–3.624)	0.708 (0.264–1.893)	1.556 (0.728–3.348)	2.217 (0.918–5.383)
Coeff on number of hospital admissions	0.043 (− 1.040–1.125)	0.143 (− 0.773–1.059)	0.539* (0.026–1.051)	0.133 (− 0.566–0.832)
Coeff on length of hospitalization	0.831** (0.300–1.363)	0.511* (0.055–0.966)	0.701* (0.108–1.294)	0.090 (− 0.768–0.947)
Coeff on hospitalization costs	0.179 (− 0.368–0.726)	0.337 (− 0.087–0.761)	0.201 (− 0.242–0.644)	0.125 (− 0.219–0.469)
<i>Frail # with sarcopenia</i>				
OR on the probability of being admitted to hospital	2.255* (1.174–4.333)	1.289* (1.043–1.675)	2.041* (1.093–3.803)	1.869** (1.199–3.094)
Coeff on number of hospital admissions	0.204 (− 0.639–1.046)	0.451 (− 0.350–1.251)	0.315 (− 0.102–0.731)	0.246 (− 0.277–0.769)
Coeff on length of hospitalization	0.166 (− 0.442–0.775)	0.183 (− 0.387–0.754)	0.209 (− 0.250–0.667)	− 0.072 (− 0.492–0.347)
Coeff on hospitalization costs	− 0.050 (− 0.488–0.387)	0.106* (0.0002–0.211)	0.114 (− 0.220–0.448)	0.046* (0.00005–0.092)

95% confidence intervals in parentheses. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$

Model 1 includes the interaction term between frailty status, measured by the Frailty Index or the Frailty Trait Score, and sarcopenia as the only independent variable. Model 2 enters sociodemographic characteristics (age and its square and gender) in addition to the interaction term from Model 1. Model 3 adds to Model 2 the comorbidity severity of individual according to the Charlson Index, which is medium-low if the Charlson Index score is 1 or 2; and high if the Charlson Index score is three or higher. Moreover, polypharmacy is also included if the daily number of drugs the subject is taking is 5 or more

information improving decision-making processes. Our results could certify this hypothesis, although some differences have also been observed depending on the tool with which we assess frailty.

Frailty status, and not age, has been proposed as a criterion for risk interventions in older adults [53]. As an example, frail subjects spend three times more resources than robust older adults in costs derived from

surgical hospitalization and total post-operative costs at six-months [54]. Although prevalence of sarcopenia and frailty are estimated at around 10% in community-dwelling older adults [55, 56], which could be interpreted as minor rates, its estimated relationship with adverse outcomes and high associated expenditures may lead to a costly public health problem [57, 58], as our findings have also supported. Moreover, our results

Table 6 Log-likelihood ratio tests for each regression nested model showed in Tables 3, 4 and 5

	Cross-sectional analysis		At follow-up	
	Frailty measured with the Frailty Index	Frailty measured with the FTSS	Frailty measured with the Frailty Index	Frailty measured with the FTSS
Regression results from Table 3				
M2 vs M1	359.82***		288.96***	
M3 vs M2	318.80***	323.05***	294.07***	255.98**
M4 vs M3	358.93***	367.01***	287.63***	299.02***
Regression results from Table 4				
M2 vs M1	263.48***	269.01***	270.07***	277.27***
M3 vs M2	272.31***	281.09***	286.12***	292.37***
M4 vs M3	288.82***	295.72***	290.69***	297.99***
Regression results from Table 5				
M2 vs M1	301.98***	321.14***	318.68***	326.79***
M3 vs M2	310.45***	333.37***	335.09***	341.20***

FTSS Frailty Trait Scale 5, M Model

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$

could confirm that in addition to the contribution of sarcopenia and frailty to the healthcare costs, different frailty construct can identify different individuals at risk of suffering adverse events. The use of frailty scales may be inclusive and not substitutable [59]. Furthermore, our results enhance the necessity of identifying frailty in people with sarcopenia [22] which may help policy makers in the efficient allocation of health care resources, being an opportunity for healthcare professionals to revert these ageing associated conditions.

Strengths

This study has many strengths, including the large population included and the use of two relevant frailty tools previously adjusted and validated in our cohort to assess frailty. Another strength is the excellent ascertainment of the hospitalization related outcomes which are not self-reported, but extracted from clinical records, which enabled us to estimate healthcare cost expenditures associated with each available GRD.

Muscle mass has been determined using DEXA, which is the gold-standard. Moreover, the inclusion of relevant cofounders in adjusted models contributes to the increase the strength of our findings.

Limitation

Although hospitalization has been proposed as the main health costs, we could not include other resources as physiotherapy, drugs, specialist or general practitioner visits, or diagnostic tests which are not included within the corresponding DRG.

Despite our sample size, due to the segmentation according to frailty and sarcopenia status (Supplementary Information Table S6), and the low number of hospitalized events, problems of low power to detect differences could be occurring, and subsequently, more studies should confirm our results. The results could be extended to a longer period of time in order to check whether the results obtained in the current study are consistent through a longer follow-up. Moreover, having only two points of analysis might not allow us to establish causality and, hence, the results should be interpreted with caution, suggesting associations rather than causal relationships.

Conclusions

Demographic ageing could burden health care services. Interventions to improve frailty and sarcopenia must be promoted to prevent disability and health care pressure. Strategies for early detection and integrated multidisciplinary interventions should be promoted. Our results should be used to predict future health

economic trends according to patient screening and assessment.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12877-022-03439-z>.

Additional file 1: Table S1. Toledo Study of Health Ageing Frailty Index. **Table S2.** Frailty Trait Scale 5 (FTS5) scoring. **Table S3.** Results on the association between the interaction term between frailty and sarcopenia and the hospitalization-related outcomes, both at the cross-sectional level and at-follow up. **Table S4.** Results on the association between sarcopenia and the hospitalization-related outcomes, both at the cross-sectional level and at-follow up, only on the frail older adults. **Table S5.** Results on the association between frailty and the hospitalization-related outcomes, both at the cross-sectional level and at-follow up, only on the older adults with sarcopenia. **Table S6.** Cross-tabulations of sarcopenia and frailty according to the FTS5 and the FI.

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Authors' contributions

All authors contributed to editing of the manuscript. AAB and BRS drafted the manuscript for authors to contribute and comment on. All authors contributed to interpretation of the study findings. AAB, BRS and LRM designed the study. BRS analysed the data. The corresponding author (LRM) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted and is the guarantor. The author(s) read and approved the final manuscript.

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Availability of data and materials

Data will be available upon request to the corresponding author.

Declarations

Ethics approval and consent to participate

Participant data were taken from the Toledo Study of Healthy Ageing (TSHA). TSHA is a longitudinal cohort that was designed to analyze different models of frailty and ageing and to measure the impact that frailty, comorbidity and disability may have on health system by assessing rural and urban community dwelling older adults aged 65 years or older. TSHA was performed in concordance with the Helsinki Declaration of 1975 and was approved by the Clinical Research Ethics Committee of the Toledo Hospital in Spain. All the participants signed the Informed Consent. Ethics approval and Consent to participate are provided in the related files.

Consent for publication

Not Applicable.

Competing interests

None.

Author details

¹Biomedical Research Center Network for Frailty and Healthy Ageing (CIBER-FES), Institute of Health Carlos III, Madrid, Spain. ²Department of Applied Economics, Public Economics and Political Economy, Faculty of Law, University Complutense of Madrid, Madrid, Spain. ³Biomedical Research Foundation, Getafe University Hospital, Getafe, Spain. ⁴Faculty of Health and Social Sciences, Universidad de Las Americas, Santiago, Chile. ⁵Masters and PhD Programme in Rehabilitation Sciences, Londrina State University (UEL) and University North of Paraná (UNOPAR), Londrina, Brazil. ⁶Geriatrics Department, Virgen del Valle Hospital, Toledo, Spain. ⁷Geriatrics Department, Hospital Universitario de Getafe, Getafe University Hospital, Ctra de Toledo km 12,500, 28905 Getafe, Spain.

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Discussion

The demographic transformation of the population has resulted in an increasing number of older adults[1,7]. Improvements in medicine along with other socioeconomic factors have prolonged life expectancy[1,4] but, in many cases, accompanied by chronic health problems and disabilities associated with ageing [10]. In fact, the way individuals age is highly heterogeneous and dependent on several factors such as where life courses, genetic, biological, environmental and social backgrounds that influence the final individual functional status [21,22]. This fact demands healthcare systems to adapt to the specific conditions of these individuals, where multiple chronic disease reigns over isolated acute pathology, and where function is what determines the subject's prognosis[214–217].

On the functional continuum, frailty would refer to the grey scale between white (robust) and black (disability). In this PhD dissertation, we have discussed how frailty conceptualizes the state of diminished physiological reserve and compromises the capacity to maintain homeostasis[54,55]. Cost-effective health care strategies to counteract this unhealthy ageing pattern are vital to sustain current and future health systems. Understanding the basic and physiological mechanisms by which frail subjects differ from non-frail subjects, but also how different accompanying conditions in frail subjects could condition their prognosis, is paramount to action on this geriatric syndrome. The first chapter discusses the basic and clinical mechanisms of physical activity and exercise in the prevention of impaired function in older adults. As frailty has a multisystemic etiology, interventions that act on a single mechanism without understanding the global context make such treatment useless. In fact, to date, frailty has no effective treatment to prevent or counteract it. It seems that interventions based on physical activity and exercise, especially those involving multicomponent exercise of a certain type, frequency, and intensity, appear to be the most effective in reversing certain deficits in functional capacity in older adults. Although elucidating which intervention is the most effective has not yet been achieved, we have

compiled a compendium narrative to better understand the mechanisms by which exercise benefits this condition.

Functional status, as evidenced by the state of frailty, is a dynamic entity over time[218–220]. Secondly, we demonstrate the dynamism of frailty and its association with different risks of adverse events based on the trajectories of frailty. In this second article, we found that those who spontaneously reverse their frailty status do not have an increased risk of different adverse events, such as mortality, hospitalization or disability, compared to those with a lower frailty score at the baseline. This is independent of age, so the idea that ageing necessarily parallels an inevitable decline in function seems to be unsubstantiated [23,218,219]. This idea re-emphasises the need to reverse this state of frailty, with the aim of achieving healthy ageing and avoiding periods of disability in community-dwelling older adults. On the other hand, in a second analysis, we show that small changes in frailty scores confer different risks, so that frailty may be a continuous rather than a dichotomous entity. Our results point to a dose-response relationship between frailty and an increased risk of death, hospitalization, and disability progression, even for values well below the proposed frailty thresholds[74].

Alternatively, unexpectedly, we have observed that subjects with high-frailty burden do not appear to reduce their frailty levels spontaneously, presenting monomorphic trajectories toward maintenance or worsening of frailty. This may confirm that high-frailty burden may be difficult, but not impossible, to reverse and probably points to the need for personalized interventions at early stages of frailty to prevent its progression and thus, reduce the risk of developing adverse events[221]. To this end, early and accurate detection of frailty remains necessary, as we proposed in the first article of the thesis. The clinical relevance of this finding supports the assessment of frailty levels to determine the health status of older adults and contributes to the idea that reducing the burden of frailty could be effective in reducing the risk of adverse outcomes in older age.

Subsequently, we explored whether one of the possible factors influencing this increase in frailty status could be the presence of sarcopenia. Although sarcopenia has been proposed as one of the physiological substrates of frailty[222,223] and has been shown to be two related but clearly

distinct entities[182], and with different risks of disability and mortality[183]. In this manuscript, we demonstrated that sarcopenia increases the risk of increasing frailty status and decreases the likelihood of reversing frailty, although its presence does not appear to influence mortality risk once the frailty stage is taken into account. To our knowledge, this is the first study to demonstrate the role of sarcopenia in frailty transitions and reinforces the idea of the existence of different phenotypes in older adults based on the presence or not of frailty and sarcopenia, with different clinical prognoses[183]. Influencing the effectiveness and efficiency of different treatments based on the presence or not of both entities seems to be the next step in understanding the interaction of both entities.

This PhD thesis evaluates the economic impact of frailty and sarcopenia on the healthcare system. This impact is assessed by hospitalization-related costs. According to our results, while sarcopenia hardly influences the studied outcomes in the presence of other covariates, frailty appears as a major contributor in these outcomes, especially at the longitudinal level. Moreover, when we evaluate the interaction of both entities, the probability of hospitalization increases at both cross-sectional and longitudinal levels, as well as the costs of hospitalization when frailty is measured according to the FTS5, reinforcing the usefulness of this diagnostic tool for frailty compared to other more widespread ones.

Frail older adults are at risk of premature death [108,111,183,224–226], as well as falls [108], fractures[225,227], disability[108], poor quality of life[228], increased health care costs and resources[216,229–232], hospitalization[157,233] and institutionalization[33]. Screening for frailty could be costly [216]. However, health systems are increasingly aware of the need to screen patients and determine an action plan by screening subjects who may meet these criteria [63]. This is the case, for example, in Spain, which has developed an action plan for the detection and intervention of frailty. However, the lack of consensus on a universal definition of frailty, as well as a standard screening tool, hinders this task[234].

Therefore, the implementation of successful interventions to reduce frailty and sarcopenia can improve the quality of care for older adults and promote healthy aging, as well as to reduce the impact of these entities on health care systems and strengthen their sustainability.

Clinical Implications

The sustainability of health systems is being threatened due to the increasing number of older adults visiting clinical services. As we have commented throughout this doctoral thesis, in older adults, where chronic comorbidity reigns instead of isolated acute or chronic diseases, function opens up as a new paradigm in the creation of criteria and algorithms for clinical decision [20,118,214,216]. Frail older adults present a poor performance in functional tasks, which affects their daily quality of life and favors the occurrence of adverse events such as falls, use of social and health resources, and the use of social and health care resources [13], in addition to disability or death.

Fortunately, frailty is reversible, at least partially, as we have found. Moreover, we have shown that it is the individual's current frailty state that confers the risk of adverse events, and that this state is spontaneously reversible, especially at moderate frailty loads.

According to data from this doctoral thesis, between 9% and 26% of subjects with sarcopenia who did not meet frailty criteria will develop frailty after three years, compared with 2% and 4% of those who do not meet these criteria of sarcopenia. This compelling data reinforce the need to create effective prevention strategies for preventing not only frailty, as an entity intimately related to various adverse health events in older adults, but also sarcopenia, as a preliminary step to frailty. Although it is true that frailty is a multicomponent entity, and sarcopenia affects only the physical domain (neuromuscular component)[234], sarcopenia stands as one of the main risk factors for frailty.

Therefore, it plays a crucial role in promoting comprehensive care for older adults to promote a holistic approach by identifying and treating these two conditions. Multiple metabolic, hematologic, and inflammatory biomarkers have been shown to be associated with frailty and sarcopenia. In fact, in community-dwelling individuals in whom both entities coexist, albumin was negatively associated with both entities, regardless of age and the clinical setting. Likewise, in individuals younger than 75, IL-6 also showed such an association. Moreover, community-

dwelling older adults with frailty and sarcopenia also had higher circulating levels of tumor necrosis factor-alpha (TNF- α) compared to their robust and non-sarcopenic counterparts, respectively [235]. The identification of these biomarkers is key in reaching therapeutic targets amenable to pharmacological enhancement. Multiple drugs have been proposed as candidates for the treatment of frailty and sarcopenia, without being approved for treating both geriatric entities[236]. In fact, lifestyle interventions are currently the central treatment for both entities[236].

Both physical activity and exercise may reduce the risk of frailty, as we developed in the first objective of the thesis, and sarcopenia [237–239]. Within the different types of physical exercise, muscular strength exercise has been proposed as the reference treatment to counteract the loss of muscle mass associated with age, improving neuromuscular performance and cellular adaptations [240–243]. However, its combination with aerobic exercise could be more effective in improving muscle mass and strength in older adults with sarcopenia[244]. Multicomponent exercise, i.e., exercise that composed of different types of exercise, such as cardiovascular exercise, strength exercise, balance exercise, and flexibility exercise, seems to be the most suitable when dealing with frail patients[245,246].

The implementation and inclusion of older adults in interventions based on physical exercise seems to be mandatory. However, much remains to be defined in aspects such as frequency, intensity, time, or type of exercise in older adults, especially when frailty and sarcopenia coexist. According to the World Health Organization, older adults should perform at least 150 min of moderate-intensity aerobic exercise or 75 min of vigorous intensity spread over 3 or more days per week and perform a balance and strength training program of at least moderate intensity involving all muscle groups for 3 or more days per week[247]. Although clinicians and public health professionals should encourage decreased sedentary lifestyles and promote physical activity and exercise in patients with chronic conditions [248], adherence to these recommendations may not be suitable for all individuals, and the need for individualization is paramount. Therefore, efforts are needed to implement exercise-based interventions. In fact, even

unsupervised interventions are safe and effective for certain variables of function in community-dwelling older adults [249,250], as well as in individuals with mild cognitive impairment or mild dementia[251].

On the other hand, similarly to the case for drugs, the variability of response to exercise is high, and relies on multiple factors,[252,253]. Accordingly, detailed and individualized prescriptions could improve exercise-associated outcomes [253]. Nevertheless, further rigorous research is needed in this field[246,247,254].

The results of these Thesis, taken as a whole suggest the need for establishing a clinical pathway once the patient is diagnosed of prefrailty/frailty, taking into account the role of sarcopenia in determining the transitions along the frailty status. Furthermore, to know if sarcopenia is present, can modify the program of physical exercise to be implemented in these patients. Moreover, recent studies have shown that assessment of both sarcopenia and frailty in outpatient settings is feasible[264,265] although its use is not yet widespread [266]. Now is the time, then, to move more confidently towards its implementation in daily clinical practice, with the aim of avoiding precariousness in public health systems and prioritizing care focused on the optimal functionality of the individual.

Conclusions

1. Physical activity is a key element in the prevention and treatment of the loss of physical function, expressed through the frailty syndrome. The implementation of multicomponent physical exercise programs according to the functional status of the patient should be a public health priority to prevent this geriatric condition.

2. Frailty is a physiological construct that can be assessed continuously, demonstrating a proportional dose-effect relationship against adverse events in the elderly population. Moreover, this construct is dynamic and reducing the burden of frailty reduces the risk of mortality, hospitalization, and disability.

3. Sarcopenia influences the spontaneous transition in frailty states over time, suggesting the existence of different frailty phenotypes with different clinical prognoses. Assessing the presence or not of frailty, as well as sarcopenia, seems to be a priority in the daily clinical management of older adults.

4. Demographic aging could place a burden on health services. Frailty is associated with increased hospitalization costs and may mediate the potential effects of sarcopenia, which appears to influence only the likelihood of be hospitalized. Early detection strategies and integrated multidisciplinary interventions that reduce frailty and sarcopenia status should be promoted to positively impact the economic and public health burden.

Conclusiones

1. La actividad física es un elemento clave en la prevención y tratamiento de la pérdida de función física, expresada mediante el síndrome de la fragilidad. La implantación de programas de ejercicio físico multicomponente de acuerdo con el estado funcional del paciente ha de ser un elemento de salud pública prioritario para prevenir esta condición.
2. La fragilidad es un constructo fisiológico que puede ser evaluado de manera continua, demostrando una relación dosis-efecto proporcional frente a los eventos adversos en la población mayor. Además, este constructo es dinámico y la reducción de la carga del mismo, reduce el riesgo de mortalidad, hospitalización y discapacidad.
3. La sarcopenia influye en la transición espontánea a estadios de fragilidad a lo largo del tiempo, sugiriendo la existencia de diferentes fenotipos de fragilidad con diferentes pronósticos clínicos. Evaluar la presencia o no de la fragilidad, así como de la sarcopenia, parecen ser prioritarios en el manejo clínico diario de los adultos mayores.
4. El envejecimiento demográfico podría suponer una carga para los servicios sanitarios. La fragilidad se asocia con un aumento de los costes de hospitalización, pudiendo actuar como mediador en los efectos potenciales de la sarcopenia, que parece influir sólo en la probabilidad de ser hospitalizado. Deben promoverse estrategias de detección precoz e intervenciones multidisciplinares integradas que reduzcan el estado de fragilidad y sarcopenia, con el fin de impactar de manera positiva en la carga económica y de salud pública.

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Appendix

Appendix 1: Supplementary material of Chapter 2.

Table S1. Demographic characteristics of the sample according to the FTS5 score.

Variable	All	FTS5 (≥0 & ≤10)	FTS5 (>10 & ≤15)	FTS5 (>15 & ≤20)	FTS5 (>20 & ≤25)	FTS5 (>25)	p-value
N (%)	975	142 (14.56)	208 (21.33)	272 (27.89)	207 (21.23)	146 (12.97)	<0.001
Age, mean (SD)	73.14 (4.69)	70.86 (3.27)	71.88 (4.08)	73.21 (4.81)	74.57 (4.91)	74.99 (4.75)	<0.001
Gender, men (%)	423 (43.38)	94 (66.20)	106 (50.96)	126 (46.32)	67 (32.37)	30 (20.55)	<0.001
FTS5 basal, mean (SD)	18.08 (6.79)	7.97 (1.87)	13.17 (1.36)	17.66 (1.46)	22.83 (1.31)	28.96 (3.30)	<0.001
Change in FTS5 per year, mean (SD)	-0.01 (1.56)	1.08 (1.30)	0.45 (1.51)	-0.12 (1.52)	-0.50 (1.45)	-0.82 (1.27)	<0.001
Dependent according Katz Index score ≤5, n (%)	124 (12.72)	5 (3.52)	15 (7.21)	30 (11.03)	28 (13.53)	46 (31.51)	<0.001
MMSE, mean (SD)	24.44 (4.39)	26.45 (3.03)	25.13 (3.80)	24.75 (4.01)	23.17 (5.10)	22.52 (4.81)	<0.001
Charlson Index, mean (SD)	0.94 (1.43)	0.67 (0.99)	0.79 (1.42)	1.03 (1.44)	1.06 (1.53)	1.08 (1.59)	0.023
Educational level	647 (66.70)	70 (49.65)	125 (60.39)	194 (71.59)	146 (71.22)	112 (76.71)	<0.001
No School, n (%)	162 (16.70)	34 (24.11)	42 (20.29)	32 (11.81)	35 (17.07)	19 (13.01)	<0.001
Primary School Incomplete, n (%)	161 (16.60)	37 (26.24)	40 (19.32)	45 (16.61)	24 (11.71)	15 (10.27)	<0.001
Primary School Complete or Superior, n (%)	4.06 (2.72)	3.20 (2.58)	3.48 (2.45)	4.07 (2.54)	4.43 (2.88)	5.20 (2.89)	<0.001
Number of Drugs per day, mean (SD)	391 (40.10)	44 (30.99)	70 (33.65)	107 (39.34)	88 (42.51)	82 (56.16)	<0.001
Polypharmacy, n (%)	211 (21.64)	20 (14.08)	32 (15.38)	70 (25.74)	46 (22.22)	43 (29.45)	<0.001
Death, n (%)	393 (40.31)	54 (38.03)	62 (29.81)	108 (39.71)	95 (45.89)	74 (50.68)	<0.001
Hospitalization, n (%)	183 (29.66)	18 (16.82)	40 (26.85)	47 (26.70)	41 (36.61)	37 (50.68)	<0.001
Worsening Disability, n (%)	204 (26.56)	18 (15.79)	41 (23.43)	56 (25.57)	47 (29.56)	42 (41.58)	0.002

In bold: $p < 0.05$. Mean (SD): continuous variables. N, %: categorical variable. FTS5: Frailty Trait Scale 5. MMSE: Mini-Mental State Examination.

Appendix 1. Frailty Trait Scale 5 (FTS5) score.

Score	BMI, kg/m ²		PASE	Gait Speed ^a	Grip strength, kg		Progressive Romberg		
					Women	Men	Score	Position Seconds	Seconds
0	23.01-26.99		>194	<2.45	>22	>29	0	Tandem	≤10
1	27-28.99	21.01-23	174.61-194	2.45-2.99	19.81-22	26.11-29	2.5	Tandem	3.01-9.99
2	29-30.99	19.01-21	155.21-174.6	3.00-3.54	17.61-19.8	23.21-26.1	5	Tandem	≤3
3	31-32.99	17.01-19	135.81-155.2	3.55-4.09	15.41-17.6	20.31-23.2		Semitandem	≤10
4	33-34.99	15.01-17	116.41-135.8	4.10-4.64	13.21-15.4	17.41-20.3	7.5	Semitandem	<10
5	35-36.99	13.01-15 ^b	97.01-116.4	4.65-5.19	11.01-13.2	14.51-17.4		Side by side	≤10
6	37-38.99	11.01-13 ^b	77.61-97	5.20-5.74	8.81-11.0	11.61-14.5	10	Side by side	<10
7	39-40.99	NA	58.21-77.6	5.75-6.29	6.61-8.8	8.71-11.6			
8	41-42.99	NA	38.81-58.2	6.30-6.84	4.41-6.6	5.81-8.7			
9	43-44.99	NA	19.41-38.8	6.85-7.39	2.21-4.4	2.91-5.8			
10	≤45	NA	0-19.4	≤7.4	0-2.2	0-2.9			

BMI: Body Mass Index. PASE: Physical Activity Scale for the Elderly.

FTS₅ includes all the items of the table (range 0-50), and frail participants are those with FTS₅ scores >25.

^a: Gait speed refers to time in accomplish 3-metres at usual pace in seconds.

^b: Model estimation.

Appendix 2: Supplementary material of Chapter 3.

Supplementary Material 1. Differences in the cut-off points of the criteria for defining frailty in the TSHA according to Fried's originals.

	Frailty Phenotype Criteria	TSHA Frailty Phenotype Criteria
Weight loss	In the last year, have you lost more than 10 pounds (4.54 kg) unintentionally? No , Yes If answer is yes, this criterion is positive.	
Exhaustion	Using the CES-D, the following two statements are read asking how often in the last week did you feel this way? I felt that everything I did was an effort I could not get going 0 ¼ rarely or none time (<1 day) 1 ¼ some or little time (1e2 days) 2 ¼ a moderate amount of the time (3e4 days) 3 ¼ most of the time Persons answering “2” or “3” to either of these questions are categorized as positive.	
Slowness	Gait speed stratified by gender and height Men Height ≤173 cm.≤0.76 m/s Height >173 cm.≤0.65 m/s Women Height ≤159 cm.≤0.76 m/s Height >159 cm.≤0.65 m/s	Gait speed stratified by gender and height Men Height <160 cm.≤0.38 m/s Height ≥160-<164 cm.≤0.43 m/s Height ≥164-<168 cm.≤0.46 m/s Height ≥168 cm.≤0.5 m/s Women Height <148 cm.≤0.43 m/s Height ≥148-<156 cm.≤0.38 m/s Height ≥156 cm.≤0.33 m/s
Weakness	Grip strength stratified by gender and BMI quartiles: Men BMI ≤24. ≤29 kg BMI 24.1-26. ≤30 kg BMI 26.1-28. ≤30 kg BMI >28. ≤32 kg Women BMI ≤23. ≤17 kg BMI 23.1-26. ≤17.3 kg BMI 26.1-29. ≤18 kg BMI >29. ≤21 kg If grip strength is lower than these respective cut-offs, the criterion is positive	Grip strength stratified by gender and BMI quartiles: Men BMI <25.91 _ ≤19.01 kg BMI ≥25.91 _ ≤22.01 kg Women BMI <25.91 _ ≤10.01 kg BMI ≥25.91- <28.76 _ ≤12.01 kg BMI ≥28.76- <31.99 _ ≤11.01 kg BMI ≥31.99 _ ≤12.01 kg If grip strength is lower than these respective cut-offs, the criterion is positive
Low Physical Activity	Kcal of leisure physical activity stratified by gender: Men <383 Kcal (to walk at least 2:30 hours per week). Women <270 Kcal (to walk at least 2 hours per week)	PASE score <27.8571

BMI, body mass index; CES-D, Center for Epidemiological Studies, Depression Scale; TSHA: Toledo Study for Healthy Ageing. PASE: Physical Activity Score for the Elderly.

Supplementary Material 2. Frailty Trait Scale 5 (FTS₅) score.

Score	BMI, kg/m ²		PASE	Gait Speed ^a	Grip strength, kg		Progressive Romberg		
					Women	Men	Score	Position Seconds	Seconds
0	23.01-26.99		>194	<2.45	>22	>29	0	Tandem	≤10
1	27-28.99	21.01-23	174.61-194	2.45-2.99	19.81-22	26.11-29	2.5	Tandem	3.01-9.99
2	29-30.99	19.01-21	155.21-174.6	3.00-3.54	17.61-19.8	23.21-26.1	5	Tandem	≤3
3	31-32.99	17.01-19	135.81-155.2	3.55-4.09	15.41-17.6	20.31-23.2		Semitandem	≤10
4	33-34.99	15.01-17	116.41-135.8	4.10-4.64	13.21-15.4	17.41-20.3	7.5	Semitandem	<10
5	35-36.99	13.01-15 ^b	97.01-116.4	4.65-5.19	11.01-13.2	14.51-17.4		Side by side	≤10
6	37-38.99	11.01-13 ^b	77.61-97	5.20-5.74	8.81-11.0	11.61-14.5	10	Side by side	<10
7	39-40.99	NA	58.21-77.6	5.75-6.29	6.61-8.8	8.71-11.6			
8	41-42.99	NA	38.81-58.2	6.30-6.84	4.41-6.6	5.81-8.7			
9	43-44.99	NA	19.41-38.8	6.85-7.39	2.21-4.4	2.91-5.8			
10	≤45	NA	0-19.4	≤7.4	0-2.2	0-2.9			

BMI: Body Mass Index. PASE: Physical Activity Scale for the Elderly.

FTS₅ includes all the items of the table (range 0-50), and frail participants are those with FTS₅ scores >25.

^a: Gait speed refers to time in accomplish 3-metres at usual pace in seconds.

^b: Model estimation.

Supplementary Material 3. Characteristics of participants according to the presence or absence of sarcopenia.

Variable	All	No sarcopenic	Sarcopenic	p-value
N (%)	1538	1190 (77.37)	348 (22.63)	
Age (SD)	74.73 (5.73)	73.91 (5.51)	77.53 (5.57)	<0.001
Gender, male (%)	700 (45.51)	640 (53.78)	60 (17.24)	<0.001
Charlson Index (SD)	1.18 (1.59)	1.08 (1.48)	1.52 (1.89)	<0.001
FTS5 No Frail (%)	1377 (89.53)	1154 (96.97)	223 (64.08)	<0.001
FTS5 Frail (%)	161 (10.47)	36 (3.03)	125 (35.92)	
Fried Robust (%)	1058 (68.79)	899 (75.55)	159 (45.69)	<0.001
Fried Prefrail (%)	436 (28.35)	272 (22.86)	164 (47.13)	
Fried Frail (%)	44 (2.86)	19 (1.60)	25 (7.18)	
Cognitive impairment or dementia (%)	241 (15.98)	83 (24.70)	158 (13.48)	<0.001
At-risk of malnutrition and malnourished (%)	368 (24.93)	139 (41.62)	229 (20.05)	<0.001

Data are expressed as mean (SD) and frequency (%). In bold: p-value <0.05. N: Number of the sample. FTS5: Frailty Trait Scale 5. SD: standard deviation.

Supplementary Material 4. Risk of worsening, maintenance, and improvement in frailty status according to the presence or absence of sarcopenia, nutritional and cognitive status.

Frailty tool	Basal frailty state	Basal Sarcopenia State	Worsening				Staying the same				Improving			
			Model 1		Model 2		Model 1		Model 2		Model 1		Model 2	
			OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Frailty Phenotype	Robust	No Sarcopenic	1	<0.001	1	<0.001	2.48 (1.64; 3.76)	<0.001	2.43 (1.59; 3.69)	<0.001	NA		NA	
		Sarcopenic	2.32 (1.50; 3.60)		2.23 (1.43; 3.48)		1		1		NA		NA	
	Prefrail	No Sarcopenic	1	0.035	1	0.047	1	0.018	1	0.026	2.06 (1.22; 3.49)	0.006	1.93 (1.13; 3.31)	0.016
		Sarcopenic	2.47 (1.06; 5.73)		2.37 (1.01; 5.57)		1.77 (1.10; 2.83)		1.73 (1.07; 2.81)		1		1	
	Frail	No Sarcopenic	NA		NA		1	0.35	1	0.35	2.96 (0.41; 21.46)	0.28	3.42 (0.45; 26.00)	0.24
		Sarcopenic	NA		NA		2.50 (0.37; 17.08)		2.52 (0.36; 17.64)		1		1	
Frailty Trait Scale 5	No frail	No Sarcopenic	1	<0.001	1	<0.001	5.20 (3.26; 8.33)	<0.001	5.10 (3.18; 8.20)	<0.001	NA		NA	
		Sarcopenic	4.68 (2.91; 7.54)		4.57 (2.82; 7.40)		1		1		NA		NA	
	Frail	No Sarcopenic	NA		NA		1	0.62	1	0.46	1	0.49	1	0.75
		Sarcopenic	NA		NA		1.30 (0.46; 3.62)		1.49 (0.52; 4.26)		1.49 (0.47; 4.71)		1.21 (0.38; 3.84)	

In bold: p-value <0.05. Model 1: adjusted by age, sex, Charlson Index, and nutritional status. Model 2: adjusted by age, sex, Charlson Index, and cognitive status.

Supplementary Material 5. Risk of death within the same frailty status according to the presence or absence of sarcopenia and cognitive and nutritional status.

Frailty tool	Basal frailty state	Basal Sarcopenia State	Model 4		Model 5	
			HR (95% CI)	p-value	HR (95% CI)	p-value
Frailty Phenotype	Robust	No Sarcopenic to (%)	3.00 (0.71; 12.69)	0.14	2.99 (0.71; 12.69)	0.14
		Sarcopenic to (%)	1		1	
	Prefrail	No Sarcopenic to (%)	0.71 (0.38; 1.30)	0.26	0.68 (0.37; 1.26)	0.22
		Sarcopenic to (%)	1		1	
	Frail	No Sarcopenic to (%)	1.49 (0.48; 4.62)	0.49	1.47 (0.48; 4.56)	0.50
		Sarcopenic to (%)	1		1	
Frailty Trait Scale 5	No frail	No Sarcopenic to (%)	1.73 (0.78; 3.87)	0.18	1.68 (0.75; 3.76)	0.21
		Sarcopenic to (%)	1		1	
	Frail	No Sarcopenic to (%)	0.99 (0.43; 2.28)	0.98	0.96 (0.42; 2.22)	0.93
		Sarcopenic to (%)	1		1	

Model 1: adjusted by age, sex, Charlson Index, and nutritional status. Model 2: adjusted by age, sex, Charlson Index, and cognitive status.

Appendix 3: Supplementary material of Chapter 3.

Table S1. Toledo Study of Health Ageing Frailty Index.

	Rockwood Frailty Index	TSHA Frailty Index	Score
1.	Help bathing	Same	Yes =1, No =0
2.	Help dressing	Same	Yes =1, No =0
3.	Help getting in/out of chair and bed	Same	Yes =1, No =0
4.	Help walking a round house	Same	Yes =1, No =0
5.	Help eating	Same	Yes =1, No =0
6.	Help grooming	Same	Yes =1, No =0
7.	Help using toilet	Same	Yes =1, No =0
8.	Help up stairs	Same	Yes =1, No =0
9.	Help lifting 10 lbs	Same	Yes =1, No =0
10.	Help shopping	Same	Yes =1, No =0
11.	Help with housework	Same	Yes =1, No =0
12.	Help with meal preparations	Same	Yes =1, No =0
13.	Help taking medication	Same	Yes =1, No =0
14.	Help with finances	Same	Yes =1, No =0
15.	Lost more than 10 lbs in the last year	Same	Yes =1, No =0
16.	Selfrating of health	Same	Very poor =1, Poor =0.75, Regular =0.5, Good =0.25, Very good =0
17.	How health has changed in last year	Same	Much better =0, Better =0, Same =0, Worse =1, Much worse =1
18.	Stayed in bed at least half the day due to health (in las month)	During the past moth how often have yo gone or has visited the doctor for being	Any time =0, Once =0.5, Twice or more =1
19.	Cut down on usual activity (in the last month): Activity. Worst quintile of PASE	Activity (Physical Activity Scale for the Elderly, PASE)	Worst quintile =1, Rest =0
20.	Walk outside	Same	Any time =1, Once or twice=0.5, Three times or more =0
21.	Feel everything is an effort	Same	Most of time =1, Some time =0.5, Rarely =0
22.	Feel depressed	Feel depressed or anxious	Not =0, Moderately =0.5, Very =1
23.	Feel happy	Same	Very or pretty happy =0, neither happy nor unhappy =0.5, Very o rather unhappy =1
24.	Feel lonely	Can you talk about your problems with someone close at least your family and friends	Never or almost never =1, Sometimes =0.5, Mostly or always =0
25.	Have trouble getting going	Do you feel you can do anything you propose?	Never or almost never =1, Sometimes =0.5, Mostly or always =0
26.	High blood pressure	Same	Yes =1, Suspect =0.5, No =0
27.	Heart attack	Same	Yes =1, Suspect =0.5, No =0
28.	CHF	Same	Yes =1, Suspect =0.5, No =0
29.	Stroke	Same	Yes =1, Suspect =0.5, No =0
30.	Cancer	Same	Yes =1, Suspect =0.5, No =0
31.	Diabetes	Same	Yes =1, Suspect =0.5, No =0

32.	Arthritis	Same	Yes =1, Suspect =0.5, No =0
33.	Chronic lung disease	Same	Yes =1, Suspect =0.5, No =0
34.	MMSE	Same	<10= 1, 11-17=0.75, 18-20= 0.5, 21-24=0.25, >24 =0
35.	Peak Flow	Forced expiratory volume in 1 second (FEV) (litres)	<1.39
36.	Shoulder strength	Same	Men <10.84 =1, Women<6.4 =1, Other values =0
37.	BMI	Same	<18.5 or ≥ 30 =1, 25 -<30 =0.5, other values =0
38.	Grip strength	Same	Worst BMI quintil by sex =1, Other value =0
39.	Usual pace	Same	Worst height quintil by sex =1, Other value =0
40.	Rapid pace	Balance	1= side by side 0-9 sec or unable, other value =0

FEV: Forced expiratory volume. PASE: Physical Activity Scale for the Elderly.

Table S2. Frailty Trait Scale 5 (FTS5) scoring.

Score	BMI, kg/m ²		PASE	Gait Speed ^a	Grip strength, kg		Progressive Romberg		
					Women	Men	Score	Position Seconds	Seconds
0	23.01-26.99		>194	<2.45	>22	>29	0	Tandem	≤10
1	27-28.99	21.01-23	174.61-194	2.45-2.99	19.81-22	26.11-29	2.5	Tandem	3.01-9.99
2	29-30.99	19.01-21	155.21-174.6	3.00-3.54	17.61-19.8	23.21-26.1	5	Tandem	≤3
3	31-32.99	17.01-19	135.81-155.2	3.55-4.09	15.41-17.6	20.31-23.2		Semitandem	≤10
4	33-34.99	15.01-17	116.41-135.8	4.10-4.64	13.21-15.4	17.41-20.3	7.5	Semitandem	<10
5	35-36.99	13.01-15 ^b	97.01-116.4	4.65-5.19	11.01-13.2	14.51-17.4		Side by side	≤10
6	37-38.99	11.01-13 ^b	77.61-97	5.20-5.74	8.81-11.0	11.61-14.5	10	Side by side	<10
7	39-40.99	NA	58.21-77.6	5.75-6.29	6.61-8.8	8.71-11.6			
8	41-42.99	NA	38.81-58.2	6.30-6.84	4.41-6.6	5.81-8.7			
9	43-44.99	NA	19.41-38.8	6.85-7.39	2.21-4.4	2.91-5.8			
10	≤45	NA	0-19.4	≤7.4	0-2.2	0-2.9			

BMI: Body Mass Index. PASE: Physical Activity Scale for the Elderly.

FTS₅ includes all the items of the table (range 0-50), and frail participants are those with FTS₅ scores >25.

^a: Gait speed refers to time in accomplish 3-metres at usual pace in seconds.

^b: Model estimation.

Table S3. Results on the association between the interaction term between frailty and sarcopenia and the hospitalization-related outcomes, both at the cross-sectional level and at-follow up

	Cross-sectional analysis		At follow-up	
	Frailty measured with the Frailty Index	Frailty measured with the FTS5	Frailty measured with the Frailty Index	Frailty measured with the FTS5
Model 1				
<i>Having sarcopenia</i>				
OR on the probability of being admitted to hospital	1.318 (0.934 – 1.862)	1.395 (0.957 – 2.034)	1.365* (1.005 – 1.854)	1.292 (0.916 – 1.822)
Coeff on number of hospital admissions	0.258 (-0.443 – 0.959)	0.101 (-0.683 – 0.884)	-0.095 (-0.618 – 0.429)	-0.335 (-0.728 – 0.059)
Coeff on length of hospitalization	0.264 (-0.185 – 0.713)	0.007 (-0.453 – 0.466)	-0.125 (-0.487 – 0.238)	-0.122 (-0.527 – 0.282)
Coeff on hospitalization costs	-0.005 (-0.327 – 0.317)	0.043 (-0.341 – 0.427)	-0.096 (-0.377 – 0.185)	-0.177 (-0.429 – 0.075)
<i>Being frail</i>				
OR on the probability of being admitted to hospital	2.851** (1.333 – 6.101)	1.301 (0.520 – 3.256)	2.698** (1.298 – 5.608)	3.092** (1.454 – 6.575)
Coeff on number of hospital admissions	0.391 (-0.694 – 1.477)	0.467 (-0.311 – 1.245)	0.733** (0.241 – 1.226)	0.165 (-0.561 – 0.891)
Coeff on length of hospitalization	1.302*** (0.745 – 1.859)	0.891** (0.261 – 1.521)	0.985** (0.371 – 1.599)	0.337 (-0.510 – 1.184)
Coeff on hospitalization costs	0.380 (-0.240 – 1.001)	0.362 (-0.070 – 0.795)	0.259 (-0.207 – 0.726)	-0.045 (-0.579 – 0.490)
<i>Frail # with sarcopenia</i>				
OR on the probability of being admitted to hospital	0.930 (0.346 – 2.499)	1.026 (0.355 – 2.965)	0.693 (0.267 – 1.800)	0.505 (0.205 – 1.244)
Coeff on number of hospital admissions	-0.418 (-1.874 – 1.039)	-0.162 (-1.423 – 1.099)	-0.196 (-0.977 – 0.586)	0.476 (-0.460 – 1.412)
Coeff on length of hospitalization	-1.142 (-2.323 – 0.039)	-0.462 (-1.331 – 0.407)	-0.402 (-1.193 – 0.388)	-0.114 (-1.098 – 0.871)
Coeff on hospitalization costs	-0.380 (-1.210 – 0.449)	0.150 (-0.468 – 0.768)	-0.071 (-0.676 – 0.534)	0.279 (-0.390 – 0.948)
Model 2				
<i>Having sarcopenia</i>				
OR on the probability of being admitted to hospital	1.361 (0.928 – 1.994)	1.450 (0.960 – 2.189)	1.666** (1.178 – 2.356)	1.615* (1.108 – 2.355)
Coeff on number of hospital admissions	0.567 (-0.340 – 1.474)	0.401 (-0.579 – 1.380)	-0.100 (-0.737 – 0.536)	-0.340 (-0.795 – 0.115)
Coeff on length of hospitalization	0.314 (-0.229 – 0.857)	0.034 (-0.479 – 0.547)	-0.203 (-0.661 – 0.255)	-0.211 (-0.691 – 0.269)
Coeff on hospitalization costs	0.078 (-0.248 – 0.405)	0.111 (-0.271 – 0.493)	-0.085 (-0.374 – 0.203)	-0.158 (-0.425 – 0.109)
<i>Being frail</i>				
OR on the probability of being admitted to hospital	2.154 (0.963 – 4.821)	0.910 (0.348 – 2.379)	2.027 (0.937 – 4.389)	2.645* (1.129 – 6.200)
Coeff on number of hospital admissions	0.416 (-0.823 – 1.655)	0.363 (-0.778 – 1.504)	0.687* (0.135 – 1.240)	0.321 (-0.410 – 1.053)
Coeff on length of hospitalization	1.256*** (0.716 – 1.796)	0.945** (0.380 – 1.510)	0.918** (0.250 – 1.585)	0.348 (-0.538 – 1.235)

	Cross-sectional analysis		At follow-up	
	Frailty measured with the Frailty Index	Frailty measured with the FTS5	Frailty measured with the Frailty Index	Frailty measured with the FTS5
Coeff on hospitalization costs	0.379 (-0.205 – 0.962)	-0.258 (-0.648 – 0.131)	0.312 (-0.139 – 0.763)	0.100 (-0.410 – 0.610)
<i>Frail # with sarcopenia</i>				
OR on the probability of being admitted to hospital	1.025 (0.367 – 2.860)	1.256 (0.423 – 3.731)	0.739 (0.274 – 1.994)	0.525 (0.197 – 1.400)
Coeff on number of hospital admissions	-0.465 (-2.015 – 1.084)	-0.082 (-1.595 – 1.430)	-0.149 (-0.965 – 0.666)	0.334 (-0.565 – 1.233)
Coeff on length of hospitalization	-1.142 (2.316 – 0.032)	-0.578 (-1.423 – 0.266)	-0.344 (-1.164 – 0.475)	-0.124 (-1.146 – 0.897)
Coeff on hospitalization costs	-0.343 (-1.112 – 0.426)	0.094 (-0.490 – 0.677)	-0.060 (-0.626 – 0.507)	0.149 (-0.454 – 0.752)
Model 3				
<i>Having sarcopenia</i>				
OR on the probability of being admitted to hospital	1.199 (0.812 – 1.769)	1.265 (0.836 – 1.915)	1.477* (1.040 – 2.098)	1.452 (0.989 – 2.132)
Coeff on number of hospital admissions	0.401 (-0.437 – 1.240)	0.255 (-0.664 – 1.174)	-0.163 (-0.747 – 0.421)	-0.466 (-0.943 – 0.011)
Coeff on length of hospitalization	0.156 (-0.368 – 0.680)	-0.096 (-0.597 – 0.405)	-0.295 (-0.741 – 0.150)	-0.381 (-0.866 – 0.105)
Coeff on hospitalization costs	0.057 (-0.261 – 0.376)	0.073 (-0.248 – 0.394)	-0.131 (-0.398 – 0.135)	-0.219 (-0.498 – 0.059)
<i>Being frail</i>				
OR on the probability of being admitted to hospital	1.562 (0.700 – 3.488)	0.678 (0.255 – 1.806)	1.508 (0.701 – 3.246)	2.120 (0.931 – 4.828)
Coeff on number of hospital admissions	0.043 (-1.040 – 1.125)	0.143 (-0.773 – 1.059)	0.539* (0.026 – 1.051)	0.133 (-0.566 – 0.832)
Coeff on length of hospitalization	0.831** (0.300 – 1.363)	0.511* (0.055 – 0.966)	0.701* (0.108 – 1.294)	0.090 (-0.768 – 0.947)
Coeff on hospitalization costs	0.179 (-0.368 – 0.726)	-0.337 (-1.115 – 0.442)	0.201 (-0.242 – 0.644)	-0.012 (-0.531 – 0.506)
<i>Frail # with sarcopenia</i>				
OR on the probability of being admitted to hospital	1.266 (0.452 – 3.544)	1.592 (0.525 – 4.822)	0.870 (0.324 – 2.335)	0.595 (0.229 – 1.551)
Coeff on number of hospital admissions	-0.240 (-1.690 – 1.209)	0.052 (-1.261 – 1.366)	-0.061 (-0.825 – 0.703)	0.578 (-0.325 – 1.481)
Coeff on length of hospitalization	-0.821 (-1.637 – 1.363)	-0.231 (-1.000 – 0.538)	-0.197 (-0.959 – 0.565)	0.219 (-0.785 – 1.224)
Coeff on hospitalization costs	-0.287 (-0.999 – 0.426)	0.158 (-0.714 – 1.030)	0.044 (-0.497 – 0.586)	0.278 (-0.346 – 0.902)

95% confidence intervals in parentheses. *** p<0.001, ** p<0.01, * p<0.05

Model 1 includes the interaction term between frailty status, measured by the Frailty Index or the Frailty Trait Score, and sarcopenia, in addition to each of them individually as the only independent variables. Model 2 enters sociodemographic characteristics (age and its square and gender) in addition to the interaction term from Model 1. Model 3 adds to Model 2 the comorbidity severity of individual according to the Charlson Index, which is medium-low if the Charlson Index score is 1 or 2; and high if the Charlson Index score is three or higher. Moreover, polypharmacy is also included if the daily number of drugs the subject is taking is 5 or more.

Table S4. Results on the association between sarcopenia and the hospitalization-related outcomes, both at the cross-sectional level and at-follow up, only on the frail older adults.

	Cross-sectional analysis		At follow-up	
	Sarcopenia if frailty is measured via the Frailty Index	Sarcopenia if frailty is measured via the FTS5	Sarcopenia if frailty is measured via the Frailty Index	Sarcopenia if frailty is measured via the FTS5
Model 1				
OR on the probability of being admitted to hospital	1.226 (0.483 – 3.113)	1.431 (0.529 – 3.872)	0.946 (0.381 – 2.347)	0.652 (0.282 – 1.506)
Coeff on number of hospital admissions	-0.159 (-1.454 – 1.135)	-0.062 (-1.061 – 0.938)	-0.290 (-0.878 – 0.297)	0.142 (-0.714 – 0.997)
Coeff on length of hospitalization	0.878* (0.149 – 1.608)	-0.455 (-1.202 – 0.292)	-0.527 (-1.238 – 0.184)	-0.236 (-1.140 – 0.668)
Coeff on hospitalization costs	-0.385 (-1.160 – 0.390)	0.193 (-0.297 – 0.683)	-0.167 (-0.710 – 0.376)	0.102 (-0.522 – 0.727)
Model 2				
OR on the probability of being admitted to hospital	1.301 (0.455 – 3.717)	2.208 (0.747 – 6.529)	1.103 (0.397 – 3.065)	0.937 (0.372 – 2.365)
Coeff on number of hospital admissions	-0.244 (-1.442 – 0.955)	0.467 (-1.660 – 2.593)	-0.308 (-0.895 – 0.279)	0.083 (-0.824 – 0.991)
Coeff on length of hospitalization	0.862* (0.185 – 1.539)	-0.413 (-1.493 – 0.667)	-0.543 (-1.297 – 0.211)	-0.290 (-1.370 – 0.790)
Coeff on hospitalization costs	-0.502 (-1.266 – 0.263)	0.325 (-0.299 – 0.948)	-0.280 (-0.737 – 0.178)	-0.022 (-0.602 – 0.558)
Model 3				
OR on the probability of being admitted to hospital	1.551 (0.521 – 4.616)	2.497 (0.869 – 7.174)	1.091 (0.393 – 3.029)	0.933 (0.370 – 2.350)
Coeff on number of hospital admissions	-0.813 (-1.702 – 0.077)	0.470 (-0.971 – 1.911)	-0.271 (-0.779 – 0.236)	0.210 (-0.608 – 1.027)
Coeff on length of hospitalization	0.813* (0.124 – 1.503)	-0.331 (-1.251 – 0.590)	-0.437 (-1.023 – 0.149)	-0.149 (-1.053 – 0.755)
Coeff on hospitalization costs	-0.480 (-1.165 – 0.206)	0.293 (-0.258 – 0.844)	-0.234 (-0.661 – 0.193)	0.092 (-0.463 – 0.647)

95% confidence intervals in parentheses. *** p<0.001, ** p<0.01, * p<0.05.

Model 1 includes sarcopenia as the only independent variable. Model 2 enters sociodemographic characteristics (age and its square and gender) in addition to sarcopenia. Model 3 adds to Model 2 the comorbidity severity of individual according to the Charlson Index, which is medium-low if the Charlson Index score is 1 or 2; and high if the Charlson Index score is three or higher. Moreover, polypharmacy is also included if the daily number of drugs the subject is taking is 5 or more.

Table S5. Results on the association between frailty and the hospitalization-related outcomes, both at the cross-sectional level and at follow up, **only on the older adults with sarcopenia**

	Cross-sectional analysis		At follow-up	
	<u>Frailty measured with the Frailty Index</u>	<u>Frailty measured with the FTS5</u>	<u>Frailty measured with the Frailty Index</u>	<u>Frailty measured with the FTS5</u>
Model 1				
OR on the probability of being admitted to hospital	2.651** (1.408 – 4.991)	1.334 (0.782 – 2.277)	1.870* (1.013 – 3.454)	1.561 (0.951 – 2.560)
Coeff on number of hospital admissions	-0.026 (-1.002 – 0.950)	0.305 (-0.692 – 1.302)	0.538 (-0.072 – 1.147)	0.641* (0.048 – 1.234)
Coeff on length of hospitalization	0.160 (-0.483 – 0.802)	0.429 (-0.173 – 1.031)	0.583* (0.083 – 1.082)	0.223 (-0.280 – 0.727)
Coeff on hospitalization costs	0.001 (-0.553 – 0.553)	-0.212 (-0.656 – 0.231)	0.189 (-0.199 – 0.576)	0.234 (-0.170 – 0.638)
Model 2				
OR on the probability of being admitted to hospital	2.314* (1.175 – 4.559)	1.181 (0.682 – 2.045)	1.583 (0.820 – 3.056)	1.468 (0.864 – 2.493)
Coeff on number of hospital admissions	-0.019 (-1.077 – 1.040)	0.447 (-0.462 – 1.356)	0.684 (-0.004 – 1.371)	0.692* (0.145 – 1.240)
Coeff on length of hospitalization	0.117 (-0.619 – 0.853)	0.416 (-0.151 – 0.983)	0.637* (0.104 – 1.170)	0.237 (-0.231 – 0.705)
Coeff on hospitalization costs	0.126 (-0.381 – 0.634)	0.123* (0.013 – 0.233)	0.443* (0.101 – 0.786)	0.352* (0.016 – 0.688)
Model 3				
OR on the probability of being admitted to hospital	2.261* (1.129 – 4.526)	1.167 (0.659 – 2.065)	1.348 (0.688 – 2.642)	1.296 (0.743 – 2.261)
Coeff on number of hospital admissions	-0.131 (-1.047 – 0.785)	0.474 (-0.498 – 1.446)	0.600 (-0.144 – 1.344)	0.756** (0.224 – 1.289)
Coeff on length of hospitalization	0.112 (-0.570 – 0.795)	0.322 (-0.251 – 0.896)	0.587* (0.082 – 1.091)	0.274 (-0.202 – 0.751)
Coeff on hospitalization costs	0.051 (-0.423 – 0.526)	0.046 (-0.431 – 0.531)	0.442* (0.091 – 0.794)	0.375* (0.039 – 0.711)

95% confidence intervals in parentheses. *** p<0.001, ** p<0.01, * p<0.05

Model 1 includes frailty status, measured by the Frailty Index or the Frailty Trait Score, as the only independent variable. Model 2 enters sociodemographic characteristics (age and its square and gender) in addition to frailty. Model 3 adds to Model 2 the comorbidity severity of individual according to the Charlson Index, which is medium-low if the Charlson Index score is 1 or 2; and high if the Charlson Index score is three or higher. Moreover, polypharmacy is also included if the daily number of drugs the subject is taking is 5 or more.

Table S6. Cross-tabulations of sarcopenia and frailty according to the FTS5 and the FI.

		Sarcopenia		Total
		Without Sarcopenia	With Sarcopenia	
Frailty, according to the FTS5	No frail	1,027	190	1,217
	Frail	28	114	142
Frailty, according to the FI	No frail	1,025	251	1,276
	Frail	30	53	83
Total		1,055	304	1,359

FTS5: Frailty Trait Scale 5. FI: Frailty Index.