

DOUTORAMENTO
GERONTOLOGIA E GERIATRIA

New Tools for the Screening, Prevention and Mitigation of Frailty

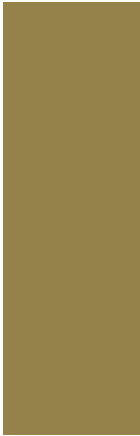
Luís Filipe Midão

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New Tools for the Screening, Prevention and Mitigation of Frailty

Luís Filipe da Silva Midão



LUÍS FILIPE DA SILVA MIDÃO

New Tools for the Screening, Prevention and Mitigation of Frailty

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Orientador:

Professor Doutor Elísio Costa

Professor Auxiliar

Faculdade de Farmácia da Universidade do Porto

Co-orientadoras:

Professora Doutora Constança Paúl

Professora Catedrática

Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto

Professora Doutora Mafalda Duarte

Professora Coordenadora

Instituto Superior de Saúde

*Foi o tempo que dedicaste à tua Rosa,
que a fez tão importante...*

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Midão L, Brochado P, Almada M, Duarte M, Paúl C, Costa E. **Frailty Status and Polypharmacy Predict All-Cause Mortality in Community Dwelling Older Adults in Europe**. Int J Environ Res Public Health. 2021 Mar 30;18(7):3580. doi: 10.3390/ijerph18073580. PMID: 33808273; PMCID: PMC8036295.

Manfredi G, Midão L, Paúl C, Cena C, Duarte M, Costa E. **Prevalence of frailty status among the European elderly population: Findings from the Survey of Health, Aging and Retirement in Europe**. Geriatr Gerontol Int. 2019 Aug;19(8):723-729. doi: 10.1111/ggi.13689. Epub 2019 May 30. PMID: 31146300.

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Resumo:

A transição demográfica para uma população envelhecida introduziu desafios complexos na área da saúde, particularmente a fragilidade, que é caracterizada por um declínio na capacidade fisiológica e uma maior suscetibilidade a eventos adversos de saúde. A fragilidade prejudica significativamente a qualidade de vida e impõe um fardo substancial aos sistemas de saúde, havendo, portanto, uma necessidade de estratégias eficazes de deteção, prevenção e mitigação.

Este trabalho foi motivado pelo compromisso com uma compreensão abrangente da questão multifacetada da fragilidade dentro da população mais velha, visando avaliar a sua prevalência na Europa, a sua associação com a polimedicação e mortalidade, os seus fatores de risco e impactos subsequentes. Foi também motivada pela ambição de melhorar as práticas clínicas através da identificação de biomarcadores de fragilidade relevantes em pacientes com doença renal crónica, um grupo particularmente afetado por esta síndrome. Finalmente, este projeto visou adaptar culturalmente e validar uma ferramenta de avaliação de fragilidade amplamente reconhecida, o Indicador de Fragilidade de Groningen, para a população europeia portuguesa e integrar a sua aplicação numa app de mHealth, analisando a sua validade e fiabilidade, com o objetivo de facilitar intervenções oportunas e personalizadas.

A metodologia de pesquisa foi estruturada para abordar a complexidade da fragilidade de uma maneira multidimensional. Um estudo de prevalência foi conduzido em 18 países europeus utilizando a base de dados SHARE, empregando uma versão operacionalizada do Fenótipo de Fragilidade de Fried, para estabelecer uma base para as métricas de fragilidade. Uma análise longitudinal foi realizada para explorar a influência da polimedicação na mortalidade em idosos pré-frágeis e frágeis. Uma revisão sistemática foi conduzida seguindo o Manual da Cochrane para Revisões Sistemáticas de Intervenções para consolidar as evidências sobre biomarcadores em pacientes frágeis e pré-frágeis com doença renal crónica. Finalmente, uma análise psicométrica foi realizada para validar o Indicador de Fragilidade de Groningen em português europeu e testar a sua validade e fiabilidade da FRAILSURVEY, uma inovadora aplicação de saúde de fragilidade.

Os resultados indicaram prevalência de pré-fragilidade de 42.9% e de fragilidade de 7.7%, aumentando com a idade avançada e sendo mais comum entre as mulheres. A inter-relação da polimedicação com a fragilidade emergiu como um fator crítico a influenciar a mortalidade, especialmente em homens idosos. A revisão sistemática destacou a heterogeneidade nas associações de biomarcadores com a fragilidade entre pacientes com DRC, revelando a natureza multifatorial da condição. A adaptação do

Indicador de Fragilidade de Groningen ao contexto português europeu demonstrou propriedades psicométricas fortes, e a sua implementação na app FRAILSURVEY foi validada, destacando o potencial da app para utilização clínica generalizada.

Este trabalho contribuiu para o conhecimento da epidemiologia da fragilidade e fatores inter-relacionados como a polimedicação. A adaptação cultural bem-sucedida e validação de uma ferramenta de avaliação de fragilidade, juntamente com a sua integração em tecnologia de saúde, representam um avanço significativo nas estratégias de deteção precoce e tratamento personalizado. Este trabalho estabelece uma base sólida para a continuação da investigação e o desenvolvimento de intervenções destinadas a atenuar o impacto da fragilidade, melhorando assim os cuidados e a qualidade de vida da população idosa em toda a Europa.

Palavras-chave:

Fragilidade, mHealth, Indicador de Fragilidade de Groningen, FRAILSURVEY.

Abstract:

The demographic shift towards an ageing population has introduced complex healthcare challenges, particularly frailty, which is characterised by a decline in physiological capacity and increased susceptibility to adverse health events. Frailty significantly impairs the quality of life and imposes a substantial burden on healthcare systems, therefore, there is a need for effective screening, prevention, and mitigation strategies.

This research was driven by a commitment to a thorough comprehension of the multifaceted issue of frailty within the ageing population, aiming to evaluate its prevalence in Europe, its association with polypharmacy and mortality, its risk factors, and subsequent impacts. It was also driven by the ambition to enhance clinical practices through the identification of relevant biomarkers in chronic kidney disease patients, a group notably burdened by frailty. Finally, this project aimed to culturally adapt and validate a widely recognised frailty assessment tool, the Groningen Frailty Indicator, for the European Portuguese population and to pioneer its application in a mHealth app, while analysing its validity and reliability, aiming to thereby facilitate timely and customised interventions.

The research methodology was structured to address the complexity of frailty in a multi-dimensional manner. An extensive prevalence study was conducted across 18 European countries using the SHARE database, using an operationalized version of Fried's Phenotype criteria, to establish a baseline for frailty metrics. A longitudinal analysis was performed to explore the influence of polypharmacy on mortality rates in pre-frail and frail older adults. A systematic review was conducted following the Cochrane Handbook for Systematic Reviews of Interventions to consolidate the evidence on biomarkers in frail and pre-frail CKD patients. Finally, a psychometric analysis was undertaken to validate the Groningen Frailty Indicator in European Portuguese and to test its reliability within the innovative FRAILSURVEY health application.

The results indicated a prevalence of pre-frailty of 42.9% and of frailty of 7.7%, increasing with advanced age and being more common among women. The interrelation of polypharmacy with frailty emerged as a critical factor influencing mortality, especially in older men. The systematic review highlighted the heterogeneity in biomarker associations with frailty among CKD patients, revealing the multifactorial nature of the condition. The adaptation of the Groningen Frailty Indicator to the European Portuguese context demonstrated strong psychometric properties, and its deployment in the FRAILSURVEY app was validated, showcasing the app's potential for widespread clinical utilisation.

The thesis contributes to the field by advancing the knowledge of frailty epidemiology and interrelated factors such as polypharmacy. The successful cultural adaptation and validation of a frailty assessment tool, coupled with its integration into health technology, represent a leap forward in early detection and personalised treatment strategies. This work lays a solid foundation for ongoing research and the development of interventions aimed at ameliorating frailty's impact, thereby enhancing the care and quality of life for the ageing population across Europe.

Keywords:

Frailty, mHealth, Groningen Frailty Indicator, FRAILSURVEY

Abbreviature list

AMD	Age-Related Macular Degeneration
CAD	Coronary artery disease
CFS	<i>Clinical Frailty Scale</i>
CHF	Congestive heart failure
CKD	Chronic kidney disease
COPD	Chronic Obstructive Pulmonary Disease
CVD	Cardiovascular diseases
EFS	<i>Edmonton Frail Scale</i>
EHRs	Electronic health records
FI	<i>Frailty Index</i>
GFI	<i>Groningen Frailty Indicator</i>
GFR	Glomerular filtration rate
GH	Growth hormone
HPA	Hypothalamic-pituitary-adrenal
ICC	Intraclass Correlation Coefficient
IGF-1	Insulin-like growth factor-1
IL-6	Interleukin-6
IoT	Internet of Things
NCDs	Non-communicable diseases
SHARE	Survey of Health, Ageing and Retirement in Europe
TFI	<i>Tilburg Frailty Indicator</i>
TNF- α	Tumour necrosis factor-alpha
UV	Ultraviolet

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CHAPTER I

Introduction

Introduction

1 Population Ageing

In the 21st century, we are witnessing a profound shift in the world's population dynamics, one that is reshaping communities, economies, and governance globally. This shift is the ageing of the population. Thanks to significant improvements in healthcare, better standards of living, and lower birth rates, people are living longer than ever before. With this longevity comes a host of complex issues and prospects that call for a deep and broad understanding of how this ageing trend affects us all [1-3].

At the core of population ageing is the inexorable increase in both the absolute and relative numbers of older adults, whom the World Health Organisation classifies as those aged 65 years and over. This demographic evolution is a global phenomenon that echoes through diverse continents and surpasses cultural, economic, and political divides. A confluence of factors underpins this profound change [4, 5]. Advances in medical science and enhancements in public health measures have prolonged human lifespans, enabling a greater number of individuals to achieve a longer life expectancy. Concurrently, there has been a reduction in birth rates across numerous global regions, resulting in a demographic structure where the population of older individuals exceeds that of the younger generation [6, 7].

Population ageing has significant implications across sectors. One of the most profound impacts of population ageing is felt in economies [8, 9]. As the workforce ages and retires, concerns arise regarding labour shortages, reduced productivity, and increased pressure on pension systems [10, 11]. Moreover, the balance between the active working-age population and retirees can strain social safety nets, placing fiscal burdens on governments and demanding reforms to ensure sustainable welfare systems [12, 13]. Ageing populations also present complex healthcare challenges. Older adults have higher rates of chronic diseases and health conditions, increasing demands on healthcare systems [14-16]. Innovative strategies for older care and geriatric medicine are becoming essential to ensure the quality of life and comprehensive care for the older population [17-19]. Governments and policymakers deal with these shifting dynamics, striving to balance addressing the unique needs of older citizens and fostering economic growth and social cohesion. Reforms span retirement ages, pension systems, healthcare models, and labour policies [20-22].

As individuals progress through the various stages of life, the psychosocial aspects of ageing play a pivotal role in shaping their experiences and well-being [23, 24]. Ageing

often brings about cognitive changes, with shifts in memory and processing speed. However, it is essential to recognise that ageing also confers wisdom and a wealth of life experience. Emotional well-being varies among older adults, with some enjoying heightened emotional stability and life satisfaction while others may contend with challenges like depression and anxiety [25, 26]. Maintaining robust social connections is vital to preserving mental and emotional health, as loneliness and social isolation can adversely affect the older. The dynamic nature of family roles and the loss of loved ones can also impact the psychological landscape of older individuals [27-29].

1.1 Dynamics of a Greying World

1.1.1 Global Perspective

Worldwide, trends and statistics on ageing underscore a global demographic shift with far-reaching implications. As life expectancies increase and birth rates decline, the proportion of older individuals worldwide is rising [1, 8]. In 2020, the United Nations estimated that around 9.3% of the world's population was aged 65 and over. Compared with 2021, it's estimated that by 2050, the global population of older adults will nearly double, reaching an unprecedented 1.6 billion individuals. In 2100, there will be 3.2 billion older adults. In numerical terms, this means that by the end of the century, the older population will surpass the number of children under 15 for the first time in history [30]. This phenomenon is accentuated in regions with advanced economies, where the share of older citizens is notably higher [31]. The rise in old-age dependency ratios, indicative of a shrinking working-age population relative to older people, poses challenges for social welfare systems and economic sustainability [32, 33].

Contributing to the global ageing phenomenon is a complex interplay of factors that transcend geographical boundaries [34]. Advances in healthcare and medical technologies have led to extended life expectancies, enabling individuals to live longer and healthier lives [35]. Coupled with declining birth rates in many countries, these factors contribute to the demographic shift [36]. Urbanisation and changing societal norms have altered family structures, often leading to smaller family sizes and impacting intergenerational support systems [37]. The "demographic transition," where countries move from high birth and death rates to low birth and death rates, is also instrumental in driving ageing trends on a global scale [38, 39]. Additionally, economic development and improved living conditions have played a role in lowering birth rates and enhancing

healthcare access, further shaping the trajectory of ageing populations worldwide [36, 40].

1.1.2 European Dynamics

Trends and statistics on ageing in Europe underscore the profound demographic transformation across the continent. With a steady increase in the proportion of older individuals, Europe is facing a significant shift in its population composition. Eurostat data reveals that in 2020, approximately one-fifth of the European Union's population was aged 65 and over, indicative of an ageing trend projected to persist [41]. This trend is manifested in rising old-age dependency ratios, reflecting the challenge of maintaining support structures for an ageing population [42]. It is essential to acknowledge the variability among European countries, as demographic dynamics differ due to factors such as birth rates and migration patterns. In facing the future, Europe must address the implications of these trends, developing comprehensive strategies to navigate the social, economic, and healthcare consequences of its ageing population [43].

Contributing to the ageing phenomenon in Europe are multifaceted factors shaping the demographic landscape, such as the post-World War II baby boomers reaching retirement age, further accentuating the demographic shift. Migration patterns can also influence ageing trends within and outside Europe by altering population distributions [44]. Moreover, regions with low birth rates, such as Southern and Eastern Europe, are experiencing more pronounced ageing trends in [42]. Projections and implications of the ageing population in Europe highlight the urgency of strategic planning to address the forthcoming demographic challenges. Projections indicate a substantial increase in the proportion of older individuals by 2050, with approximately one-third of the population potentially aged 65 and over [45].

1.1.3 Portuguese Scenario

Portugal, like many European nations, is undergoing its demographic transformation. Statistics Portugal reports that the proportion of older individuals in the population has been steadily increasing. Based on the 2011 census, 19.0% of Portugal's population was aged 65 or older. Notably, the 2021 census recorded a significant increase to 23.4%. Projections suggest that this percentage will further rise in the years ahead. Estimates anticipate that by 2080, the proportion of individuals aged 65 and above will surge to 37.5% of the entire population, leading to a profound shift in the country's age structure

[46-49]. Several factors contribute to Portugal's ageing population, such as the migration of younger individuals seeking better economic opportunities, exacerbating the ageing trend [50]. Family dynamics are also transforming. Traditionally, Portuguese families relied on intergenerational support. Still, as younger generations pursue opportunities beyond borders, the responsibility of older care often falls to alternative solutions, further impacting societal norms and family structures [51]. This places Portugal among the countries with the highest projected growth rates in the older population within the European Union [42].

1.2 Challenges and Opportunities of an Ageing Population

The challenges and opportunities posed by population ageing present a complex and multifaceted scenario for societies worldwide. As populations, organisations face the challenges of adapting social welfare systems, healthcare services, and labour markets to accommodate a larger older demography [36, 39, 52].

1.2.1 Challenges

The challenges an ageing population poses are multifaceted and require careful consideration across various sectors, such as healthcare, economics, and social dynamics. Addressing these challenges requires a collaborative effort involving governments, healthcare systems, businesses, and communities to ensure people's dignified and fulfilling quality of life as they age [53, 54].

One issue is the escalating pressure on health and social welfare frameworks. As more of the population enters old age, there is an increased demand for healthcare services, long-term care facilities, and support for chronic conditions. This can lead to resource shortages, higher healthcare costs, and a need for innovative approaches to ensure accessible and quality care for older adults [55-57]. Economic implications are another critical aspect. A shrinking workforce due to ageing can potentially lead to reduced productivity and economic growth [9, 33]. The dependency ratio, which measures the number of non-working individuals (typically the older and children) to the working-age population, can rise significantly. This places pressure on pension systems, social security, and taxation policies. Governments and industries must adapt to this changing demographic landscape by implementing policies encouraging older individuals to remain in the workforce longer while addressing potential ageism and ensuring fair employment opportunities [58, 59]. Furthermore, the ageing population

challenges the traditional family structure and intergenerational relationships. With smaller family sizes and geographical dispersion, the caregiving burden often falls on a limited number of family members. Balancing work, caregiving responsibilities and personal well-being becomes intricate. Loneliness and social isolation among the older adults are also concerns that need attention. Community programs and technological solutions can play a role in alleviating these challenges by fostering social connections and providing accessible services [12, 20, 60].

1.2.2 Opportunities

Population ageing offers a range of promising opportunities that hold the potential to reshape societal dynamics and create positive impacts on various fronts [1, 9, 61]. The older generation's considerable experience, knowledge, and wisdom present an invaluable resource for society. This wealth of expertise can be tapped into for fostering innovation, facilitating mentorship programs, and promoting intergenerational knowledge exchange, leading to a more enriched and culturally vibrant community [62-64]. The concept of productive ageing emerges as a pivotal prospect. Numerous individuals maintain their physical and mental agility well into their senior years. Harnessing their skills through flexible work arrangements, volunteering initiatives, and ongoing education enhances overall productivity and expands the economy. This reinforces that age is not a barrier to meaningful and impactful contributions [65].

The escalating demand for services due to an ageing population catalyses innovative advancements within the healthcare system. Technologies such as telemedicine, mobile applications, and wearable health devices stand to revolutionise healthcare delivery, tailored to the needs of older adults and simultaneously alleviating the pressures on healthcare systems [66, 67]. Moreover, the silver economy, encompassing goods and services tailored to older consumers, offers a growing market that fuels economic growth and job opportunities [68].

1.2.3 A Holistic Approach

The challenges and opportunities an ageing population presents are paramount in shaping the future of societies worldwide. This demographic shift demands a comprehensive and all-encompassing approach that transcends traditional boundaries and involves various stakeholders, including governments, policymakers, healthcare providers, industries, and communities. The goal is to address the multifaceted

challenges effectively while harnessing the immense potential and contributions that older individuals can offer [1, 34, 69].

One of the primary facets of this holistic approach involves rethinking and adapting social safety nets. As the demographic composition changes, social welfare systems must evolve to accommodate the evolving needs of older citizens. This entails ensuring that pensions, healthcare services, and social support mechanisms are sustainable and tailored to provide older people with a dignified and fulfilling life. This adjustment is crucial to mitigate economic disparities and promote social equity among different age groups [58, 59].

Furthermore, transforming healthcare systems is imperative in meeting the healthcare demands of an ageing population. Healthcare providers and institutions should shift their focus from primarily addressing acute conditions to adopting a more comprehensive, patient-centred approach that accounts for chronic diseases, senior care, and preventive measures [70-72]. Integrating technology and telemedicine into healthcare delivery can enhance access and convenience, particularly for older individuals in remote or underserved areas [73].

Promoting intergenerational connections is another critical aspect of this holistic approach. Encouraging meaningful interactions between older and younger generations fosters mutual understanding, reduces age-related stereotypes, and creates a supportive environment. This intergenerational exchange of knowledge and experiences benefits both groups and can lead to innovative solutions to common challenges [62-64].

Age-inclusive policies are central to this approach. Governments and institutions should actively promote and enforce policies that combat ageism, discrimination, and social exclusion [74]. Creating age-friendly environments, from accessible public spaces to age-appropriate educational opportunities, ensures that older individuals remain active, engaged, and valued members of society [75].

Population ageing is, indeed, a transformative force that necessitates proactive responses. Rather than viewing ageing solely as a demographic challenge, societies should recognise it as a source of diverse strengths and experiences. Older populations are a source of wisdom, talents, and skills that can significantly contribute to communities' well-being and economies' vitality. By embracing this holistic approach, societies can pave the way for a future where older individuals are supported in their golden years and recognised as integral contributors to their societies' social, cultural, and economic aspects.

2 Ageing, Chronic Conditions, Age-Related Diseases, and Geriatric Syndromes

The global demographic landscape is profoundly transforming, with an ever-expanding ageing population commanding increasing attention in healthcare [57]. Chronic conditions, age-related diseases, and geriatric syndromes are intricately interconnected, as ageing is not a solitary process but unfolds within an individual's health and medical history. These conditions often coexist, complicating healthcare management [76, 77]. Comorbidities further exacerbate this complexity, and polypharmacy is frequently employed to address these intricate health needs [78].

To comprehensively address the healthcare needs of an ageing population, it is imperative to understand the intricate relationships between ageing, chronic conditions, age-related diseases, geriatric syndromes, comorbidities, and polypharmacy. By exploring these themes in depth, we can gain insights into an ageing demographic's challenges, develop strategies to optimise care and pave the way for future innovations and advancements in geriatric medicine.

2.1 Ageing and Its Physiological Changes

Ageing is characterised by the gradual and inevitable passage of time, leading to physiological changes in the human body. These changes affect nearly every organ and system and contribute to the complexities of ageing. Understanding the natural ageing process is essential for healthcare providers and researchers to address the unique healthcare needs of older adults [79-81]. The natural ageing process begins from birth and continues throughout an individual's lifespan. It is influenced by genetic factors, lifestyle choices, and environmental exposures, making it a highly individualised journey whose rate and impact vary among individuals [82].

Researchers have identified nine significant cellular and molecular factors in the ageing process. These factors include the accumulation of DNA damage, shortened telomeres, epigenetic modifications, disrupted proteostasis, impaired nutrient sensing, dysfunctional mitochondria (leading to oxidative stress), cellular senescence, depletion of stem cells, and compromised intercellular communication. These events contribute to a persistent, low-level inflammatory condition called "inflammageing" [83, 84]. In unhealthy ageing, the body struggles to counteract this inflammatory burden effectively. In contrast, healthy ageing is associated with a reduced frequency of inflammatory

responses and more efficient anti-inflammatory mechanisms. This imbalance towards chronic inflammation ultimately leads to inadequate tissue repair and tissue degeneration [85, 86].

Ageing has a profound impact on various organ systems within the human body. The cardiovascular system, for instance, undergoes noticeable changes as arterial walls stiffen and atherosclerosis becomes more common, raising the risk of hypertension, heart disease, and strokes [85]. Similarly, the musculoskeletal system experiences significant alterations, marked by a decline in muscle mass and bone density, contributing to conditions like sarcopenia and osteoporosis, heightening the risk of fractures and falls [87].

The nervous system is not immune to the effects of ageing, with structural and functional changes leading to neuronal loss, alterations in neurotransmitter function, and reduced brain volume. These changes can result in cognitive decline and increase vulnerability to neurodegenerative diseases such as Alzheimer's and Parkinson's [88]. Age-related hormonal shifts in the endocrine system are central to the ageing process. Declines in sex hormones like oestrogen and testosterone can impact reproductive health, bone density, and muscle mass. At the same time, alterations in insulin sensitivity can contribute to the development of type 2 diabetes [89].

The immune system also changes with age, resulting in a less robust immune response known as immunosenescence, a key player in cancer development [90]. Moreover, the respiratory system experiences changes in lung elasticity and function, with reduced lung capacity and respiratory muscle strength, potentially decreasing tolerance for physical activity [91]. Age-related alterations also affect the gastrointestinal system, reducing digestive enzyme production and slowing transit time, potentially causing digestive discomfort, and affecting nutrient absorption [92]. Finally, the renal system undergoes structural and functional changes, including a decreased glomerular filtration rate. This can impact the kidney's ability to efficiently filter waste products, potentially leading to kidney diseases [93].

2.2 Chronic Conditions in Older Adults

As individuals age, they become more susceptible to developing chronic conditions, which are long-term health issues that persist over an extended period. These conditions significantly impact the health and well-being of older adults and pose unique challenges to healthcare systems and providers [78, 94].

Chronic conditions, also known as chronic diseases or non-communicable diseases (NCDs), are health conditions that typically progress slowly and persist over a prolonged period. Unlike acute illnesses, which have a sudden onset and often resolve relatively quickly, chronic conditions endure and often require ongoing management and care. These conditions can affect multiple organ systems and lead to various complications and disabilities [95].

Chronic conditions exhibit several shared characteristics. They are characterised by their extended duration, often persisting for years or even a lifetime, with no spontaneous resolution. These conditions progress slowly, frequently worsening over time if not effectively managed. Their causes are typically complex, involving many factors such as genetic predisposition, lifestyle elements (like diet, physical activity, and smoking), and environmental influences (including pollution and occupational exposures). Chronic conditions can profoundly affect an individual's quality of life, limiting physical and cognitive function, impinging on daily activities, and causing pain, discomfort, or disability. Managing these conditions necessitates long-term medical care, medication oversight, lifestyle adjustments, and regular monitoring by healthcare professionals [96, 97]. Several chronic diseases are particularly prevalent among older adults.

2.2.1 Cardiovascular diseases

Cardiovascular diseases (CVD) are the leading cause of morbidity and mortality among people aged 65 and older, and their incidence tends to rise as individuals grow older [98, 99]. CVD is responsible for 82% of deaths in individuals aged 65 and above [100]. The occurrence of conditions such as hypertension, congestive heart failure (CHF), coronary artery disease (CAD), arrhythmias, atrial fibrillation, peripheral arterial disease, valvular heart disease, and stroke is around 40% in individuals aged 40 to 59 years. Still, it significantly escalates to 79-86% in those aged 80 and above [101].

Ageing significantly influences the physiology of the cardiovascular system, rendering individuals more susceptible to a spectrum of cardiovascular diseases. One of the principal alterations in ageing cardiovascular physiology is increasing arterial stiffness. As the years advance, arteries lose their flexibility, compromising their elasticity. Consequently, this leads to an elevation in systolic blood pressure and a widened pulse pressure, imposing added strain on the heart and heightening the likelihood of hypertension [102, 103]. Furthermore, ageing is a principal contributor to the genesis and progression of atherosclerosis. With the passage of time, fatty deposits, cholesterol accumulations, and calcium build up within arteries. These plaque formations narrow the

arterial routes, culminating in diminished blood flow and an elevated risk of heart attacks and strokes [104].

Another notable effect of ageing is alterations in the heart's structural composition. The left ventricle may undergo thickening, while the right ventricle may dilate. These structural modifications can impede cardiac function, potentially contributing to heart failure, a condition characterised by the heart's inability to pump blood efficiently. Moreover, the capacity of the heart to pump blood progressively diminishes with age. The maximum heart rate attainable during physical exertion declines, and the heart becomes less responsive to variations in demand. Consequently, it affects the body's ability to respond to physical stress [85, 105]. Ageing also engenders changes in heart valves, such as calcification and stiffening, which can compromise valve function and lead to conditions like aortic stenosis or mitral regurgitation [106].

2.2.2 Diabetes

Diabetes rates among adults aged 65 and older may fluctuate depending on geographic location and demographic factors, yet it's well-established that diabetes becomes increasingly prevalent as individuals age. In the United States, approximately 33% of adults aged 65 or older are affected by diabetes. It is among the non-communicable diseases that pose significant global public health challenges and economic burdens. Projections indicate that by 2030, diabetes will become the 7th most common cause of death worldwide [107, 108].

Ageing affects the physiology of metabolic systems, significantly elevating the susceptibility to diabetes and other metabolic disorders among older adults. One of the primary physiological transformations associated with advancing age is the development of insulin resistance [109]. As individuals age, their cells become less responsive to insulin, a critical hormone responsible for regulating blood sugar levels. This insensitivity can result in elevated blood glucose concentrations, a hallmark feature of type 2 diabetes. Moreover, age-related changes in body composition play a crucial role in exacerbating insulin resistance [39, 108, 109]. Older individuals often experience a decrease in muscle mass and an increase in fat mass, which can further contribute to metabolic dysfunction. This intricate interplay between age-related physiological alterations and metabolic health underscores the heightened risk of diabetes with ageing [110, 111].

Genetic factors also wield significant influence over the physiology of metabolic disorders in the ageing population. Family history and genetic predispositions can

significantly elevate an individual's vulnerability to type 2 diabetes. These genetic influences interact with lifestyle choices, including diet and physical activity, to determine an individual's likelihood of developing these metabolic disorders [112]. Furthermore, the ageing process often coincides with the cumulative impact of environmental stressors, such as unhealthy dietary habits and sedentary lifestyles. These factors, experienced over many years, can further amplify the risk of metabolic disorders in older adults [113].

2.2.3 Musculoskeletal Diseases

The musculoskeletal system physiology is also impacted by ageing. Musculoskeletal conditions are prevalent among the older population. A systematic critical literature review found that back pain had the highest reported prevalence at 29%, followed by osteoarthritis and osteoporosis at 17%. Rheumatoid arthritis accounted for 8% of cases, while ankle/foot pain and knee pain each had an 8% prevalence. Hip pain stood at 5%, and shoulder and hand/wrist pain at 5% and 3%, respectively. Elbow pain had the lowest reported prevalence at 3% [87, 114].

One of the primary physiological changes associated with ageing is the gradual loss of bone density, a condition known as osteoporosis. Over time, bones become less dense and more porous, making them fragile and susceptible to fractures, particularly in the hips, spine, and wrists. This decline in bone density is influenced by hormonal changes, including a decrease in oestrogen in women during menopause and a reduction in testosterone in men, both of which contribute to diminished bone health [115, 116]. Additionally, genetic factors and lifestyle choices, such as inadequate calcium intake and lack of weight-bearing exercise, play pivotal roles in the development of osteoporosis in older adults [117]. Another musculoskeletal disorder in ageing individuals is osteoarthritis, characterised by the deterioration of joint cartilage. The physiological changes in ageing joints, including wear and tear and decreased production of synovial fluid, contribute to the development of osteoarthritis [118]. This condition often affects weight-bearing joints such as the knees, hips, and spine, resulting in pain, stiffness, and reduced mobility. Genetic predispositions can also play a role in osteoarthritis, with family history influencing an individual's risk [118].

Ageing individuals may also experience back pain, which can be attributed to age-related changes in the spinal discs, muscles, and ligaments. Discs lose some of their water content and become less flexible, reducing spinal flexibility, and increasing susceptibility to disc herniation. Additionally, changes in the musculature and ligaments of the back can contribute to discomfort and pain. While back pain is often multifactorial,

it becomes more prevalent with age, impacting the overall quality of life and mobility of older adults [119, 120].

2.2.4 Chronic Obstructive Pulmonary Disease

Ageing impacts the respiratory system, and one of the prominent age-related changes in respiratory physiology is the reduction in lung function. As individuals advance in age, their lung elasticity diminishes, and lung compliance may decrease, resulting in a reduction in lung capacity and the ability to exhale fully. These physiological shifts can lead to reduced efficiency in oxygen exchange and an elevated vulnerability to respiratory infections and conditions [121, 122].

Environmental factors and lifestyle choices also intersect with ageing-related changes in the respiratory system, amplifying the risk of respiratory diseases. Throughout a lifetime, exposure to environmental stressors, such as smoking or air pollutants, can significantly impact lung health. Over the years, cumulative damage from these exposures has contributed to developing chronic respiratory conditions, such as Chronic Obstructive Pulmonary Disease (COPD) [123, 124]. Additionally, lifestyle factors like physical inactivity and suboptimal nutrition can exacerbate respiratory issues, reducing overall lung resilience [91, 122].

Chronic Obstructive Pulmonary Disease, encompassing conditions like chronic bronchitis and emphysema, is a prevalent respiratory disease among older adults. It was reported that the prevalence of COPD among older adults is around 9% [125, 126]. Smoking is a primary risk factor for COPD, with cumulative exposure over the years leading to lung damage and airway obstruction. The pathophysiology of COPD involves chronic inflammation of the airways and the destruction of lung tissue. This condition not only diminishes lung function but also affects the overall quality of life for older individuals [127]. Addressing respiratory disorders in the ageing population requires a comprehensive approach encompassing medical treatment, lifestyle modifications, and preventive measures.

2.2.5 Chronic Kidney Disease

Kidney function is intricately tied to ageing, undergoing notable physiological changes as individuals age. These age-related alterations in kidney physiology can significantly affect overall health and well-being [93, 128]. One of the most prominent changes is a decline in renal mass and the number of functional nephrons, the basic filtration units of

the kidney. This loss of nephrons is a natural part of ageing and results in a decreased ability of the kidneys to filter and excrete waste products effectively. Consequently, patients may experience a gradual decline in glomerular filtration rate (GFR), which measures the kidney's filtering capacity. This reduced GFR can affect the clearance of drugs and waste products from the body, potentially necessitating medication dosage adjustments and increasing the risk of toxin accumulation [93, 129].

ESKD patients undergoing haemodialysis often experience an accelerated ageing process marked by telomere shortening, a key indicator of cellular aging, and an increased accumulation of advanced glycation end products, which alter cellular functions and increase oxidative stress [130, 131]. Chronic inflammation, a hallmark of both ESKD and ageing, is exacerbated by the dialysis process and contributes significantly to this phenomenon [132]. Clinically, accelerated aging in haemodialysis patients is evident through early onset of cardiovascular complications like arterial stiffness, musculoskeletal changes such as bone loss and muscle wasting, and an increased risk of cognitive decline [133].

Age-related changes in renal blood flow and hormonal regulation are pivotal in kidney function. Reduced renal blood flow can impact the kidneys' ability to filter blood and regulate fluid and electrolyte balance. Additionally, alterations in the renin-angiotensin-aldosterone system, a crucial hormonal pathway for blood pressure regulation, can lead to conditions like hypertension in older individuals. This, in turn, can exacerbate kidney damage and elevate the likelihood of developing chronic kidney disease (CKD) [134, 135]. The ageing kidney experiences structural changes in the form of glomerulosclerosis, tubulointerstitial fibrosis, and the accumulation of lipofuscin, a pigment associated with cellular ageing. These structural alterations can impair the kidneys' ability to concentrate urine and regulate electrolyte balance, potentially leading to issues like dehydration and electrolyte imbalances [93, 128, 136]. Moreover, the presence of these structural changes is a risk factor for the development and progression of CKD. This condition becomes more prevalent in the older population, affecting two in every five older individuals [137].

2.3 Age-Related Diseases

Age-related diseases constitute a significant component of the healthcare landscape for older adults. These conditions are characterised by their association with ageing and often result from complex interactions between genetic, environmental, and lifestyle factors [76, 109].

2.3.1 Neurodegenerative diseases

Advancing age is one of the primary risk factors for the development of neurodegenerative diseases. These diseases can profoundly impact cognitive functions such as memory, attention, language, and problem-solving abilities. Indeed, in a European study, the prevalence rates for cognitive impairment across different domains were as follows: 13.0% for temporal orientation, 24.8% for numeracy, 27.6% for verbal fluency, and 50.5% for memory [138, 139].

The physiological processes underlying neurodegeneration in ageing individuals are multifaceted and involve intricate cellular and molecular mechanisms. One of the hallmark features of neurodegenerative diseases is the accumulation of abnormal protein aggregates within the brain [140, 141]. In conditions like Alzheimer's disease, beta-amyloid plaques and tau tangles progressively accumulate, disrupting neuronal function and leading to cognitive decline. Age-related changes in protein homeostasis and clearance mechanisms, including autophagy and proteasomal degradation, become less efficient with age. This reduced capacity to clear abnormal proteins contributes to their accumulation and the neurodegenerative cascade [142, 143].

According to a meta-analysis of Alzheimer's disease in Europe, its prevalence among older adults is 5.05%. Regional variations were observed, with southern European countries, such as Spain, Italy, and Greece, showing a mean higher prevalence (6.88%) compared to northern European countries, such as France and Netherlands (4.31%) [144].

The ageing brain experiences alterations in neurotransmitter systems, which play a pivotal role in cognitive and motor functions. For instance, the decline in dopamine production and receptors in the ageing brain is associated with Parkinson's disease (PD), which, in developed nations, is estimated to affect approximately 0.3% of the overall population [145]. The prevalence increases with age, with around 1.0% of individuals over 60 years old and 3.0% of those over 80 years old being affected by PD. In Europe, the estimated prevalence rates for PD vary between 65 and 12,500 cases per 100,000 individuals [146].

These changes affect communication between nerve cells and can lead to motor deficits. Additionally, oxidative stress and inflammation, which tend to increase with age, contribute to neuronal damage and neuroinflammation, further exacerbating the neurodegenerative process. The ageing brain faces challenges related to vascular health and blood flow. Reduced cerebral blood flow and microvascular changes can impact nutrient and oxygen delivery to brain cells [147, 148]. This vascular compromise

is particularly relevant in vascular dementia, where impaired blood supply contributes to cognitive impairment. Moreover, the blood-brain barrier, responsible for protecting the brain from harmful substances, becomes less effective with age, potentially allowing neurotoxic molecules to enter the brain and exacerbate neurodegeneration [149].

2.3.2 Cancer

In 2012, approximately 6.7 million new cancer cases were detected among individuals aged 65 and older, accounting for 47.5% of all newly diagnosed cancer cases worldwide [150]. Among individuals aged 75 or older globally, the most commonly diagnosed cancers include non-melanoma skin cancer (with an incidence rate of 847 per 100,000), followed by colon and rectum cancer (253/100,000), lung cancer (248/100,000), prostate cancer (182/100,000), stomach cancer (138/100,000), and breast cancer (115/100,000). The leading causes of mortality by cancer within this population are lung, colon and rectum, stomach, prostate, pancreatic, and breast cancer [151].

Cancer and ageing are intimately intertwined, as the risk of developing cancer significantly increases with age. This complex relationship is rooted in the physiological changes that occur in the ageing body, making it more susceptible to the development and progression of cancer. Understanding the physiological aspects of cancer in the context of ageing is crucial for both prevention and treatment strategies [152].

One of the key physiological factors contributing to the age-related increase in cancer risk is the cumulative accumulation of genetic mutations and cellular damage over time. Cellular repair and DNA damage response mechanisms become less efficient with age, leading to the persistence of genetic mutations. These mutations can disrupt normal cellular processes, including those involved in cell cycle regulation and DNA repair, increasing the likelihood of uncontrolled cell growth and the formation of malignant tumours [153]. The ageing immune system undergoes significant changes, which can have profound implications for cancer development. The immune system's ability to detect and eliminate cancerous cells declines with age, known as immune senescence.

Additionally, chronic inflammation, which becomes more prevalent with ageing, often called inflammageing, can create a microenvironment favourable for cancer progression. The immune system may also become less responsive to immunotherapies, making cancer treatment in older individuals more challenging [154-156]. Hormonal changes associated with ageing can influence cancer development, particularly in hormone-sensitive cancers like breast and prostate cancer. The decline in sex hormone production, such as oestrogen and testosterone, can alter the hormonal environment in

the body. These hormonal changes can impact the growth and proliferation of hormone-sensitive tumours, either promoting or inhibiting cancer progression, depending on the specific cancer type and hormonal context [157, 158].

2.3.3 Age-Related Macular Degeneration and Cataracts

Age-Related Macular Degeneration (AMD) is a progressive eye condition that primarily impacts the macula, a critical small region located at the centre of the retina situated at the back of the eye. The macula plays a pivotal role in central vision, enabling us to precisely discern intricate details, read, identify faces, and carry out tasks necessitating acute, central vision [159, 160]. AMD is linked to the build-up of drusen beneath the retinal pigment epithelium, disturbing the exchange of nutrients with photoreceptor cells. This condition is marked by the gradual decline of the macula, resulting in the loss of central vision, while peripheral vision remains unaffected [161, 162].

Cataracts are a prevalent ocular condition characterised by the opacification of the eye's natural lens, which is typically transparent and allows light to penetrate the retina at the back of the eye. The lens of the human eye primarily consists of water and proteins arranged meticulously to uphold clarity and enable the focused transmission of light onto the retina. Over time, owing to several factors, such as ageing, exposure to ultraviolet (UV) light, smoking, and diabetes, these proteins can undergo alterations that cause them to aggregate and become non-transparent. This phenomenon, where the lens becomes cloudy, is called a cataract [163, 164]. As a cataract progresses, it disperses and obstructs incoming light, resulting in distorted or hazy vision. This clouding can worsen gradually, making it challenging to perceive objects, particularly in low-light conditions like night-time, and giving rise to glare or halos around light sources. Cataracts can develop due to various factors, with age-related cataracts being the most common. The standard approach to restoring clear vision involves surgically removing the clouded lens and replacing it with an artificial one [165, 166].

2.3.4 Hearing Loss

Age-related hearing loss, known as presbycusis, is a common condition that affects a significant portion of the older population. It arises from a complex interplay of physiological and environmental factors. One of the primary contributors to age-related hearing loss is the gradual deterioration of sensory hair cells within the cochlea, the

auditory organ in the inner ear. These hair cells detect sound vibrations and convert them into electrical signals transmitted to the brain for interpretation [167, 168]. Over time, the cumulative effects of ageing, genetics, and environmental exposures, such as prolonged exposure to loud noises throughout one's life, lead to damage and loss of these critical hearing cells. Additionally, structural changes in the cochlea, including alterations in the basilar membrane's elasticity and reduced blood supply, further impair the ability to perceive sounds accurately [169].

Age-related hearing loss typically starts with a decline in high-frequency hearing, impacting the ability to discern consonants in speech. This loss can result in difficulties in understanding conversations, especially in noisy environments, leading to social isolation and decreased overall quality of life [170]. Auditory nerve fibres may also undergo degeneration, affecting the transmission of sound signals to the brain. Diagnosis is typically conducted through comprehensive hearing evaluations, which assess the degree and nature of hearing loss. Management strategies often involve hearing aids to amplify sounds and improve communication. Cochlear implants may be considered for severe hearing loss cases [171]. While age-related hearing loss is a natural consequence of ageing, addressing it through early diagnosis and appropriate interventions can significantly improve an older individual's ability to engage in daily activities and maintain social connections [172].

2.4 Comorbidities in Older Age

Comorbidities, often referred to as comorbid conditions or multimorbidities, are characterised by the simultaneous presence of two or more distinct medical conditions within an individual. These conditions can interact in various ways, influencing clinical presentation, management, and outcomes [173, 174]. Among older adults, comorbidities are highly prevalent, with estimates suggesting that between 55% and 98% of individuals aged 60 and over have at least two chronic diseases [175]. Cardiovascular diseases are the most common comorbid conditions, with ischemic heart disease being one the most prevalent. Notably, nearly all older adults with CVD have multiple comorbidities, and it's estimated that around 70% of people over 70 will develop CVD along with other non-cardiovascular comorbidities. A significant national survey of Medicare beneficiaries aged 65 and older revealed that CVD often coexists with conditions like diabetes, anaemia, and arthritis, highlighting the complex healthcare landscape for older individuals [79].

Several factors contribute to the high prevalence of comorbidities in older adults. Cumulative health risks, including exposure to risk factors like hypertension and diabetes over time, can lead to multiple comorbidities. Age-related physiological changes, such as alterations in the immune system and reduced organ reserve, increase susceptibility to chronic conditions [94, 175, 176]. Lifestyle choices made over a lifetime, including diet, physical activity, and smoking, also influence the development of comorbidities. Furthermore, extended life expectancy provides more time for accumulating chronic conditions, making it more likely for older adults to experience multiple age-related diseases [177].

Comorbidities significantly impact health and introduce complexities into diagnosis and management, particularly for older adults. These associated conditions complicate the diagnostic process as they can obscure the presentation of specific health issues, leading to delays in identifying and addressing health concerns [174]. Additionally, treatment interactions become intricate when multiple comorbidities are involved, potentially resulting in complex drug interactions that require careful consideration. Moreover, comorbidities frequently lead to polypharmacy, where individuals manage various medications simultaneously, increasing the risk of medication errors or non-adherence [178].

The implications of comorbidities extend beyond diagnosis and treatment complexities, affecting older adults' overall health and quality of life. These conditions can contribute to functional decline, impacting mobility, cognitive function, and daily independence. The burden of managing multiple comorbidities negatively influences an individual's quality of life, as the need for frequent medical appointments, complex medication regimens, and lifestyle modifications can become overwhelming [179, 180]. This, in turn, leads to increased healthcare utilisation, including hospitalisations, specialist visits, and rehabilitation services, straining healthcare systems and resources. The psychological impact of dealing with comorbidities should not be underestimated, as it often leads to emotional distress, anxiety, and depression among older adults [181]. Moreover, the economic burden of comorbidities is substantial, encompassing costs associated with medical appointments, medications, and treatments [174].

2.5 Polypharmacy

Comorbidities and polypharmacy are two interconnected healthcare challenges that often confront older adults. Polypharmacy is the concurrent use of five or more medications, including prescription drugs, over-the-counter remedies, and dietary

supplements, usually resulting from addressing these comorbidities and other health challenges over time. However, polypharmacy brings challenges like potential medication interactions, adherence issues, an increased risk of falls, cognitive impairment, and medication-related hospitalisations [78, 138, 182].

Effectively addressing these complex issues requires a balanced approach that considers the benefits of medication in managing chronic conditions and the potential risks associated with multiple drug use. Healthcare providers play a crucial role in managing comorbidities and polypharmacy in older adults by conducting comprehensive assessments, fostering care coordination among various providers, and prioritising individualised goals of care [178, 183]. Regular medication reviews are essential to assess the necessity and safety of each medication and deprescribing; the cautious reduction or discontinuation of unnecessary or harmful drugs should be considered when appropriate and in consultation with the patient. Moreover, simplifying medication regimens, monitoring for adverse effects, providing patient education, and emphasising lifestyle interventions are vital components of managing these challenges [184, 185].

2.6 Geriatric Syndromes

Geriatric syndromes encompass a range of multifactorial clinical conditions common among older adults and often involve multiple physiological systems. [79, 103] These syndromes are distinct from specific diseases and are characterised by their complex aetiology and the interaction of various factors [186].

Falls and their consequences are prominent geriatric syndromes [187, 188]. In a European study involving 18 countries and over 40,000 participants aged 55 and older, 8.2% reported having experienced at least one fall in the previous six months. Notably, the age groups of 75-84 years and 85 and older reported higher rates of falls at 12.0% and 19.0%, respectively [182]. The physiological changes associated with ageing, such as decreased muscle mass, reduced bone density, and impaired balance control, increase the risk of falls in older individuals. Muscle strength and coordination, vital for maintaining balance, decline with age. Age-related changes in vision and proprioception also reduce an older person's ability to detect and respond to environmental hazards [189, 190].

Incontinence, both urinary and faecal, is another common geriatric syndrome with underlying physiological factors. Age-related changes in the urinary system, including decreased bladder capacity and muscle tone, can contribute to urinary incontinence. Similarly, gastrointestinal tract and pelvic floor muscle changes can lead to faecal

incontinence. These physiological changes are compounded by cognitive impairment and mobility limitations, making incontinence challenging for older adults [191, 192].

Delirium is recognised as a significant geriatric syndrome characterised by sudden and fluctuating changes in mental status, including confusion and altered consciousness. Underlying medical conditions or medications commonly trigger it and can lead to adverse outcomes in older adults, such as more extended hospital stays, increased mortality, and cognitive decline [193, 194]. Delirium is considered a critical concern in geriatric care, highlighting the importance of prompt recognition and intervention to address its underlying causes and provide supportive care [195].

Sarcopenia is a geriatric syndrome characterised by progressive muscle mass, strength, and function loss that occurs with ageing. It is a common condition in older adults and can lead to various adverse health outcomes, including decreased mobility, falls, frailty, and impaired quality of life [196, 197]. Sarcopenia is often multifactorial, influenced by inadequate nutrition, physical inactivity, hormonal changes, and chronic inflammation [198].

Frailty is a multidimensional syndrome characterised by decreased physiological reserve and increased vulnerability to stressors, involving a complex interplay of physical, psychological, and social factors. Frail individuals are at higher risk of adverse health outcomes, including falls, disability, hospitalisation, and mortality [199, 200].

3 Frailty

In the field of geriatric medicine and research, the concept of frailty has emerged as a complex and multifaceted construct that holds profound implications for understanding the health and well-being of older adults [201-203]. Characterised by increased vulnerability and diminished physiological reserves, frailty transcends chronological age to encompass a range of interrelated physical, cognitive, and psychosocial factors [204, 205]. Defining and conceptualising frailty has been marked by an evolution that reflects a deeper understanding of the ageing process and the intricate interplay of various dimensions within it [206].

Defining frailty is challenging due to its intricate nature and the multifaceted factors it encompasses. At its core, frailty is marked by a heightened susceptibility to stressors and an increased risk of adverse health outcomes. Unlike traditional disease-based models, frailty captures a unique state of vulnerability that can exist independently of specific illnesses [200, 207]. This distinction underscores the significance of understanding frailty as a distinct entity within the geriatric spectrum [204, 208].

The journey to define frailty has been influenced by historical context and evolving perspectives on ageing. In the past, ageing was often simplified as a linear process, with chronological age as the primary marker of health status. However, as researchers delved deeper into the experiences of older adults, it became evident that more than age alone was needed to capture the complexity of health trajectories [200, 208-210]. In the late 20th century, frailty gained recognition as a distinct geriatric syndrome. Researchers sought to move beyond age as the sole determinant of health by exploring the contributing factors contributing to vulnerability in older adults [199, 211]. This paradigm shift led to the acknowledgement of the importance of frailty assessments in capturing the nuanced variations in health status among older individuals [202].

Frailty's definition goes beyond physical frailty to encompass cognitive, psychological, and social dimensions. The evolving definitions of frailty have profound implications for research and clinical practice [212]. In research, the multidimensional nature of frailty has led to interdisciplinary explorations of its underlying mechanisms. Genetic, biological, psychological, and social factors are all being investigated to comprehensively understand frailty's development and progression [213]. This holistic approach underscores the importance of considering the interconnectedness of various factors in shaping frailty's manifestation [214].

As frailty continues to evolve, it remains a cornerstone of geriatric research and healthcare. The diverse definitions and frameworks reflect the complexity of the ageing

process and the need to capture its nuances [200, 208, 215]. From Fried's Phenotype to the recognition of cognitive, psychological, and social dimensions, the journey to define frailty reveals the depth of understanding required to address the health challenges faced by older adults.

In ageing-related research, frailty is a reminder that age is not a linear trajectory but a complex interplay of factors. By acknowledging frailty's multidimensional nature, researchers and healthcare practitioners can better tailor interventions to enhance older individuals' well-being and quality of life. The evolving interpretations of frailty open doors to a more comprehensive perspective on ageing, acknowledging the multitude of life experiences and embracing the complexity of elements that influence health and vulnerability in older age.

3.1 Pathophysiology of Frailty

Although frailty is prevalent among older adults, its underlying pathophysiological mechanisms are intricate and multifactorial [200, 202]. To offer a comprehensive grasp of the complex pathophysiology underlying frailty, it is essential to recognise the contributions of multiple physiological systems. These systems encompass musculoskeletal, inflammatory, endocrine, neurological, vascular, cardiovascular, and metabolic components, all playing crucial roles in the onset and advancement of frailty [214].

A fundamental pillar in the pathophysiology of frailty is the musculoskeletal system. Sarcopenia, characterised by the age-related loss of muscle mass and function, is a critical frailty feature. This process results from an imbalance between muscle protein synthesis and degradation and the impaired regenerative capacity of muscle cells [197, 216]. Sarcopenia leads to muscle weakness, reduced physical performance, and, ultimately, frailty. Additionally, changes in bone density and quality that occur with ageing contribute to the increased risk of fractures, further exacerbating the clinical manifestations of frailty [217, 218].

Inflammageing plays a pivotal role in the pathophysiology of frailty [85, 219, 220]. Chronic, low-grade inflammation is a hallmark of ageing, characterised by elevated levels of pro-inflammatory cytokines, notably interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF- α), in frail individuals [221-225]. This chronic inflammatory state is implicated in muscle wasting and insulin resistance. The intricate interplay between inflammation and other physiological systems, such as the endocrine system, amplifies the complexity of frailty's pathophysiology [226]. Dysregulation of the endocrine system, particularly the

hypothalamic-pituitary-adrenal (HPA) axis and the insulin-like growth factor-1 (IGF-1) axis, has also been implicated [89, 226].

Elevated cortisol levels due to HPA axis dysregulation can lead to muscle catabolism and loss of bone density. Simultaneously, decreased growth hormone (GH) and IGF-1 levels contribute to muscle mass decline and overall frailty [223, 227, 228].

Frailty is not solely a consequence of physical decline; cognitive and neurological factors also play pivotal roles. Brain ageing, neuroinflammation, and neurodegenerative processes contribute to cognitive impairment and depressive symptoms associated with frailty [229, 230]. Neurological factors can significantly influence an individual's ability to perform daily activities and maintain independence, further contributing to the clinical presentation of frailty [202, 211].

Vascular and cardiovascular changes are intricately intertwined with the pathophysiology of frailty [85]. Atherosclerosis, endothelial dysfunction, and reduced cardiac output are common age-related vascular changes that can exacerbate frailty. Impaired blood flow affects muscle perfusion, contributing to muscle wasting and weakness. Furthermore, reduced cardiovascular reserve limits an individual's ability to respond to physiological stressors, ultimately increasing their vulnerability [231].

Metabolic dysfunction, including insulin resistance and dyslipidaemia, represents an integral component of frailty's pathophysiology [214]. Insulin resistance may impair muscle glucose uptake and contribute to muscle atrophy, while dyslipidaemia can lead to a pro-inflammatory state and cardiovascular dysfunction [232]. These metabolic changes are often interconnected with inflammation and hormonal dysregulation, further highlighting the complexity of frailty's pathophysiology [233].

3.2 Dimensions of Frailty

3.2.1 Physical Frailty

In geriatric medicine, physical frailty is significant, illuminating the intricate dynamics between an individual's physical well-being and overall quality of life as they age [202]. Beyond mere consideration of chronological age, physical frailty delves into the complex interplay of physiological changes, chronic conditions, and lifestyle factors collectively contributing to this increased vulnerability [234]. Understanding the essence of physical frailty is essential for fostering a comprehensive approach to geriatric care that encompasses the physiological aspects of ageing and the broader context in which they occur [202, 235].

Physical frailty is rooted in vulnerability arising from a diminished physiological reserve. It arises from various factors, including age-related physiological changes, chronic health conditions, and lifestyle factors [202, 236]. This interplay results in a decline in strength, endurance, and overall functional capacity, rendering individuals more susceptible to stressors such as infections, falls, and hospitalisations [237].

The markers and measurements of physical frailty revolve around assessing an individual's physical capabilities. Grip strength, gait speed, and physical activity levels are common physical frailty indicators. Moreover, the "Fried Frailty Phenotype," which encompasses components like slow walking speed, weak grip strength, and unintentional weight loss, provides a standardised framework to identify and categorise physical frailty [238, 239]. Physical frailty among individuals aged 50 and above in Europe was found to be 20.8% of pre-frail individuals and 5.4% of frail individuals, with a higher prevalence observed among women [240, 241]. In another European study that included only individuals aged 70 or older, overall frailty and pre-frailty prevalence stood at 3.0% and 43.0%, respectively. Portugal exhibited the highest prevalence of frailty at 13.7%, while Austria recorded the lowest at 0%. As for pre-frailty, Portugal also had the highest prevalence, with a rate of 57.3%, whereas Germany had the lowest at 37.1% [242].

The impact of physical frailty is profound, affecting an individual's health and overall quality of life. As muscle mass decreases and physical function declines, older adults may experience difficulties performing daily activities such as dressing, bathing, and walking [243]. This loss of independence can lead to a cycle of reduced physical activity, further exacerbating the state of frailty. Additionally, physical frailty is associated with an increased risk of falls, fractures, hospitalisations, and mortality [182, 244-247].

The interplay of physical frailty with psychological and social dimensions is noteworthy. Physical health issues can restrict an individual's ability to engage in social activities, potentially leading to isolation. Conversely, social isolation can further hinder opportunities for physical activity, contributing to the progression of physical frailty. Additionally, psychological factors such as low self-esteem and anxiety can influence and be influenced by physical frailty [248-250].

Preventing and addressing physical frailty necessitates a multifaceted approach. Regular physical activity, particularly resistance training, is pivotal in maintaining muscle mass and strength [251]. Nutritional interventions, including adequate protein intake, can support muscle health [252]. Additionally, managing chronic conditions and optimising medications are crucial in mitigating the progression of frailty [253].

3.2.2 Social Frailty

Social frailty has emerged as a concept shedding light on the intricate connection between an individual's social well-being and overall quality of life during the ageing process [254]. Going beyond the physical aspects, social frailty delves into the emotional and psychological dimensions of social disconnection and vulnerability. Understanding the dynamics of social frailty is pivotal for fostering a holistic approach to geriatric care that encompasses physical health and the psychosocial dimensions of ageing [250, 255-257].

Social frailty goes beyond mere isolation. It encompasses a broader spectrum of social well-being. It arises when an individual experiences limited social interactions, reduced participation in meaningful activities, and a lack of strong support networks. Unlike physical frailty, which often focuses on physiological decline, social frailty focuses on the emotional toll of social disconnection.

Measuring social frailty involves examining an individual's social network, engagement in social activities, and perceived support level. Indicators range from the frequency of interactions to involvement in community events. Some assessment tools explore the emotional aspects, considering feelings of loneliness and isolation. A systematic review found that, in hospital settings, the incidence of social frailty revolves around 47%, while in community-based studies, it was about 19%. When comparing studies within specific countries, the prevalence of social frailty was observed to be at its lowest in China (4.9%), followed by Spain (11.6%), Japan (16.2%), Korea (26.6%), European urban centres (29.2%), and the Netherlands (27.2%) [258]. A recent study revealed that social frailty in China stands at approximately 15%, with a higher prevalence in rural regions compared to urban areas [259]. The varying metrics employed to evaluate social frailty can readily account for the diversity in values.

The impact of social frailty extends deeply into overall health and life quality. Limited social engagement can lead to feelings of loneliness and depression, exacerbating mental health challenges [260]. Situations such as the recent COVID-19 pandemic show how assessing social frailty becomes crucial in preventing late-life neuropsychiatric disorders [261]. Those struggling with social frailty often lack the emotional sustenance needed to cope with life's stressors, rendering them more susceptible to adverse health outcomes [249, 262]. Furthermore, social isolation can limit the adoption of healthy behaviours, contributing to physical decline [248].

Social frailty is closely linked with both physical and psychological well-being. Physical health constraints may impede social involvement, leading to social isolation.

Conversely, social isolation can contribute to sedentary behaviour, fuelling physical frailty. Psychological factors like low self-esteem and anxiety can also instigate and result from social frailty [263, 264].

Preventing and addressing social frailty requires a comprehensive approach. Encouraging older adults to participate in social activities, engage in community networks, and cultivate support systems can enhance their sense of belonging and emotional well-being [265, 266]. The digital era, with technology and virtual platforms, offers opportunities to bridge distances and foster connections. Engaging older adults in activities that resonate with their interests can infuse life with purpose and interpersonal bonds [267]. Addressing social frailty necessitates recognising that older adults' well-being encompasses more than physical health. Integrating social assessments into geriatric care plans can help identify at-risk patients and inform interventions that stimulate engagement [268].

3.2.3 Psychological Frailty

In geriatric care, psychological frailty emerges as a significant facet, highlighting the intricate interplay between an individual's emotional and cognitive well-being and overall quality of life as they age. This concept explores the emotional vulnerabilities, cognitive challenges, and mental health factors collectively contributing to a state of frailty [269, 270]. Understanding psychological frailty is crucial for cultivating a comprehensive approach to geriatric care encompassing physical health and the psychological dimensions of ageing [210, 271].

Psychological frailty encompasses emotional vulnerabilities and cognitive challenges that older adults may encounter. It is characterised by a decline in emotional resilience, cognitive flexibility, and the ability to cope with stressors [270]. This frailty is often rooted in various factors, including age-related changes in brain function, loss experiences, and chronic illnesses' impact on mental health [272-275]. Markers and measurements of psychological frailty centre around evaluating an individual's emotional well-being and cognitive functioning. These assessments may include emotional resilience, cognitive processing speed, memory function, and adapting to new situations. Furthermore, evaluating an individual's perceptions of their mental health and emotional responses to stressors is crucial to understanding psychological frailty [270, 276].

The impact of psychological frailty is profound, influencing an individual's emotional and cognitive well-being and overall quality of life. As psychological frailty progresses, individuals may experience heightened anxiety, depression, and feelings of

helplessness. Coping mechanisms may become less effective, leading to difficulties in managing life's challenges and adapting to new situations [269, 277]. Furthermore, cognitive challenges associated with psychological frailty can affect an individual's ability to make decisions, solve problems, and engage in daily activities [278].

The interplay of psychological frailty with physical and social dimensions adds depth to its understanding. Physical health issues, such as chronic pain or illness, can exacerbate emotional vulnerabilities and contribute to psychological frailty [279]. Similarly, social isolation and limited social support can exacerbate feelings of loneliness and contribute to the progression of psychological frailty. Moreover, the experience of psychological frailty can impact an individual's social interactions and relationships, creating a complex interrelationship [260].

3.2.4 Frailty as a Biopsychosocial Syndrome

Frailty, viewed as a biopsychosocial syndrome, offers a comprehensive lens through which to understand the intricate interplay of biological, psychological, and social factors that collectively shape the ageing process [199, 213, 238]. This multidimensional concept recognises that ageing is a complex process from physical changes, emotional dynamics, and social interactions. Understanding frailty in this holistic context is pivotal for fostering a comprehensive approach to geriatric care that addresses the diverse dimensions of ageing [199, 213, 280].

At its core, frailty as a biopsychosocial syndrome acknowledges that ageing entails more than physical decline. It encompasses the biological changes that come with age, such as decreased muscle mass, reduced physiological reserves, and increased vulnerability to stressors [239, 242]. However, it extends beyond the physical domain to encompass psychological vulnerabilities, such as cognitive decline, emotional challenges, and mental health factors [270, 276]. Additionally, frailty recognises the social dynamics at play, including isolation, social support networks, and community engagement [255].

This comprehensive view of frailty is patentable by markers and measurements encompassing all three dimensions. Physiological indicators, such as grip strength and gait speed, capture the biological aspect. Psychological assessments delve into cognitive function, emotional well-being, and mental health. Social evaluations encompass social networks, support systems, and participation in community activities [239, 281, 282].

What makes frailty particularly intricate is the complex interplay among these three dimensions. Physical health challenges foster psychological distress, while psychological struggles impede social interactions and engagement. Reciprocally, social isolation can heighten both physical and psychological frailty, forming a cyclic pattern that intensifies frailty's impact across all dimensions [283]. Considering its complex biopsychosocial nature, this interdependence emphasises the need for comprehensive approaches to address and manage frailty.

3.3 Frailty Assessment

In the last decades, many tools have emerged for assessing frailty. These instruments have undergone validation, establishing a clear connection between frailty and adverse health outcomes in older individuals, and fall into two categories [284]:

1. *Frailty Phenotype Instruments*: These primarily rely on motor and activity measurements, culminating in a composite score that spans from robust to frail.
2. *Frailty Index Instruments*: These incorporate a more comprehensive array of factors, including co-morbidities, social variables, psychological conditions, and measures of functional and cognitive decline. The more "conditions" a person exhibits, the higher their frailty score [203, 215, 285].

Frailty assessment is a crucial process in healthcare, particularly for older adults, to determine an individual's vulnerability level and risk of adverse health outcomes, including falls, hospitalisation, disability, and mortality. Various tools and methods are used to assess frailty, and the choice of assessment depends on the healthcare setting, available resources, and the specific needs of the patient [286, 287].

3.3.1 Frailty Assessment Tools

There is a wide range of tools based on different approaches to assess frailty, considering physical, psychological, and social aspects, enabling healthcare professionals to better understand and address frailty in older adults [209].

1. *Fried Frailty Phenotype*: Fried's Phenotype model defines frailty based on five criteria: unintentional weight loss, weakness, self-reported exhaustion, slow walking speed, and low physical activity. Individuals are classified as robust (0 criteria), pre-frail (1-2 criteria), or frail (3 or more criteria). It's widely recognised for its simplicity and effectiveness in identifying physical frailty but may not capture cognitive or psychosocial aspects [239].

2. *Clinical Frailty Scale (CFS)*: The original Clinical Frailty Scale assesses frailty across seven levels, from very fit to terminally ill. Clinical judgment relies on categorising individuals, considering comorbidities, functional impairment, and cognitive decline. Its multidimensional approach makes it suitable for many older adults but may require trained healthcare professionals [288].
3. *Frailty Index (FI)*: The Frailty Index quantifies frailty as a fraction, considering accumulated deficits across multiple domains. It provides continuous measurement, offering a nuanced understanding of frailty, but necessitates a large dataset for construction [289].
4. *PRISMA-7*: The PRISMA-7 is a brief screening tool used to assess the risk of functional decline and frailty in older adults. PRISMA stands for "Program of Research to Integrate Services for the Maintenance of Autonomy," it was developed in Canada as part of a program to identify individuals at risk of functional decline. The 7 questions in PRISMA-7 cover various health and functional status domains, including mobility, cognitive function, and self-reported health [290].
5. *Groningen Frailty Indicator (GFI)*: The GFI comprises 15 self-report questions that assess physical, cognitive, and psychosocial domains of frailty, including mobility, social support, and depression [282, 291].
6. *Tilburg Frailty Indicator (TFI)*: TFI evaluates frailty across physical, psychological, and social domains. Respondents answer 15 questions, with higher scores indicating increased frailty. It's beneficial for identifying frailty in community-dwelling older adults due to its comprehensive approach and ease of self-reporting [281].
7. *Edmonton Frail Scale (EFS)*: The EFS evaluates frailty's physical, cognitive, and psychosocial aspects. It involves both self-report and clinical assessment, providing a comprehensive picture of frailty, but it may require trained personnel for administration [292].

Different frailty assessment tools have different characteristics. Some require clinical data, others require physical tests, and some are just questionnaires. Some can be used for self-assessment, while others cannot, as they require a certain level of expertise to apply. Some are suitable for use only in primary or acute care settings, while others can be used in the community. Some are faster, while others take longer [286, 293]. All of these characteristics are important to consider when making decisions. However, they all benefit the patient, the family and caregivers, healthcare professionals, or social care professionals.

Validating frailty scales in multiple languages significantly advances the quality of care for ageing populations worldwide. This crucial process ensures that these instruments accurately reflect the diverse manifestations of frailty across different linguistic and cultural contexts, facilitating early detection and intervention. Moreover, such validation supports comparative research studies, enabling a deeper understanding of frailty as a global health concern and fostering international collaboration in developing best practices for managing and preventing frailty in older adults. Several frailty scales are already available in European Portuguese, but the GFI is not one of them [294-298].

3.3.2 Frailty Assessment Benefits

Frailty assessments are valuable tools for identifying at-risk individuals and tailoring interventions to their needs. By recognising frailty early, healthcare practitioners can develop strategies to prevent functional decline and mitigate adverse health outcomes [207, 286].

3.3.2.1 Early Intervention

Early intervention through frailty assessment is akin to a proactive healthcare compass, guiding providers to detect the subtle signs of frailty in older adults before they burgeon into more severe health challenges [299]. Timely identification is pivotal, as frailty typically creeps in gradually, often unnoticed. Once identified, healthcare teams can deploy preventive measures tailored to the individual's needs, spanning physical exercises to maintain muscle strength and balance, dietary interventions to ensure adequate nutrition, and targeted management of specific health conditions that contribute to frailty [214, 300]. Frailty is somewhat malleable. Although complete reversal might not be achievable, addressing the underlying factors can slow its progression and enhance an individual's quality of life. Consequently, early detection plays a crucial role in managing frailty effectively [301].

3.3.2.2 Tailored Care

The essence of frailty assessment lies in its ability to unveil a personalised roadmap for care. This is no one-size-fits-all approach; instead, it's a meticulous crafting of care plans that consider the unique attributes of each frail individual. Beyond addressing physical frailty, it delves into cognitive, emotional, and social dimensions [286, 302].

These tailored care plans can profoundly engage patients recognising their strengths and vulnerabilities [303]. The multidimensional approach to care fosters resilience by addressing emotional well-being and maintaining social connections. It creates a patient-centric healthcare environment that empowers frail individuals to participate in their health journey [304].

3.3.2.3 Reduced Hospitalizations

In healthcare, frailty assessment is paramount to protect frail individuals from hospitalisation. Knowing that the patient is frail and giving him a personalised intervention can reduce the likelihood of acute health events that could lead to hospital admissions [305]. By focusing on fall prevention, medication management, and the handling of chronic diseases, healthcare teams can help frail individuals reduce the number of hospital stays [306, 307]. The benefits ripple out, encompassing frail individuals' well-being and healthcare systems' fiscal health. Reduced hospitalisations translate into cost savings, allowing resources to be channelled more efficiently, thereby ensuring that healthcare can be delivered where it's needed most [308].

3.3.2.4 Medication Management

For frail individuals, the potential hazard of medication side effects and interactions becomes less reliable [309, 310]. Medication management isn't merely about pill counts; it's about optimising treatment regimens to preserve frail individuals' well-being. It includes deprescribing, where unnecessary or harmful medications are carefully phased out, simplifying regimens, and reducing the risk of adverse reactions [311]. Within medication management, frailty assessment is needed towards safer and more productive pharmaceutical care [310].

3.3.2.5 Prevention of Falls

Frailty assessment is essential in fall prevention, which can impact the lives of older adults. It operates as an early warning system, identifying at-risk individuals and triggering a cascade of preventive measures [182, 312]. These measures encompass physical interventions, such as strength and balance exercises and home modifications, and psychological support to mitigate the fear of falling, which can contribute to fall risk

[244]. By preventing falls, frailty assessment not only safeguards physical health but also protects against these traumatic events' psychological and social consequences.

4 mHealth and Frailty

4.1 Defining mHealth and its Role in Healthcare

Mobile health, commonly called mHealth, represents a transformative force in healthcare delivery and management. At its core, mHealth encompasses using mobile devices, such as smartphones and tablets, to provide medical services, health monitoring, and healthcare information dissemination [313-315]. The essence of mHealth lies in its ability to extend healthcare services beyond traditional clinical settings. It leverages the widespread availability of mobile devices, which have become an integral part of modern life, to bridge gaps in healthcare accessibility, affordability, and quality. Unlike conventional healthcare models, which often require patients to visit medical facilities, mHealth brings healthcare to the palm of the patient's hand [316-318].

One of the fundamental aspects of mHealth is its versatility. It encompasses various applications and services that cater to diverse healthcare needs. From simple wellness and fitness apps that help individuals track their physical activity and nutrition to complex telemedicine platforms that enable remote consultations with healthcare providers, mHealth offers various solutions [319, 320]. Additionally, it can aid in managing chronic conditions, promoting medication adherence, and delivering health education [321-327].

The significance of mHealth becomes particularly evident when considering its role in healthcare access. Access to healthcare services can be a huge challenge for many individuals, especially those in underserved or remote areas. mHealth is a powerful equaliser, enabling people to consult with healthcare professionals, receive timely medical advice, and access health information regardless of geographic location [328, 329]. This accessibility empowers patients and facilitates early intervention and preventive care, ultimately leading to better health outcomes [330, 331].

mHealth contributes to patient engagement and self-management. Through mobile apps and wearable devices, individuals can actively monitor their health metrics, make informed decisions about their well-being, and adhere to treatment plans. This shift from passive patients to engaged healthcare consumers fosters a sense of responsibility for one's health and can lead to more proactive healthcare behaviours [320, 332].

4.2 Telemedicine and Remote Monitoring

The advent of telemedicine and remote monitoring technologies has led to a new era in healthcare, offering innovative solutions to address the unique challenges of frail ageing populations. Telemedicine encompasses various healthcare services delivered remotely, often facilitated through digital communication technologies. This transformative approach to healthcare delivery can impact how frailty is managed, assessed, and prevented [333, 334].

One of the fundamental benefits of telemedicine is its ability to enhance access to healthcare services, especially for older adults who may face mobility issues or live in remote areas. Travelling to healthcare facilities can be physically taxing and logistically challenging for frail individuals. This not only improves accessibility but also reduces the burden on caregivers and family members who may otherwise need to facilitate medical visits [335, 336].

The adoption of Telemedicine and Remote Monitoring has increasingly gained more followers, showcasing its remarkable effectiveness as an alternative healthcare delivery method. Simultaneously, it emerged as a pivotal solution in supporting healthcare accessibility during the pandemic, further amplifying its utilisation [337-340].

4.3 mHealth-Based Frailty Assessment Tools

mHealth-based tools enhance the accuracy and comprehensiveness of frailty assessments. Traditional assessments often rely on periodic clinical evaluations, which may not capture the nuances of an individual's day-to-day functioning. In contrast, mHealth tools can provide a holistic view of a person's health by collecting data over extended periods [293, 341]. This longitudinal approach enables the identification of subtle changes and trends that may indicate the onset of frailty or its progression, acting as biomarkers of frailty [342].

There are already some mHealth tools for frailty. iCompanion is an example. It's an app that incorporates frailty questions and games. Studies show it's an excellent tool for helping older adults identify frailty and prevent it from worsening [343]. The Brain-M App is a tablet application created explicitly to enable cognitive rehabilitation for individuals in their homes experiencing frailty. This app focuses on enhancing spatial memory, attention, and executive functions. Preliminary results showed good usability and improved executive function and memory performances [344].

Another example is an app that assesses frailty through the Rapid Geriatric Assessment, which performed well in identifying frail individuals, allowing for early identification of older adults, especially during the pandemic period [345, 346]. mHealth was already used to manage frailty through an 8-week exercise and nutrition home-based intervention to target frailty. It was well received by the participants, who found it safe to use and showed to improve physical frailty scores [347]. Other mHealth apps are mainly for assessing frailty and are a feasible way of assessing frailty [348, 349]. FrailSafe is another app for the detection of frailty, and that enables tailored interventions [350]. GERAS virtual frailty rehabilitation is a multicomponent rehabilitation program that can be delivered remotely to frail older adults, and that could be a feasible way of providing care for socially isolated groups [351].

The interactivity and feedback mechanisms embedded in mHealth-based frailty assessment tools can be pivotal in fostering patient engagement. Users receive personalised insights and recommendations based on their assessment results, empowering them to make informed decisions about their health [352]. Additionally, these tools can incorporate educational components, providing users with valuable information about frailty, its risk factors, and strategies for prevention and management. There is, however, a lack of tools for the Portuguese population.

4.4 Promoting Physical Activity and Nutrition

Promoting physical activity and proper nutrition stands at the forefront of strategies to combat frailty in ageing populations. Numerous apps help individuals track their physical activity, plan workouts, monitor nutrition, and make healthier food choices. These apps can be valuable tools for promoting and maintaining a healthy lifestyle [353, 354].

Recognising the intricate relationship between physical health and frailty, interventions targeting these areas can prevent, delay, or mitigate the effects of frailty in older adults [355]. Apps to promote physical exercise offer, among others, workout plans, exercise demonstrations, and tracking tools to help users stay physically active. They may include features like step counting, personalised workouts, and training programs for specific fitness goals. Nutrition apps focus on assisting users to make healthier food choices, manage their diets, and track their calorie intake. They often provide databases of food items, meal-planning tools, and features for logging food consumption. These applications have proven effective in promoting a healthy diet, weight control and enhancing physical activity [356-361]. However, there needs to be more evidence-based apps, emphasising the imperative for creating mobile apps informed by robust evidence [362].

4.5 Cognitive Health and Brain Training Apps

Cognitive health is an essential aspect of overall well-being, and brain training apps have gained popularity as tools to help maintain and improve cognitive function and, therefore, can be a great ally in addressing frailty in ageing populations. These apps are designed to challenge and stimulate various aspects of cognitive function, such as memory, attention, problem-solving, and language skills [363].

While brain training apps can be enjoyable and potentially beneficial, their efficacy in preventing cognitive decline or improving cognitive function remains a subject of ongoing research and debate. However, some mHealth solutions have already proven to be effective in reducing brain atrophy, shown to have beneficial effects on brain health, to be an effective method to target the cognitive deficits associated with brain injury, to enhance cognitive function overall, and to improve depressive symptoms in people with cognitive impairment [364-369].

It's important to note that, as with all health apps, not all brain training apps are equal. Some are backed by scientific research and designed in collaboration with experts in cognitive psychology, while others may lack empirical support. Therefore, individuals seeking these apps should exercise discernment and select those with evidence-based approaches [370].

4.6 Challenges and Ethical Considerations in mHealth for Frailty

As mHealth interventions become increasingly integrated into the care of frail individuals, several challenges and ethical considerations come to the forefront. These issues are critical for healthcare professionals, policymakers, and researchers to navigate as they seek to harness the potential of technology while ensuring the well-being and ethical treatment of frail individuals [371, 372].

One of the primary challenges in implementing mHealth solutions for frailty is the digital divide. Frail individuals, especially those from disadvantaged socioeconomic backgrounds, may need smartphones, tablets, or Internet access. This divide can exacerbate health inequalities, as those needing mHealth interventions the most may be the least likely to benefit from [373-375]. Ensuring equitable access to technology and mHealth tools is a pressing ethical concern [376].

Designing mHealth applications and devices that are user-friendly and accessible to frail individuals is paramount. Challenges include addressing age-related impairments in vision, hearing, and dexterity [377, 378]. Collecting and storing sensitive health

information through mHealth platforms raises significant privacy and data security concerns [379, 380]. Often dealing with multiple health conditions, frail individuals may be particularly vulnerable to health data breaches. Ethical considerations demand robust data protection measures, informed consent procedures, and transparency in data usage [381].

Obtaining informed consent for mHealth interventions can be complex, especially if frail individuals have cognitive impairments that affect their decision-making capacity. Striking a balance between respecting autonomy and ensuring protection from harm is an ethical challenge [382]. Many mHealth applications rely on algorithms and artificial intelligence for decision support. Ethical concerns arise when these algorithms exhibit biases that disproportionately affect frail individuals, leading to disparities in care [383]. Implementing mHealth solutions requires financial resources. Ethical dilemmas may arise regarding allocating funds for technology versus other healthcare needs. Balancing the potential benefits of mHealth with competing healthcare priorities is a challenge that policymakers must address transparently and equitably [384].

4.7 Future Horizons of mHealth in Frailty Care

The future of mobile health in frailty care is poised for remarkable growth and innovation. As technology advances and our understanding of frailty deepens, mHealth is expected to play an increasingly pivotal role in transforming how we assess, manage, and improve the lives of frail individuals [316, 370]. The future of mHealth in frailty care promises highly personalised interventions. Through advanced data analytics and artificial intelligence, mHealth platforms can tailor interventions to each frail individual unique needs and characteristics [333, 385]. Whether it's exercise routines, nutritional guidance, medication management, or cognitive training, these interventions will be precisely calibrated to maximise effectiveness and minimise risks.

The Internet of Things (IoT) and wearable devices are set to revolutionise frailty care. Wearables will become increasingly sophisticated, capable of continuously monitoring vital signs, activity levels, sleep patterns, and more [332, 386]. These devices will seamlessly integrate with mHealth platforms, providing real-time data that empowers healthcare providers to make timely interventions. For frail individuals, this means more proactive and preventive care [355, 387].

Seamless integration between mHealth platforms and electronic health records (EHRs) will enhance care coordination and data sharing [388, 389]. This interoperability will reduce redundancy, improve communication, and ultimately enhance the quality of

care. As technology becomes more ubiquitous, mHealth solutions will become increasingly accessible worldwide [390]. This includes reaching underserved and remote populations. Mobile apps designed for frailty assessment, intervention, and education will be available in multiple languages and culturally sensitive. The goal will be to ensure that the benefits of mHealth are accessible to all, regardless of geography or socioeconomic status [391].

The future of mHealth in frailty care will also entail ongoing ethical discussions. As technology advances, ethical considerations around privacy, data security, informed consent, and algorithmic fairness will remain at the forefront. Striking the right balance between innovation and ethical safeguards will be an ongoing challenge [392, 393].

Aims of the study

The global demographic landscape is undergoing a profound transformation, characterised by an unprecedented increase in the ageing population. As life expectancies rise, societies face the complex challenges of the ageing process, including the prevalence of frailty among older adults. Frailty, a state of increased vulnerability resulting from age-related declines in physical, cognitive, and psychological capacities, has emerged as a pivotal concern within the field of geriatric health and well-being. Addressing this multifaceted issue requires innovative approaches that span the domains of research, assessment, and intervention.

This thesis presents a holistic approach to frailty among older adults within a European context, employing a multifaceted methodology to dissect its prevalence, implications, and management. The general and specific objectives are described as follows:

General Objective 1 – Explore the prevalence of frailty across Europe.

- 1.1. Study frailty prevalence and discrepancies across countries.
- 1.2. Understand which are the criteria that contribute most to frailty.

General Objective 2 – Examine how frailty and the use of multiple medications influence mortality rates among older adults.

- 2.1. Assess the prevalence of polypharmacy among older adults identified as pre-frail and frail.
- 2.2. Evaluate the 30-month survival rates of the older population suffering from frailty and polypharmacy.
- 2.3. Explore which age groups and gender are most affected by these conditions.

General Objective 3 – Systematically review of frailty markers in ESKD patients.

- 3.1. Conduct a review of clinical and biochemical markers associated with pre-frailty and frailty in dialysis and pre-dialysis patients, a population particularly affected by frailty.

General Objective 4 – Translation and validation of the Groningen Frailty Indicator into European Portuguese, integrating it into the cutting-edge FRAILSURVEY health application, and testing the app validity and reliability.

- 4.1. Translate and validate the Groningen Frailty Indicator into European Portuguese.
- 4.2. Create and develop an innovative app for frailty assessment - FRAILSURVEY.
- 4.3. Study the validity and reliability of the app as a frailty assessment instrument.

Collectively, this academic endeavour strives to illuminate the complexities of frailty and reinforce both the theoretical and practical realms of gerontology and geriatrics. By integrating data-centric analysis, cross-cultural insights, and technological advancements, this work aspires to improve the quality of life for older populations.

Outline of the thesis

The main objective of this thesis is to provide a comprehensive exploration of frailty in older adults, focusing on the development and utilisation of new tools to enhance our understanding of this phenomenon. The thesis is structured into different parts.

Chapter I offered a comprehensive theoretical contextualization. It begins with an exposition on ageing within global, European, and national paradigms, transitioning into the challenges and opportunities presented by an ageing demographic, a phenomenon especially pronounced in Portugal. A detailed explanation of the physiology of ageing follows, encompassing chronic and age-associated diseases, comorbidity, and the consequent polypharmacy, whilst also addressing prevalent geriatric syndromes. The focus then shifts to frailty, explaining its pathophysiology and its multidimensional nature. The chapter further outlines the prevalence of frailty, noting the challenges inherent in comparative studies due to the variety of definitions and assessment tools. The discussion proceeds to the significance of evaluating frailty, examining existing methodologies, and acknowledging that the Groningen Frailty Indicator has not been validated in European Portuguese. The chapter concludes by considering the advances in technology, particularly mHealth, its definition, advancements relating to frailty, and the promising potential it holds in healthcare management.

Chapter II focuses on the experimental work that was carried out to meet the objectives already mentioned. It navigates through the intricacies of each objective, presenting an exhaustive examination of frailty's diverse spectrum. The 4 general objectives of this thesis resulted in 4 manuscripts that are included in the chapter.

Manuscript I

Among countless definitions and assessment tools, frailty exhibits considerable variation in its prevalence within Europe's ageing demographics. While consensus underscores its widespread nature, evident in roughly 10% of those aged 60 or older and 25% among those aged ≥ 85 years. This manuscript sets out to examine frailty on a European level, using data from the Survey of Health, Ageing and Retirement (SHARE), harnessing the breadth of data available to the public sphere to probe the extent, patterns, and diversity of frailty across the European scenario. By dissecting these variations, we aim to enrich the discourse on the influence of frailty and to decode the role that distinct cultural, economic, and geographical factors may have in shaping its

landscape. This foundational work seeks to map the contours of frailty in Europe's older populations.

Manuscript II

Polypharmacy, the simultaneous administration of several drugs to a single patient, is often linked with frailty, particularly among the older population. While the use of multiple medications can be essential for older adults due to the prevalence of various chronic diseases, it may also aggravate frailty. The risk of negative drug interactions, adverse medication reactions, and non-adherence with drug regimens can intensify frailty, diminishing the patient's functional capacity and life quality. Moreover, the presence of frailty can complicate the pharmacodynamics and pharmacokinetics of medications, requiring more careful management and often dosage adjustments. The interaction between polypharmacy and frailty is intricate and reciprocal. Polypharmacy might precipitate or heighten frailty, yet frail patients often receive numerous drug prescriptions due to their complex health needs. Both polypharmacy and frailty elevate the risk of mortality; polypharmacy can trigger medication errors and serious reactions, while frailty indicates a lower physiological reserve and increased vulnerability to stressors, including illnesses and medical interventions. This manuscript sought to ascertain the influence of frailty and polypharmacy on mortality within a 30-month timeframe, utilising a cohort from the SHARE study comprising individuals aged 65 and above.

Manuscript III

Recognizing the heightened vulnerability faced by people undergoing dialysis, this manuscript's primary aim was to consolidate the existing knowledge on clinical and biochemical markers relevant to frail and pre-frail patients with chronic kidney disease, both in pre-dialysis and dialysis settings. For that, a systematic review was conducted in following the Cochrane Handbook for Systematic Reviews of Interventions, which sought to synthesise information on biomarkers in frail and pre-frail patients with chronic kidney disease (CKD), both undergoing and approaching dialysis. The objective was to identify biomarkers that could serve as effective instruments to augment the efficacy of clinical practice in geriatric medicine. The review was designed to offer a substantial level of evidence and to assist research teams, policymakers, funding agencies, and peer reviewers who have a vested interest in this area.

Manuscript IV

The fundamental and final contribution of this thesis lies in the translation and validation of the Groningen Frailty Indicator into European Portuguese, which is lacking in the Portuguese geriatric sphere. This process will allow for a broader application of the GFI in Portuguese-speaking populations. Also, this manuscript discussed the integration of the translated GFI into a new healthcare application, FRAILSURVEY, testing its validity and reliability as a tool for assessing frailty. This technological innovation aims to provide an easy-to-use and accessible platform for frailty assessment, facilitating early interventions and personalized care strategies, filling the gap in the existence of such solutions in Portugal.

To provide an overview, in the next table (Table 1) the core components of the thesis and the integration of its scientific outputs into this document are presented, emphasizing the methodologies used.

Table 1 Overview of the thesis objectives, methodologies used and results.

Objective	Methodology	Results	Index
1.1. Study frailty prevalence and discrepancies across countries.	A cross-national database, SHARE, was used to conduct a cross-sectional study to assess the prevalence of frailty status and to understand the impact of each of the criteria in the assessment of frailty. A descriptive analysis of the data collected was carried out, and the prevalence results were standardized by age and sex, using the standard European population of 2013.	Manfredi G, Midão L, Paúl C, Cena C, Duarte M, Costa E. Prevalence of frailty status among the European elderly population: Findings from the Survey of Health, Aging and Retirement in Europe. <i>Geriatr Gerontol Int.</i> 2019 Aug;19(8):723-729. doi: 10.1111/ggi.13689. Epub 2019 May 30. PMID: 31146300.	Chapter II, Manuscript I, page 55
1.2. Understand which are the criteria that contribute most to frailty.			
2.1. Assess the prevalence of polypharmacy among older adults identified as pre-frail and frail.	Using different waves of SHARE data, and through a cohort study approach, a descriptive study was carried out on the relationship between polypharmacy and frailty, and a 30-month survival study was carried out.	Midão L, Brochado P, Almada M, Duarte M, Paúl C, Costa E. Frailty Status and Polypharmacy Predict All-Cause Mortality in Community Dwelling Older Adults in Europe. <i>Int J Environ Res Public Health.</i> 2021 Mar 30;18(7):3580. doi: 10.3390/ijerph18073580. PMID: 33808273; PMCID: PMC8036295.	Chapter II, Manuscript II, page 72
2.2. Evaluate the 30-month survival rates of the older population suffering from frailty and polypharmacy.			
2.3. Explore which age groups and gender are most affected by these conditions.			

3.1. Conduct a review of clinical and biochemical markers associated with pre-frailty and frailty in dialysis and pre-dialysis patients, a population particularly affected by frailty.	A systematic review was performed following the Cochrane Handbook for Systematic Reviews of Interventions. The protocol for this systematic review was registered on PROSPERO under the registration number CRD42020215525.	Pereira A, Midão L, Almada M, Costa E. Pre-Frailty and Frailty in Dialysis and Pre-Dialysis Patients: A Systematic Review of Clinical and Biochemical Markers. Int J Environ Res Public Health. 2021 Sep 11;18(18):9579. doi: 10.3390/ijerph18189579. PMID: 34574503; PMCID: PMC8467352.	Chapter II, Manuscript III, page 99
4.1. Translate and validate the Groningen Frailty Indicator into European Portuguese.	For the development of the European Portuguese version of the Groningen Frailty Indicator, the self-report instrument guidelines defined by the ISPOR Task Force for Translation and Cultural Adaptation were followed	Midão L, Duarte M, Sampaio R, Almada M, Dias CC, Paúl C, Costa E. Validation and reliability of a smartphone application for self-assessment of frailty based on the Groningen Frailty Indicator: FRAILSURVEY. Submitted to Journal of Medical Internet Research. JMIR Publications	Chapter II, Manuscript IV, page 124
4.2. Create and develop an innovative app for frailty assessment - FRAILSURVEY.	FRAILSURVEY development was based on an accessibility principle for older adults, to guarantee greater autonomy to use it. Considerations such as vision, hearing, motor control and cognition were considered.		
4.3. Study the validity and reliability of the app as a frailty assessment instrument.	A randomized repeated crossover design was employed using the paper form of the Groningen Frailty Indicator and the smartphone application FRAILSURVEY.		

Chapter III

In this chapter, we synthesize and critically evaluate the outcomes of the research conducted for this thesis. Each segment of the study is integrated into a comprehensive analysis, providing a platform for a holistic discussion. We then draw a general conclusion, encapsulating the key findings and their implications. This thesis addresses several identified gaps, including the absence of comparative frailty studies across Europe, the unavailability of a Portuguese adaptation of the Groningen Frailty Indicator, and the gap in frailty-related technology in Portugal. The fulfilment of these gaps is not only demonstrated but also their advantages are expounded upon. Through this endeavour, we offer an in-depth discourse on the significance of these contributions, highlighting how they advance the current understanding and management of frailty within the European and Portuguese contexts, and how they align with technological advancements in health care. This comprehensive discussion provides a closure to the thesis while setting a foundation for future research and practice in the field.

CHAPTER II

Experimental Section

Manuscript I

Prevalence of frailty status among the European elderly
population: Findings from the Survey of Health, Ageing and
Retirement in Europe.

Manfredi G*, Midão L*, Paúl C, Cena C, Duarte M, Costa E.

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Wiley Periodicals, Inc.

Aim: In the present study, we aimed to update the data of frailty status in the European community-dwelling population of older adults, based on the latest data released (wave 6) of the Survey of Health, Aging and Retirement in Europe database, and to study the impact of each criterion on frailty assessment.

Methods: Frailty status was assessed applying a version of the Fried phenotype operationalized for the Survey of Health, Aging and Retirement in Europe. We included all participants who answered all the questions used in a frailty assessment and who disclosed their sex and, furthermore, who were aged ≥ 50 years. Our final sample was 60 816 individuals. Of these, the mean age was 67.45 ± 9.71 years; 38 497 (56.4%) were women.

Results: The overall prevalence of pre-frailty was 42.9% (ranging from 34.0% in Austria to 52.8% in Estonia), and frailty was 7.7% (ranging from 3.0% in Switzerland to 15.6% in Portugal). Pre-frailty and frailty prevalence increased along with age, and were more frequent among women. Regarding the five criteria considered on frailty assessment, exhaustion seems to be the criterion that contributes most to frailty status, followed by low activity, weakness, loss of appetite and slowness.

Conclusions: With this work, we showed that $>50\%$ of the European population aged >50 years are pre-frail/frail, which must be considered when designing interventions to reduce/postpone/mitigate the progression of this condition, thus reducing the burden associated with it.

Keywords: Community; Disability; Frailty; Public health; SHARE

Aging of the European population, also known as “the graying of Europe,” is a demographic phenomenon that results from a low number of births along with an increasing average life expectancy.¹⁻³ In 1950, just 12% of the European population was aged >65 years. Today, that number has almost doubled, rising to 19.2%; projections show that by 2050, >36% of the European population will be aged ≥65 years.^{4,5} However, living longer is not necessarily linked to active, healthy and independent aging.⁶ Indeed, unhealthy life years are approximately 20% of a person's life.⁷ Increased longevity leads to a greater expression of chronic diseases related to aging, comorbidities and geriatric syndromes, posing a serious challenge at economic and healthcare systems levels.⁸

Over the past few years, several definitions of frailty have been provided; however, there is still no consensual definition for this condition. While its concept is already accepted, its definition is still somewhat controversial. There is common agreement that frailty is a geriatric multidimensional syndrome, the signs and symptoms of which predict increased vulnerability to minor stress events and adverse outcomes, such as falls, fractures, hospitalization, disability and death.^{9,10} The progression of this condition leads a robust older person to become pre-frail and then frail, and is associated with increased use of social and healthcare services.¹¹ This geriatric syndrome represents a potentially huge public health problem due to the clinical and societal consequences of its dynamic nature, affecting not only the individual, but also his/her caregivers, the healthcare system and society.¹²

There are several tools that can be used to assess this condition, using mainly functional, biological, psychological and social domains.¹³ Given the multitude of definitions for frailty, as well as tools for assessing this condition, there is an enormous variability in the prevalence levels within the European population.¹⁴ There is general agreement that frailty is highly prevalent, affecting an average of 10% of the population aged ≥60 years and 25% of older adults aged ≥85 years.^{10,15}

The Survey of Health, Aging and Retirement in Europe (SHARE) is an international European database containing detailed information about the demographics, health, and social and economic status from representative samples of community-based populations aged >50 years.¹⁶ This project already has released data from six different waves, from 2004 to 2015, providing excellent opportunities to study frailty across Europe. The last detailed prevalence study published on frailty used data collected in 2004.¹⁷ In the present study, we intend to update the data of frailty status of the European

community-dwelling population, based on the latest data released (wave 6 – data from 2015), applying a version of the Fried phenotype operationalized to SHARE. Furthermore, we aim to study the impact of each of the five criteria in frailty assessment.

Materials and methods

In the present study, we used data from wave 6 of SHARE, collected in 2015. Wave 6 of SHARE has data from 68 231 individuals, aged between 24 and 106 years, from 18 countries: Austria, Germany, Sweden, Spain, Italy, France, Denmark, Greece, Switzerland, Belgium, Israel, Czech Republic, Poland, Luxembourg, Portugal, Slovenia, Estonia and Croatia.

SHARE is a harmonized and cross-national database that allows consistent international comparisons of many factors simultaneously, providing a dynamic picture of aging in Europe. A detailed description of the SHARE data and methodology has been published, and is available to registered users on the SHARE website (<http://www.share-project.org>).¹⁶

Frailty Criteria Assessment

Pre-frailty and frailty were defined as previously described^{18,19} using a SHARE operationalised version that is based on the five dimensions described by Fried et al.¹⁰: exhaustion, shrinking, weakness, slowness and low activity:

1. The Exhaustion criterion was fulfilled as a positive answer to the question: 'In the last month, have you had too little energy to do the things you wanted to do?'.
2. The Shrinking criterion was fulfilled by reporting a 'diminution in desire for food', answering 'What has your appetite been like in the last month?' or, in the case of an uncodable answer to this question, by responding 'less' to 'So, have you been eating more or less than usual?'.
3. Weakness was derived from the highest of four consecutive dynamometer measurements of handgrip strength (two from each hand), adjusted by gender and body mass index (BMI). This criterion was met by men whose handgrip strength was ≤ 29 and whose BMI was ≤ 24 , ≤ 30 for men with $24 < \text{BMI} \leq 28$, and ≤ 32 for men whose BMI > 28 ; and for women whose handgrip strength was ≤ 17 and whose BMI ≤ 23 , ≤ 17.3 for women with $23 < \text{BMI} \leq 26$, ≤ 18 for women with $26 < \text{BMI} \leq 29$, and ≤ 21 for men whose BMI > 29 , as proposed by Fried et al.¹⁰

4. The Slowness criterion was defined using mobility questions. Individuals who selected 'Climbing one flight of stairs without resting' or 'Walking 100 meters' to the question: 'Please tell me whether you have any difficulty doing each of the everyday activities on this card' fulfilled this criterion.
5. Low activity was satisfied in participants responding, 'One to three times a month' or 'hardly ever or never' to the question: 'How often do you engage in activities that require a low or moderate level of energy such as gardening, cleaning the car, or going for a walk?'.

One point was assigned for each fulfilled criterion; individuals with zero points were classified as robust, individuals with one or two points as pre-frail and with three to five points as frail.¹⁷

Statistical Analysis

To assess the prevalence of frailty status of SHARE participants, and to understand the impact of each of the criteria in the assessment of frailty, we carried out a descriptive analysis of the data collected. Four age groups were created (50–64, 65–74, 75–84, ≥85 years), and the prevalence results were standardized by age and sex, using the standard European population of 2013;²⁰ 95% confidence intervals (95% CI) were also calculated. Statistical analyses were carried out using IBM SPSS (version 25; IBM Corporation, Armonk, NY, USA).

Results

For the present study, from all the 68 231 SHARE wave 6 participants, we included those who answered all the questions used on frailty assessment and gender inquiry, and who were aged ≥50 years. We thus arrived at a final sample of 60 816 individuals. Of these, the mean age was 67.45 ± 9.71 years; 38 497 (56.4%) were women. Geographic distribution of pre-frail and frail individuals across Europe was unequal among the 18 evaluated countries (Fig. 1A,B). The overall prevalence of pre-frailty was 42.9% (range 34.0–52.8%). A high prevalence of pre-frailty was identified in Estonia (52.8%), Italy (49.7%) and Portugal (47.6%); whereas a lower prevalence was found in Austria (34.0%), Slovenia (36.4%) and Denmark (37.0%; Table 1). The overall prevalence of frailty was 7.7%, ranging from 3.0% to 15.6%. Portugal, Israel and Poland were the countries with higher prevalences of frailty (15.6%, 14.0% and 13.1%, respectively), whereas Switzerland, Sweden and Denmark were the countries where this

condition was less prevalent (3.0%, 4.2% and 5.0%, respectively; Table 2). An increasing prevalence of frailty status was found in individuals with higher ages. Indeed, a prevalence of pre-frailty and frailty in individuals aged 50–64 years was 38.7% and 3.0%, respectively, 41.7% and 6.0% for individuals aged 65–74 years, 50.5% and 16.0% for those aged 75–84 years, and 52.3% and 32.8% for individuals aged ≥85 years (Tables 1, 2). Substantial differences can then also be highlighted among sexes. In fact, we found higher prevalences of pre-frailty and frailty in women (45.4% and 9.1%, respectively), when compared with men (39.7% and 6.0%, respectively; Table 1).

Regarding the five criteria used on frailty assessment, exhaustion seems to be the criterion that contributes the most to frailty status (35.7 [35.2;36.1%]), followed by low activity (16.2 [15.9;16.5%]), weakness (15.8 [15.5;16.1%]), loss of appetite (8.3 [8.1;8.6%]) and slowness (5.5 [5.4;5.7%]; Table 3).

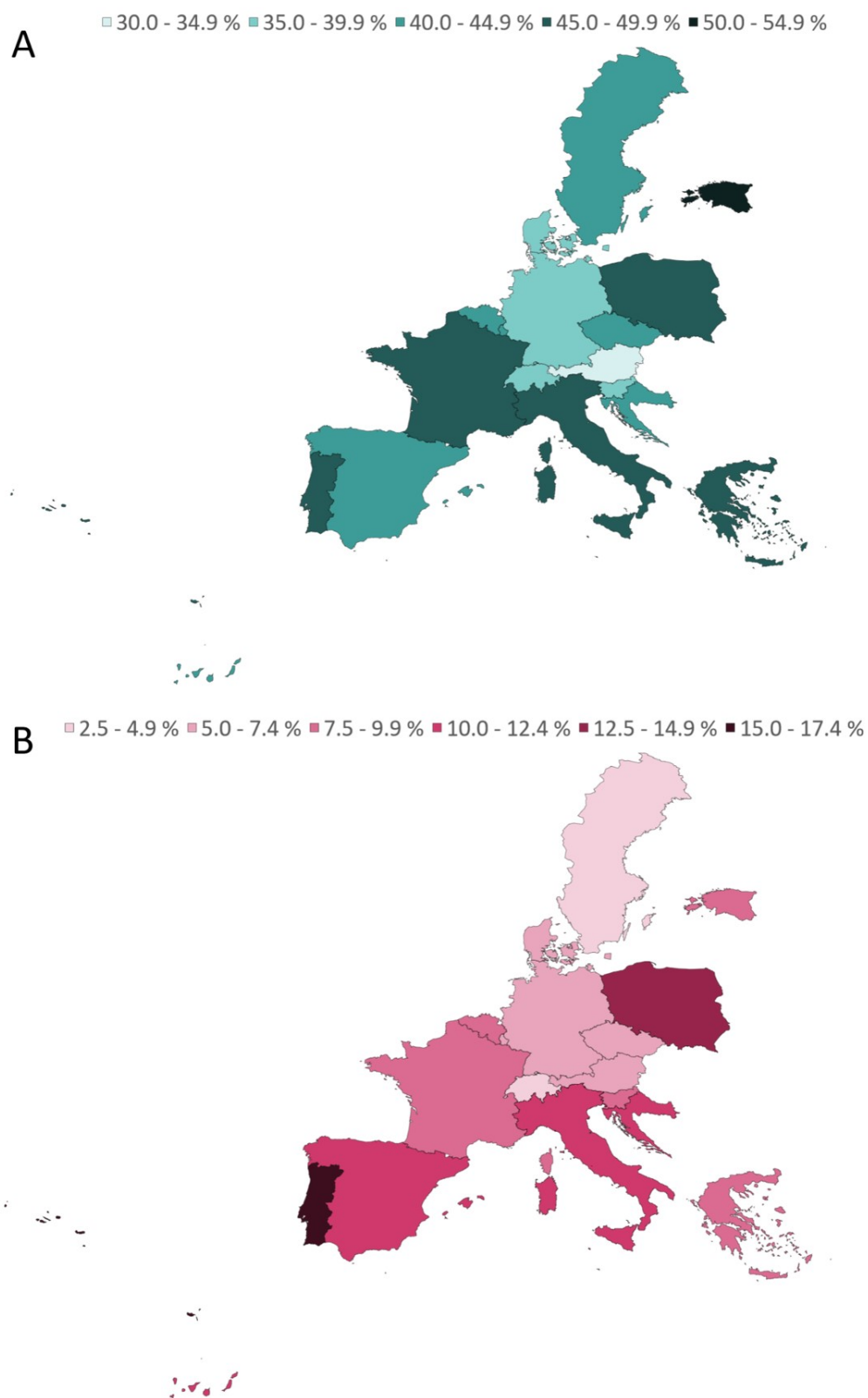


Figure 1 Prevalence of frailty status across Europe: (A) Pre-frailty across Europe; (B) Frailty across Europe.

Table 1 Prevalence of pre-frailty across Europe.

	OVERALL					MALE					FEMALE				
	Overall prevalence (95% CI)	Standardised prevalence rates (95% CI)				Overall prevalence (95% CI)	Standardised prevalence rates (95% CI)				Overall prevalence (95% CI)	Standardised prevalence rates (95% CI)			
		50-64	65-74	75-84	≥85		50-64	65-74	75-84	≥85		50-64	65-74	75-84	≥85
Austria (n=2901)	34.0 (33.6-34.5)	28.9 (28.3-29.5)	31.8 (31.0-32.5)	44.6 (43.5-45.8)	43.9 (42.1-45.8)	31.2 (30.6-31.8)	26.3 (25.5-27.2)	28.3 (27.3-29.4)	37.5 (36.0-39.0)	53.7 (50.9-56.7)	36.2 (35.6-36.9)	30.6 (29.7-31.6)	34.5 (33.4-35.6)	49.9 (48.2-51.6)	38.1 (35.7-40.6)
Germany (n=4094)	38.7 (38.2-39.2)	36.4 (35.7-37.2)	37.0 (36.2-37.8)	41.2 (40.1-42.3)	51.6 (49.7-53.7)	36.0 (35.3-36.6)	33.7 (32.7-34.7)	34.6 (33.4-35.7)	37.5 (36.0-39.0)	50.0 (47.3-52.9)	41.4 (40.7-42.1)	38.5 (37.5-39.6)	39.6 (38.4-40.8)	45.6 (44.0-47.3)	53.3 (50.4-56.2)
Sweden (n=3682)	42.4 (41.9-42.9)	40.9 (40.2-41.7)	37.0 (36.2-37.8)	47.9 (46.7-49.1)	58.6 (56.5-60.7)	38.2 (38.0-38.8)	35.1 (34.1-36.1)	34.6 (33.5-35.7)	45.6 (44.0-47.3)	50.4 (47.6-53.3)	46.0 (45.2-46.7)	45.6 (44.4-46.7)	39.0 (37.8-40.2)	50.2 (48.5-52.0)	66.2 (63.0-69.5)
Spain (n=4698)	44.0 (43.5-44.5)	36.0 (35.3-36.7)	45.4 (44.5-46.4)	56.2 (54.9-57.5)	50.0 (48.1-52.0)	42.7 (42.0-43.4)	33.3 (32.3-34.3)	42.6 (41.4-43.9)	57.9 (56.1-59.8)	54.3 (51.5-57.3)	45.1 (44.4-45.9)	38.0 (37.0-39.1)	48.0 (46.7-49.4)	54.6 (52.8-56.4)	46.7 (44.0-49.4)
Italy (n=4508)	49.7 (49.1-50.2)	47.6 (46.8-48.5)	50.1 (49.2-51.1)	52.0 (50.8-53.3)	52.4 (50.4-54.4)	45.7 (45.0-46.4)	41.0 (40.0-42.1)	45.9 (44.6-47.2)	50.7 (49.0-52.5)	56.8 (53.8-59.8)	52.9 (52.1-53.7)	52.6 (51.4-53.9)	54.0 (52.6-55.4)	53.5 (51.7-55.3)	48.0 (45.3-50.7)
France (n=3630)	46.0 (45.5-46.5)	43.2 (42.4-44.0)	43.3 (42.4-44.2)	54.2 (52.9-55.5)	51.4 (49.5-53.5)	41.3 (40.6-42.0)	38.0 (37.0-39.1)	34.7 (33.6-35.9)	53.0 (51.3-54.8)	56.0 (53.2-59.1)	50.0 (49.3-50.8)	47.4 (46.3-48.6)	50.5 (49.2-51.9)	55.0 (53.2-56.9)	49.2 (46.5-52.0)
Denmark (n=3543)	37.0 (36.5-37.5)	35.3 (34.6-36.1)	30.9 (30.1-31.6)	42.0 (40.9-43.1)	58.9 (56.8-61.1)	35.4 (34.7-36.0)	33.5 (32.6-34.5)	31.1 (30.1-32.2)	38.0 (36.5-39.5)	56.5 (53.5-59.5)	38.3 (37.7-39.0)	36.8 (35.8-37.9)	30.6 (29.6-31.7)	45.4 (43.8-47.1)	60.4 (57.4-63.5)
Greece (n=4349)	45.0 (44.5-45.5)	39.2 (38.4-39.9)	44.8 (43.9-45.8)	54.0 (52.8-55.3)	53.3 (51.3-55.4)	42.7 (42.0-43.4)	37.4 (36.3-38.4)	39.7 (38.5-40.9)	54.4 (52.7-56.3)	53.9 (51.0-56.8)	47.0 (46.3-47.7)	40.4 (39.4-41.5)	49.9 (48.6-51.3)	53.7 (51.9-55.5)	52.8 (50.0-55.7)
Switzerland (n=2705)	38.8 (38.3-39.2)	33.5 (32.8-34.2)	33.6 (32.8-34.4)	50.9 (49.7-52.2)	57.2 (55.1-59.4)	34.6 (33.9-35.2)	31.0 (30.1-32.0)	28.1 (27.1-29.2)	43.1 (41.5-44.7)	58.3 (55.4-61.4)	42.6 (41.9-43.3)	35.3 (34.3-36.3)	39.0 (37.8-40.2)	58.0 (56.2-59.9)	56.5 (53.6-59.5)
Belgium (n=5333)	43.4 (42.9-43.9)	41.2 (40.4-42.0)	40.8 (39.9-41.6)	50.2 (49.0-51.5)	49.2 (47.3-51.2)	40.4 (39.7-41.1)	36.3 (35.3-37.3)	37.3 (36.2-38.5)	47.7 (46.0-49.4)	56.9 (54.0-60.0)	46.0 (45.2-46.7)	45.1 (44.0-46.2)	43.9 (42.7-45.2)	52.3 (50.5-54.1)	42.8 (40.3-45.4)
Israel (n=1579)	41.2 (40.7-41.7)	34.1 (33.4-34.8)	41.5 (40.6-42.4)	52.7 (51.5-54.0)	49.0 (47.0-50.9)	39.1 (38.5-39.8)	30.2 (29.3-31.2)	40.2 (39.0-41.4)	52.6 (50.8-54.4)	47.8 (45.2-50.6)	42.7 (42.0-43.4)	36.6 (35.5-37.6)	42.5 (41.3-43.8)	52.9 (51.1-54.7)	50.0 (47.3-52.9)
Czech Republic (n=4427)	42.3 (41.8-42.8)	37.5 (36.8-38.3)	37.7 (36.9-38.6)	52.8 (51.5-54.1)	59.9 (57.7-62.1)	39.0 (38.3-39.7)	31.1 (30.2-32.1)	36.0 (34.8-37.1)	50.5 (48.8-52.3)	64.5 (61.4-67.7)	44.3 (43.6-45.0)	41.5 (40.4-42.6)	39.0 (37.8-40.2)	54.5 (52.7-56.3)	55.6 (52.7-58.6)
Poland (n=1628)	47.3 (46.8-47.8)	40.6 (39.8-41.3)	51.1 (50.1-52.1)	55.8 (54.5-57.1)	45.6 (43.7-47.5)	44.2 (43.5-44.9)	36.3 (35.3-37.3)	44.8 (43.6-46.1)	54.2 (52.5-56.1)	58.3 (55.4-61.4)	50.1 (49.4-50.9)	44.0 (42.8-45.1)	56.5 (55.0-57.9)	57.1 (55.3-59.0)	38.6 (36.2-41.2)
Luxembourg (n=1427)	42.8 (42.3-43.3)	38.4 (37.7-39.1)	40.2 (39.4-41.1)	49.7 (48.5-50.9)	58.8 (56.7-61.0)	36.2 (35.6-36.9)	31.8 (30.9-32.8)	33.5 (32.4-34.6)	43.8 (42.2-45.5)	52.0 (49.2-54.9)	48.7 (48.0-49.5)	43.3 (42.2-44.4)	47.4 (46.1-48.7)	55.8 (54.0-57.7)	65.4 (62.3-68.6)
Portugal (n=1412)	47.6 (47.0-48.1)	44.2 (43.4-45.0)	49.7 (48.8-50.7)	52.2 (51.0-53.5)	44.2 (42.4-46.1)	45.2 (44.5-46.0)	37.9 (36.9-39.0)	48.2 (46.9-49.6)	59.5 (57.7-61.4)	35.0 (32.7-37.4)	48.7 (47.9-49.4)	48.5 (47.4-49.7)	51.0 (49.7-52.4)	44.5 (42.9-46.2)	50.0 (47.3-52.9)
Slovenia (n=3834)	36.4 (36.0-36.9)	29.2 (28.6-29.9)	35.2 (34.4-36.0)	47.0 (45.8-48.1)	53.2 (51.2-55.2)	34.0 (33.4-34.7)	25.5 (24.7-26.4)	31.4 (30.3-32.4)	45.9 (44.3-47.6)	60.3 (57.3-63.4)	38.4 (37.7-39.0)	31.9 (30.9-32.8)	38.5 (37.3-39.7)	47.7 (46.0-49.4)	48.7 (46.0-51.5)
Estonia (n=4856)	52.8 (52.3-53.4)	49.1 (48.3-50.0)	53.1 (52.1-54.0)	60.0 (58.7-61.3)	53.1 (51.1-55.2)	50.5 (49.8-51.3)	43.6 (42.5-44.8)	51.0 (49.7-52.4)	61.6 (59.7-63.5)	56.7 (53.8-59.8)	54.4 (53.6-55.2)	52.7 (51.5-54.0)	54.3 (52.9-55.8)	59.2 (57.3-61.1)	51.1 (48.3-54.0)
Croatia (n=2210)	44.6 (44.1-45.1)	40.7 (39.9-41.5)	47.1 (46.2-48.1)	46.0 (44.8-47.2)	51.0 (49.0-53.0)	41.0 (40.4-41.7)	35.9 (34.9-36.9)	42.8 (41.4-44.1)	43.3 (41.7-44.9)	55.6 (52.7-58.6)	47.6 (46.9-48.4)	44.4 (43.2-45.5)	51.3 (50.0-52.7)	48.0 (46.4-49.7)	48.5 (45.8-51.3)
Total (n=60816)	42.9 (42.4-43.4)	38.7 (37.9-39.4)	41.7 (40.8-42.6)	50.5 (49.3-51.8)	52.3 (50.3-54.3)	39.7 (39.1-40.4)	34.3 (33.4-35.3)	38.0 (36.9-39.2)	48.7 (47.0-50.4)	54.3 (51.4-57.2)	45.4 (44.7-46.1)	41.8 (40.8-43.0)	45.0 (43.7-46.3)	52.1 (50.4-53.9)	51.2 (48.4-54.1)

Table 2 Prevalence of frailty across Europe.

	OVERALL					MALE					FEMALE				
	Overall prevalence (95% CI)	Standardised prevalence rates (95% CI)				Overall prevalence (95% CI)	Standardised prevalence rates (95% CI)				Overall prevalence (95% CI)	Standardised prevalence rates (95% CI)			
		50-64	65-74	75-84	≥85		50-64	65-74	75-84	≥85		50-64	65-74	75-84	≥85
Austria (n=2901)	7.2 (6.9-7.4)	1.6 (1.5-1.8)	4.4 (4.1-4.7)	11.6 (11-12.2)	37.2 (35.6-39.0)	5.9 (5.6-6.1)	2.5 (2.3-2.8)	4.2 (3.8-4.6)	8.6 (7.9-9.4)	23.9 (22.0-25.9)	8.0 (7.7-8.3)	1.0 (0.8-1.2)	4.6 (4.2-5.0)	13.7 (12.8-14.6)	45.1 (42.5-47.9)
Germany (n=4094)	5.2 (5.1-5.4)	1.9 (1.7-2.1)	2.5 (2.3-2.7)	9.6 (9.0-10.1)	23.5 (22.2-24.9)	4.1 (3.9-4.3)	1.2 (1.0-1.4)	2.4 (2.2-2.8)	7.1 (6.4-7.7)	18.4 (16.8-20.2)	6.4 (6.2-6.7)	2.4 (2.1-2.7)	2.6 (2.3-2.9)	12.6 (11.7-13.5)	28.6 (26.5-30.8)
Sweden (n=3682)	4.2 (4.0-4.4)	1.8 (1.7-2.0)	2.0 (1.8-2.2)	7.1 (6.6-7.5)	18.7 (17.5-19.9)	3.4 (3.2-3.6)	0.9 (0.7-1.1)	0.7 (0.6-0.9)	6.5 (5.9-7.2)	20.2 (18.4-22.0)	4.9 (4.6-5.1)	2.6 (2.4-2.9)	3.0 (2.7-3.4)	7.6 (7.0-8.3)	17.3 (15.7-19.0)
Spain (n=4698)	11.2 (11.0-11.5)	4.1 (3.8-4.3)	8.1 (7.7-8.5)	19.2 (18.5-20.0)	42.2 (40.4-44.0)	8.3 (8.0-8.7)	3.2 (2.9-3.5)	5.8 (5.3-6.3)	12.1 (11.3-13.0)	37.1 (34.7-39.6)	13.8 (13.4-14.2)	4.8 (4.4-5.2)	10.2 (9.6-10.9)	25.8 (24.5-27.0)	46.2 (43.5-48.9)
Italy (n=4508)	11.0 (10.7-11.2)	4.3 (4.1-4.5)	8.4 (8.0-8.8)	19.6 (18.8-20.4)	35.4 (33.7-37.1)	7.9 (7.6-8.2)	3.4 (3.1-3.7)	5.4 (5.0-5.9)	14.9 (13.9-15.8)	24.3 (22.4-26.3)	14.0 (13.6-14.4)	5.0 (4.6-5.4)	11.1 (10.4-11.7)	24.9 (23.7-26.2)	46.6 (43.9-49.3)
France (n=3630)	9.1 (8.9-9.3)	3.0 (2.8-3.2)	5.6 (5.3-5.9)	15.6 (14.9-16.3)	40.3 (38.5-42.1)	6.9 (6.6-7.1)	2.0 (1.8-2.3)	4.8 (4.4-5.3)	11.4 (10.6-12.3)	29.7 (27.6-31.9)	10.6 (10.3-11.0)	3.8 (3.4-4.1)	6.2 (5.7-6.7)	18.6 (17.6-19.7)	45.5 (42.9-48.2)
Denmark (n=3543)	5.0 (4.9-5.2)	0.9 (0.7-1.0)	3.3 (3.1-3.6)	10.0 (9.5-10.6)	22.0 (20.7-23.4)	4.2 (4.0-4.4)	0.6 (0.5-0.8)	2.7 (2.4-3.1)	8.0 (7.3-8.7)	19.4 (17.7-21.2)	5.8 (5.5-6.1)	1.0 (0.9-1.2)	4.0 (3.6-4.4)	11.7 (10.9-12.6)	23.6 (21.7-25.6)
Greece (n=4349)	9.9 (9.7-10.2)	4.4 (4.2-4.7)	7.0 (6.7-7.4)	16.8 (16.1-17.6)	33.9 (32.3-35.5)	7.7 (7.4-8.0)	3.7 (3.4-4.1)	5.6 (5.1-6.0)	11.7 (10.8-12.5)	27.5 (25.5-29.6)	11.9 (11.6-12.3)	4.9 (4.5-5.2)	8.5 (7.9-9.0)	21.3 (20.2-22.5)	40.5 (38.0-43.0)
Switzerland (n=2705)	3.0 (2.8-3.1)	1.0 (0.9-1.1)	2.0 (1.8-2.2)	4.4 (4.0-4.8)	13.9 (12.9-15.0)	2.8 (2.6-3.0)	1.4 (1.2-1.6)	2.6 (2.3-2.9)	3.9 (3.4-4.4)	8.3 (7.2-9.6)	3.0 (2.9-3.2)	0.7 (0.5-0.8)	1.5 (1.2-1.7)	4.9 (4.4-5.5)	17.6 (16.0-19.3)
Belgium (n=5333)	9.4 (9.2-9.7)	4.0 (3.8-4.3)	5.4 (5.1-5.8)	16.6 (15.9-17.3)	36.9 (35.2-38.6)	6.9 (6.6-7.2)	3.0 (2.7-3.3)	4.1 (3.7-4.5)	12.8 (12.0-13.7)	24.3 (22.4-26.3)	11.6 (11.2-11.9)	4.9 (4.5-5.3)	6.6 (6.2-7.1)	19.5 (18.5-20.6)	47.4 (44.7-50.2)
Israel (n=1579)	14.0 (13.7-14.3)	6.4 (6.1-6.7)	11.6 (11.1-12.1)	21.5 (20.7-22.3)	45.8 (44.0-47.7)	12.9 (12.5-13.3)	5.6 (5.2-6.0)	9.5 (8.9-10.1)	20.0 (18.9-21.1)	47.8 (45.2-50.6)	14.9 (14.5-15.3)	7.0 (6.5-7.4)	13.3 (12.6-14.1)	22.8 (21.7-24.0)	44.0 (41.4-46.7)
Czech Republic (n=4427)	7.2 (7.0-7.4)	3.1 (2.9-3.3)	5.3 (5.0-5.6)	12.4 (11.8-13.1)	24.2 (22.9-25.6)	5.9 (5.7-6.2)	3.3 (3.0-3.6)	4.3 (3.9-4.7)	7.9 (7.2-8.6)	22.4 (20.6-24.3)	8.2 (7.9-8.5)	3.0 (2.7-3.3)	6.0 (5.5-6.5)	15.9 (14.9-16.9)	25.9 (24.0-28.0)
Poland (n=1628)	13.1 (12.8-13.4)	2.9 (2.7-3.1)	8.2 (7.8-8.5)	29.8 (28.9-30.8)	45.6 (43.7-47.5)	11.0 (10.7-11.4)	2.6 (2.3-2.8)	8.6 (8.1-9.2)	25.4 (24.2-26.7)	29.2 (27.1-31.4)	14.5 (14.1-14.9)	3.1 (2.9-3.5)	7.8 (7.2-8.3)	33.6 (32.2-35.0)	54.6 (51.7-57.5)
Luxembourg (n=1427)	6.0 (5.8-6.2)	1.7 (1.5-1.8)	5.1 (4.8-5.4)	12.0 (11.4-12.6)	17.6 (16.5-18.9)	5.4 (5.2-5.7)	0.6 (0.5-0.8)	2.7 (2.4-3.1)	15.7 (14.8-16.7)	16.0 (14.5-17.7)	6.5 (6.2-6.8)	2.5 (2.2-2.8)	7.7 (7.1-8.2)	8.1 (7.5-8.9)	19.2 (17.6-21.0)
Portugal (n=1412)	15.6 (15.3-15.9)	5.9 (5.7-6.2)	12.2 (11.7-12.6)	28.6 (27.7-29.5)	48.1 (46.2-50.0)	11.5 (11.2-11.9)	1.7 (1.5-2.0)	8.0 (7.4-8.5)	19.1 (18.0-20.1)	60.0 (57.0-63.1)	19.3 (18.8-19.8)	8.8 (8.3-9.3)	15.8 (15.0-16.5)	38.7 (37.2-40.2)	40.6 (38.2-43.2)
Slovenia (n=3834)	7.6 (7.4-7.8)	1.8 (1.6-2.0)	4.7 (4.5-5.0)	16.9 (16.2-17.6)	26.3 (24.9-27.8)	5.9 (5.7-6.2)	1.4 (1.2-1.6)	4.2 (3.8-4.6)	13.0 (12.2-13.9)	19.2 (17.5-21.0)	8.7 (8.4-9.0)	2.1 (1.8-2.3)	5.2 (4.8-5.7)	19.5 (18.5-20.6)	30.8 (28.6-33.0)
Estonia (n=4856)	8.5 (8.3-8.7)	2.2 (2.0-2.3)	5.3 (5.0-5.6)	15.8 (15.1-16.4)	37.2 (35.6-39.0)	7.4 (7.1-7.7)	1.7 (1.5-1.9)	5.9 (5.4-6.4)	12.2 (11.4-13.1)	31.7 (29.6-34.0)	9.1 (8.8-9.4)	2.5 (2.2-2.7)	4.9 (4.5-5.3)	17.5 (16.5-18.6)	40.3 (37.9-42.9)
Croatia (n=2210)	11.0 (10.7-11.2)	2.9 (2.7-3.1)	7.7 (7.3-8.0)	21.5 (20.8-22.4)	41.2 (39.4-43.0)	8.1 (7.8-8.5)	1.8 (1.6-2.0)	6.1 (5.7-6.6)	14.9 (14.0-15.9)	33.3 (31.1-35.7)	13.1 (12.7-13.5)	3.7 (3.4-4.1)	9.1 (8.6-9.7)	26.6 (25.3-27.8)	45.5 (42.9-48.2)
Total (n=60816)	7.7 (7.5-8.0)	3.0 (2.8-3.2)	6.0 (5.7-6.4)	16.0 (15.4-16.8)	32.8 (31.2-34.4)	6.0 (5.8-6.3)	2.3 (2.0-2.5)	4.9 (4.5-5.3)	12.5 (11.7-13.4)	27.4 (25.4-29.5)	9.1 (8.8-9.4)	3.5 (3.2-3.9)	7.1 (6.6-7.6)	19.1 (18.0-20.2)	36.6 (34.3-39.1)

Table 3 Prevalence of the criteria used in frailty assessment.

	EXHAUSTION			APPETITE			SLOWNESS			LOW ACTIVITY			WEAKNESS		
	Overall	Male	Female	Overall	Male	Female	Overall	Male	Female	Overall	Male	Female	Overall	Male	Female
Overall (n=60816)	35.7 (35.2-36.1)	30.1 (29.5-30.7)	40.1 (39.4-40.7)	8.3 (8.1-8.6)	6.6 (6.3-6.9)	9.7 (9.4-10.1)	5.5 (5.4-5.7)	4.5 (4.3-4.7)	6.4 (6.1-6.7)	16.2 (15.9-16.5)	15.1 (14.7-15.6)	17.0 (16.6-17.5)	15.8 (15.5-16.1)	14.3 (13.9-14.7)	17.0 (16.6-17.5)
50-64 (n=25712)	30.7 (30.1-31.4)	25.2 (24.4-26.1)	34.8 (33.8-35.8)	6.4 (6.1-6.7)	5.1 (4.7-5.5)	7.3 (6.8-7.8)	2.1 (1.9-2.3)	1.9 (1.7-2.1)	2.2 (2.0-2.5)	11.9 (11.5-12.3)	11.8 (11.3-12.4)	11.9 (11.3-12.5)	6.1 (5.8-6.4)	4.7 (4.4-5.1)	7.2 (6.7-7.6)
65-74 (n=20041)	33.2 (32.4-33.9)	28.0 (27.0-29.1)	37.7 (36.6-38.9)	7.4 (7.0-7.8)	5.7 (5.2-6.2)	8.9 (8.3-9.5)	4.8 (4.5-5.1)	4.1 (3.7-4.5)	5.4 (4.9-5.8)	14.6 (14.1-15.1)	14.1 (13.4-14.9)	15.1 (14.3-15.8)	13.3 (12.8-13.8)	11.5 (10.8-12.1)	14.9 (14.1-15.6)
75-84 (n=11891)	44.5 (43.4-45.7)	38.2 (36.7-39.7)	50.1 (48.4-51.8)	12.2 (11.6-12.8)	9.4 (8.7-10.2)	14.6 (13.7-15.5)	10.7 (10.1-11.3)	8.4 (7.7-9.2)	12.5 (11.7-13.4)	24.2 (23.3-25.0)	20.8 (19.7-21.9)	27.2 (25.9-28.5)	32.7 (31.7-33.7)	30.3 (29.0-31.7)	34.7 (33.3-36.2)
≥85 (n=3172)	54.2 (52.2-56.3)	48.7 (46.0-51.5)	58.2 (55.3-61.3)	17.1 (16.0-18.3)	12.8 (11.4-14.3)	20.2 (18.5-22.1)	22.0 (20.7-23.4)	16.3 (14.8-18.0)	25.9 (23.9-27.9)	41.1 (39.4-43.0)	35.7 (33.4-38.1)	45.1 (42.5-47.8)	59.4 (57.3-61.6)	58.9 (55.9-61.9)	60.1 (57.1-63.3)

Population aging is challenging for the sustainability of healthcare systems across Europe.²¹ Awareness of and concerns about the impact of geriatric syndromes on clinical outcomes and quality of life of older adults, as well as issues related to the economic burden caused by aging, is increasing.⁹ It is thus important to redesign care processes to answer the needs of older adults, especially for complex patients, such as those who are frail. Frailty is a geriatric syndrome that results from the accumulation of defects in various physiological systems.^{9, 10} Although this syndrome is widely recognized, there is still debate on what is the best way to assess it. Many operational definitions have been introduced to try to distinguish frail from non-frail individuals. Due to its multiplicity of definitions and tools to assess it, the prevalence of frailty has been reported to be between 4.0 and 59.1% in community-based studies.^{11, 22} The estimated prevalence of frailty in older populations varies largely, due to the heterogeneity of criteria used to define it – a problem that hinders geographical comparisons.²³ From that arose the need for a study of the prevalence of the frailty condition at the European level, using the same methodology, so those results could be compared among countries. Indeed, the aim of the present study was to evaluate the prevalence of frailty status in the 18 countries included in SHARE wave 6 and the impact of each of the five criteria taken into consideration. Fried's phenotype, which consists of five different criteria: weakness, shrinking, exhaustion, low activity and slowness, is commonly used; indeed, it is considered a gold standard for measuring frailty.^{10, 24} In the present study we used an operationalized version of these criteria for the SHARE survey, which has already proven to be a robust tool in identifying populations most at risk of developing adverse outcomes.^{17, 25}

We found that 38.7% of all the individuals aged between 50 and 64 years were pre-frail and 3.0% were frail, whereas individuals aged ≥ 85 years were 1.4-fold more pre-frail and 10.9-fold more frail. Also, women appear to be more likely to develop this condition, as they presented higher percentages of frailty (16.4% vs 8.6% in men) and pre-frailty (43.4% vs 38.1% in men).²⁵ This is an effect largely reported in several studies. One of the possible explanations can be quality of life, which disfavors the female population.²⁶ Comparing data from 2004 (wave 1) with the 2015 data used in the present study (wave 6), it is possible to observe that women were almost twice as frail as men. However, the 2015 data showed that women were only 1.5-fold more prone to be frail. Also, there was an increase in the pre-frail population (39.6% vs 42.9%), and a decrease

in the frail population (9.9% vs 7.7%).¹⁷ Transposing the prevalence values for the population aged ≥ 50 years, living in 2015 in the 17 European countries represented, this means that of all 150 131 950 individuals, 64 406 607 were pre-frail and 11 560 160 were frail. These numbers are of major importance, showing that interventions are required to enhance citizens' health and quality of life across Europe. By such means, there could be an improvement in the sustainability and effectiveness of health and care systems, thereby relieving the economic burden associated with this syndrome.

The prevalence of frailty was also evaluated in wave 2 of SHARE, with different results: in that study, the prevalence of pre-frailty and frailty were 41.1% and 12.9%, respectively. Although in that study, only individuals aged ≥ 60 years were included (and this must be considered when comparing results), it might be an explanation for why the prevalences were higher than those found with waves 1 and 6.²⁵ As has been reported in several studies already, the present findings corroborate that frailty is a condition that becomes more prevalent as age advances.^{17, 18, 26}

The prevalence of frailty was found to be unequal across different countries. Northern European countries present lower prevalences of pre-frailty and frailty compared with Southern European countries. This same tendency was already observed in other studies about frailty, and is in agreement with other health indicators studied in SHARE that showed worsening conditions as one went from Northern to Southern Europe.^{17, 18, 27} Comparing the present results with those of wave 1, some important changes arose. In the age group of 50–64 years, the prevalences of pre-frailty and frailty decreased in Austria (1.5% and 2.3%, respectively), Switzerland (2.6% and 0.3%, respectively) and Spain (8.9% and 3.4%, respectively). On the other side, for this age group, in Greece there was an increase of 5.7% for pre-frailty and 1.6% for frailty prevalences. In the other countries, the tendency was the same: an increase in pre-frailty prevalence (5.0% in Sweden, 0.4% in Denmark, 5.5% in Germany, 1.9% in France and 4.1% in Italy) and a decrease of frailty prevalence (0.1% in Sweden, 2.1% in Denmark, 0.7% in Germany, 0.2% in France and 1.6% in Italy). For the older population (aged ≥ 65 years), a decrease in pre-frailty and frailty prevalences was also observed in Sweden (5.4% and 3.2%, respectively), Denmark (1.7% and 6.4%, respectively), Austria (3.5% and 0.9%, respectively), Switzerland (4.7% and 1.7%, respectively) and Spain (1.0% and 11.1%, respectively). In Germany, France, Italy and Greece, an increase in pre-frailty prevalence (4.9%, 4.5%, 5.3% and 4.0%, respectively) and a decrease in frailty prevalence (5.7%, 1.4%, 8.8% and 2.0%, respectively) were observed. For the other countries included in wave 6, no comparison was available, once they were not included in wave 1.¹⁷ These changes could be a product of the increasing awareness of frailty, as healthcare professionals and researchers have been focusing more on this subject over the past

several years. In fact, health policy initiatives have been created that focus on postponing/preventing frailty among older adults.²⁸⁻³⁰

Regarding the five criteria, exhaustion seems to be the one with the highest weight in frailty assessment for both the 50–64 years and ≥65 years age groups. In the 50–64 years age group, exhaustion (30.7%) was followed by low activity (11.9%), shrinking (6.4%), weakness (6.1%) and slowness (2.1%). Comparing these results with those obtained in wave 1, no major changes are noticed, except for slowness, which affected 6.7% of the total population in 2004, and had a decrease of 4.6% in 2015. In the older participants, aged ≥65 years, exhaustion (38.9%) was followed by weakness (24.0%), low activity (20.3%), shrinking (9.9%) and slowness (8.4), which also had a decrease since 2004 of 14.3%. This difference between the prevalence of the weakness criteria between age groups can be linked to the physical decline that occurs with age. Lower levels of slowness might be a result of increased population awareness of physical exercise and other initiatives that have been developed for promotion of physical exercise for the older population.

There were some limitations in the present study that should be noted. Most of the data used in this study (as drawn from SHARE) are self-reported; this raises some questions regarding their validity. Indeed, four of the five questions used in the frailty assessment were subjective; only one (weakness) was objective. Also, it is well known that most people who volunteer to take part in studies such as this are healthier than their peers. Thus, people with more illnesses might not have been included in the study; this could have influenced the prevalences.

In conclusion, pre-frailty and frailty were found to be highly prevalent across Europe. This is a dynamic process that must be understood as a continuum with intermediate stages that can be modified.²⁴ Frailty is not an inevitable consequence of aging, nor is it a unidirectional process. It must be identified early; this might help health and social care professionals take action, thereby improving outcomes and avoiding unnecessary harm/costs. With this work, we showed that almost 43% of the population aged ≥50 years are pre-frail, and almost 8% are frail. This means that >50% of the European population suffer a frailty status, a fact that must be considered when designing interventions to reduce/postpone/mitigate the progression of this process.

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Disclosure statement

The authors declare no conflict of interest.

References

1. Dall JLC. The Greying of Europe. *BMJ*. 1994;309(6964):1282-1285.
2. Department of Economic and Social Affairs, Population Division UN. *World Population Ageing 2015.*; 2015.
3. Bongaarts J. Human population growth and the demographic transition. *Philos Trans R Soc B Biol Sci*. 2009;364(1532):2985-2990. doi:10.1098/rstb.2009.0137.
4. Eurostat. *Population Structure and Ageing - Statistics Explained.*; 2016. doi:http://ec.europa.eu/eurostat/statistics-explained/index.php/Population_structure_and_ageing.
5. European Commission. *The 2018 Ageing Report Underlying Assumptions & Projection Methodologies EUROPEAN ECONOMY.*; 2017.
6. Oxley H. Policies for Healthy Ageing: An Overview. *OECD Heal Work Pap*. 2009;(42):6-30. doi:10.1787/226757488706.
7. OECD. *Life Expectancy and Healthy Life Expectancy at 65.*; 2012.
8. Divo MJ, Martinez CH, Mannino DM. Ageing and the epidemiology of multimorbidity. *Eur Respir J*. 2014;44(4):1055-1068. doi:10.1183/09031936.00059814.

9. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet*. 2013;381(9868):752-762. doi:10.1016/S0140-6736(12)62167-9.
10. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J et al, Fried LP, Tangen CM, Walston J et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M146-M156. doi:10.1093/gerona/56.3.M146.
11. Martin FC, Brighton P. Frailty: Different tools for different purposes? *Age Ageing*. 2008;37(2):129-131. doi:10.1093/ageing/afn011.
12. Buckinx F, Rolland Y, Reginster J-Y, Ricour C, Petermans J, Bruyère O. Burden of frailty in the elderly population: perspectives for a public health challenge. *Arch Public Heal*. 2015;73(1):19. doi:10.1186/s13690-015-0068-x.
13. Buta BJ, Walston JD, Godino JG, et al. Frailty assessment instruments: Systematic characterization of the uses and contexts of highly-cited instruments. *Ageing Res Rev*. 2016;26:53-61. doi:10.1016/j.arr.2015.12.003.
14. Keevil VL, Romero-Ortuno R. Ageing well: A review of sarcopenia and frailty. *Proc Nutr Soc*. 2015;74(4):337-347. doi:10.1017/S0029665115002037.
15. Woods NF, LaCroix AZ, Gray SL, et al. Frailty: Emergence and consequences in women aged 65 and older in the Women's Health Initiative observational study. *J Am Geriatr Soc*. 2005;53(8):1321-1330. doi:10.1111/j.1532-5415.2005.53405.x.
16. Lourenç J, Santos-silva A, Gomes M, Afonso C, Freitas P. Cardiovascular Risk Factors Are Correlated with Low Cognitive Function among Older Adults Across Europe Based on The SHARE Database. 2017;8(5):1-12. doi:10.14336/AD.2017.0128.
17. Santos-Eggimann B, Cuénoud P, Spagnoli J, Junod J. Prevalence of frailty in middle-aged and older community-dwelling Europeans living in 10 countries. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2009;64(6):675-681. doi:10.1093/gerona/glp012.
18. Romero-Ortuno R, Walsh CD, Lawlor BA, Kenny RA. A Frailty Instrument for primary care: Findings from the Survey of Health, Ageing and Retirement in Europe (SHARE). *BMC Geriatr*. 2010;10. doi:10.1186/1471-2318-10-57.
19. Romero-Ortuno R, O'Shea D, Kenny RA. The SHARE frailty instrument for primary care predicts incident disability in a European population-based sample. *Qual Prim Care*. 2011;19(5):301-309.
20. EUROSTAT. Revision of the European Standard Population - Report of Eurostat's Task Force - 2013 Edition.; 2013. doi:10.2785/11470.

21. Knickman JR, Snell EK. The 2030 problem: Caring for aging baby boomers. *Health Serv Res.* 2002;37(4):849-884. doi:10.1034/j.1600-0560.2002.56.x.
22. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: A systematic review. *J Am Geriatr Soc.* 2012;60(8):1487-1492. doi:10.1111/j.1532-5415.2012.04054.x.
23. Pialoux T, Goyard J, Lesourd B. Screening tools for frailty in primary health care: A systematic review. *Geriatr Gerontol Int.* 2012;12(2):189-197. doi:10.1111/j.1447-0594.2011.00797.x.
24. Abellan Van Kan G, Rolland Y, Bergman H, Morley JE, Kritchevsky SB, Vellas B. The I.A.N.A. task force on frailty assessment of older people in clinical practice. *J Nutr Heal Aging.* 2008;12(1):29-37. doi:10.1007/BF02982161.
25. Macklai NS, Spagnoli J, Junod J, Santos-Eggimann B. Prospective association of the SHARE-operationalized frailty phenotype with adverse health outcomes: Evidence from 60+ community-dwelling Europeans living in 11 countries. *BMC Geriatr.* 2013;13(1):1. doi:10.1186/1471-2318-13-3.
26. Romero-Ortuno R, Fouweather T, Jagger C. Cross-national disparities in sex differences in life expectancy with and without frailty. *Age Ageing.* 2014;43(2):222-228. doi:10.1093/ageing/aft115.
27. Alcser KH, Avendano M, Borsch-Supan A, et al. Health, Ageing and Retirement in Europe. First Results from the Survey of Health, Ageing and Retirement in Europe. Mannheim Research Institute for the Economics of Aging (MEA); 2005.
28. Fries JF. Frailty, heart disease, and stroke: The compression of morbidity paradigm. *Am J Prev Med.* 2005;29(5 SUPPL. 1):164-168. doi:10.1016/j.amepre.2005.07.004.
29. Salem BE, Nyamathi A, Phillips LR, Mentis JC, Sarkisian C, Brecht ML. Development of a frailty framework among vulnerable populations. *Adv Nurs Sci.* 2014;37(1):70-81. doi:10.1097/ANS.0000000000000013.
30. Wilson MG, Béland F, Julien D, et al. Interventions for preventing, delaying the onset, or decreasing the burden of frailty: An overview of systematic reviews. *Syst Rev.* 2015;4(1):128. doi:10.1186/s13643-015-0110-7.

Manuscript II

Frailty Status and Polypharmacy Predict All-Cause Mortality in
Community Dwelling Older Adults in Europe

Midão L, Brochado P, Almada M, Duarte M, Paúl C, Costa E.

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MDPI

Abstract

European population ageing is associated with frailty, a complex geriatric syndrome, and polypharmacy, both resulting in adverse health outcomes. In this study we aimed to evaluate the impact of frailty and polypharmacy, on mortality rates, within 30 months, using a cohort of SHARE participants aged 65 years old or more. Frailty was assessed using a version of Fried's phenotype criteria operationalized to SHARE while polypharmacy was defined as taking five or more drugs per day. We found a prevalence of 40.4% non-frail, 47.3% pre-frail and 12.3% frail participants. Moreover, a prevalence of polypharmacy of 31.3% was observed, being 3 three times more prevalent in frail individuals and two times in pre-frail individuals, when compared with non-frail. Individuals with both conditions had shown higher mortality rates. Comparing with non-polymedicated non-frail individuals all the other conditions are more prone to die within 30 months. Polymedicated older and male participants exhibited also higher mortality rates. This work shows polypharmacy and frailty to be associated with a higher risk of all-cause of mortality and highlights the need to decrease 'unnecessary' polypharmacy to reduce drug-related issues and also the need to assess frailty early to prevent avoidable adverse outcomes.

Keywords: Frailty, Polypharmacy, All-cause mortality, Follow-up, 30 months follow-up

The European population has been growing old over the last decades and this is expected to continue, due to better quality of life and increased life expectancy [1,2]. Higher longevity leads to a greater expression of ageing related conditions, such as chronic diseases, comorbidities, and geriatric syndromes, which poses a serious challenge at economic and health care systems levels [3,4].

Frailty, usually characterized by a reduction in physiological reserves and loss of resistance to stressors caused by deficits related to ageing, has been attracting the interest of the scientific community over the past years [5]. This geriatric syndrome represents a potentially huge public health problem due to the clinical and societal consequences of its dynamic nature, affecting not only the individuals but their caregivers, the healthcare system and society [6,7]. There are a lot of instruments to assess frailty, although, the Frailty Phenotype, defined by Fried et al., [8] is the most frequently used instrument in both research and clinical practice [9]. Being (pre-)frail is associated with various poor health outcomes, such as falls, hospitalizations, disability, low quality of life and death [5,8]. Frailty is indeed a strong predictor of all-cause mortality [10,11,12,13].

Due to the increased expression of chronic conditions with ageing, polypharmacy is a highly prevalent condition among the older population aged 65 years old or more [14]. Defined as the use of multiple drugs by a patient, the minimum number of drugs needed to define polypharmacy is variable, usually between 5 to 10. Although polypharmacy often refers to prescription drugs, it is also important to consider over-the-counter drugs, supplements, and other products [15,16]. Regardless of the number of drugs used to define polypharmacy, there was already reported that polymedicated individuals have higher rates of death, being these rates higher with an increasing number of taken drugs (1–4, 5, 6–9 or >10) [17]. Other previous studies on community-dwelling older persons showed an association between polypharmacy and all-cause mortality [18].

The relationship between these two common conditions among the older population, polypharmacy, and frailty, has been previously studied. Some studies showed that indeed polypharmacy is associated with frailty, with frail people having higher rates of polypharmacy [19,20]. Another study showed that older adults who experience polypharmacy had a higher risk of developing frailty within 3 years [19,21]. Another study over 6 years confirmed that polypharmacy significantly increases the risk of frailty in older adults [22]. Although, one of the problems found by a systematic review of the

relationship between frailty and polypharmacy was the lack of homogeneity on how frailty and polypharmacy are assessed/measured and quantified [23].

Some studies already reported that polypharmacy among pre-frail and frail individuals is associated with higher rates of mortality in Spain, the United Kingdom and France [24,25,26]. Although, to our knowledge, no study was performed studying the relation between polypharmacy and frailty in mortality, from a European perspective. Therefore, with this study, we aimed to analyse the relationship between frailty and polypharmacy, and its impact on mortality rates, within 30 months, using a cohort of the harmonized European dataset, Survey of Health, Ageing, and Retirement in Europe (SHARE), of older adults aged 65 years old or over.

Materials and Methods

Study participants

SHARE, the acronym of Survey of Health, Ageing and Retirement in Europe, is a longitudinal cohort study of community-dwelling people aged 50 years old or over, from 27 European countries plus Israel, that provides information of more than 140,000 individuals. Since its inception in 2004, SHARE has released data every 2 years, having already released seven waves of data. Wave 6 (with data from 2015) and wave 7 (with data from 2017), are the most recent waves. In this work, we used data from wave 6 and 7. From the 68,231 participants included in SHARE's wave 6, we selected those without missing data for questions related to age, gender, polypharmacy, and frailty status assessment, aged 65 years old or more, and who were followed up until wave 7, or those who died who had information about the month of decease. We extracted the data files including information on age, gender, polypharmacy and frailty, time of death (for those dada who deceased), and combined them into a single data set.

Frailty

An operationalized version of Fried's phenotype to SHARE was used to assess frailty. Frailty status was defined as previously described [27] and that is based on five dimensions: exhaustion, shrinking, weakness, slowness, and low activity.

For each fulfilled criterion, one point was assigned to each participant. Individuals with zero points were classified as robust, those with 1 or 2 points as pre-frail and those with 3 to 5 points were classified as frail.

- One point was assigned for those with a positive answer to “In the last month, have you had too little energy to do the things you wanted to do?” fulfilling the exhaustion criterion.
- Those that reported “diminution in desire for food” to “What has your appetite been like in the last month?” or, in the case of an encodable answer to this question, those that reported “less” to “So, have you been eating more or less than usual?”, had one point in the shrinking criterion.
- Weakness criteria, derived from the highest of 4 handgrip strength measurements, adjusted by gender and body mass index (BMI), and was fulfilled by men with handgrip strength ≤ 29 , ≤ 30 or ≤ 32 , if BMI ≤ 24 , $24 < \text{BMI} \leq 28$ or ≤ 32 , respectively; and by women with handgrip strength ≤ 17 , ≤ 17.3 , ≤ 18 or ≤ 21 if BMI ≤ 23 , $23 < \text{BMI} \leq 26$, $26 < \text{BMI} \leq 29$ or > 29 , respectively.
- One point was assigned for those that selected “Climbing one flight of stairs without resting” and/or “Walking 100 m” to the question: “Please tell me whether you have any difficulty doing each of the everyday activities on this card” fulfilling slowness criterion.
- Participants that answered, “One to three times a month” or “hardly ever or never” to the question “How often do you engage in activities that require a low or moderate level of energy such as gardening, cleaning the car, or going for a walk?”, fulfilled the low activity criterion.

Polypharmacy

For this work, and given the data available, polypharmacy was defined, as the concurrent use of five or more medications per day. Polypharmacy was defined as previously described [14].

Exposure and Outcomes (All-Cause Mortality)

In case the participant was deceased between wave 6 and wave 7, an “end-of-life” interview was conducted with a proxy (family or household member, or any other person of the closer social network of the deceased participant). The month and year of the death were used.

Covariates

Sociodemographic characteristics such as age and gender were self-reported, and values from wave 6 (baseline) were used.

Analysis

To assess the prevalence of frailty status, polypharmacy, and mortality, we performed a descriptive analysis of the data collected, as a first approach. Three age groups were created (65–74, 75–84, 85+ years old), and the prevalence results were standardized by age and gender.

The timeline was created with the month and year of the interview of wave 6 as month 0, until the time of death or end of observation (month and year of the death or interview, in wave 7). Survival analysis, considering the competing risk and the event of interest, was performed to analyze participants' survival. The event of interest was always death and the competing risk event was either polypharmacy and frailty (Figure 1, Figure 2 and Figure 3), a combination of polypharmacy with gender (Figure 4), or a combination of polypharmacy and age (Figure 5). Kaplan-Meier curves were used, and the log-rank test was used to evaluate the difference between groups.

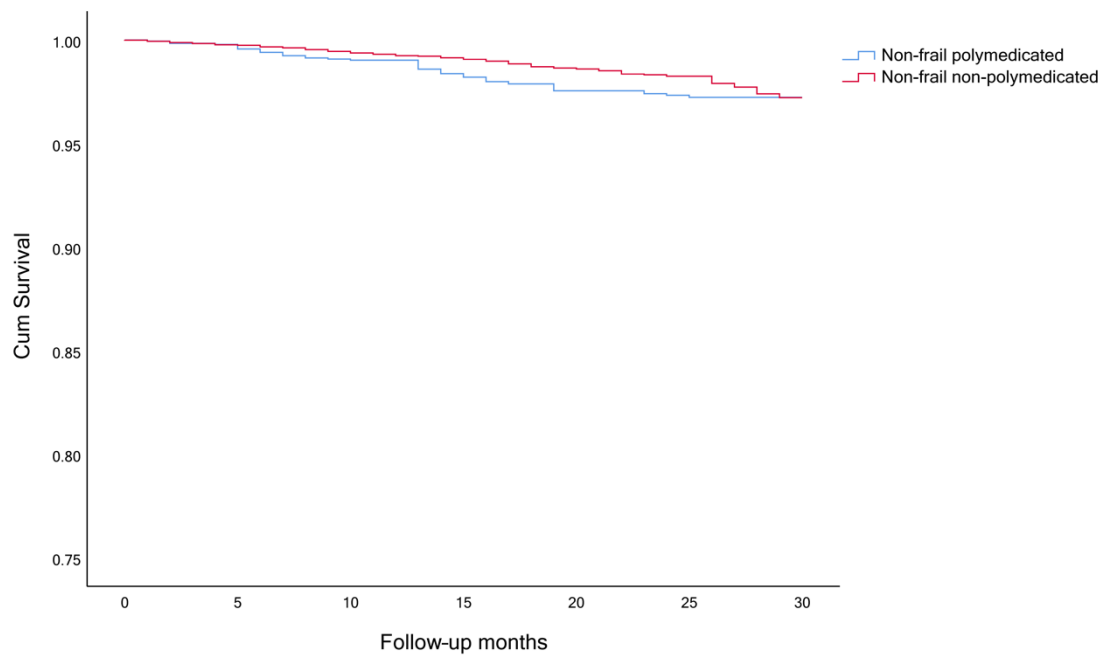


Figure 1 Survival curves for non-frail non-polymedicated and polymedicated individuals (Log rank: $p = 0.035$).

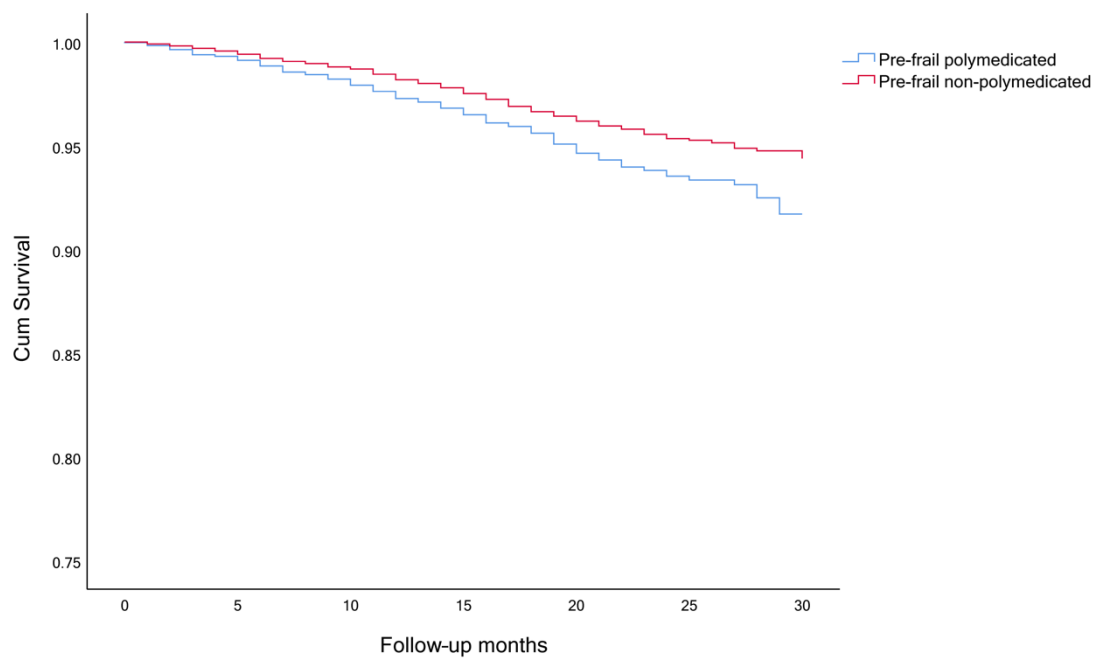


Figure 2 Survival curves for pre-frail non-polymedicated and polymedicated individuals (Log rank: $p < 0.001$).

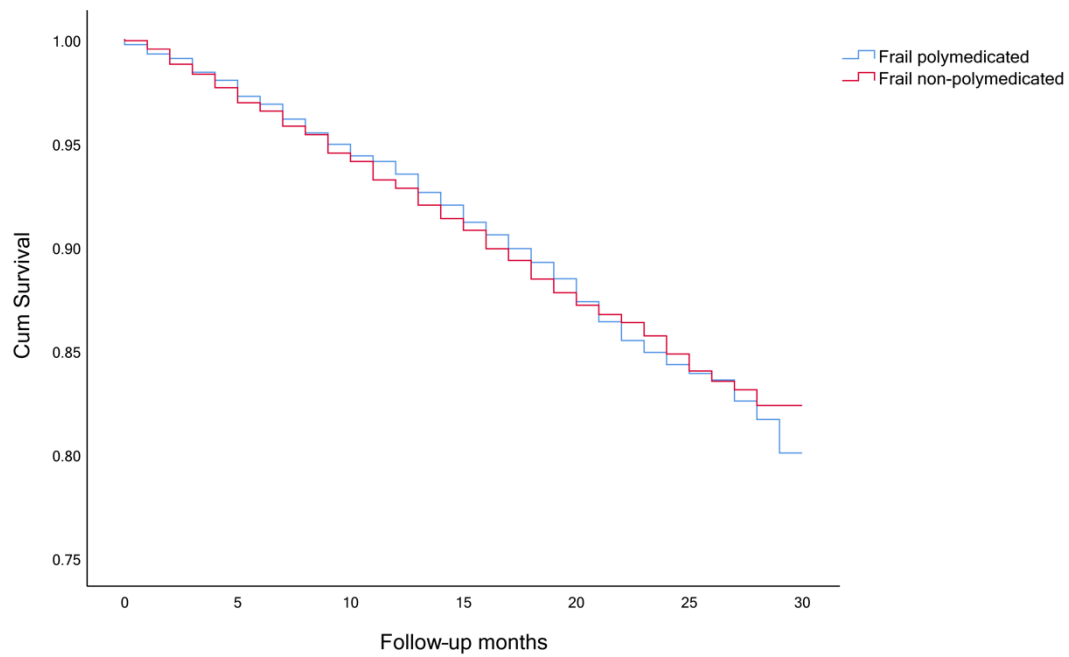


Figure 3 Survival curves for frail non-polymedicated and polymedicated individuals (Log rank: $p = 0.785$).

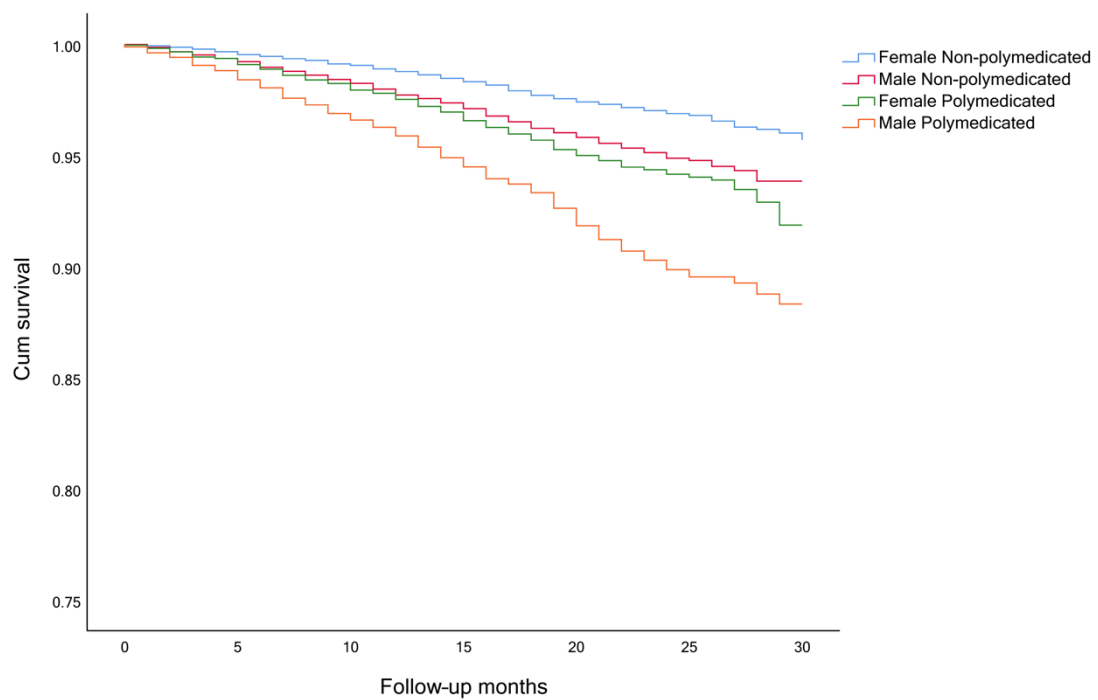


Figure 4 Survival curves non-polymedicated and polymedicated individuals split by gender (Log rank: $p < 0.001$).

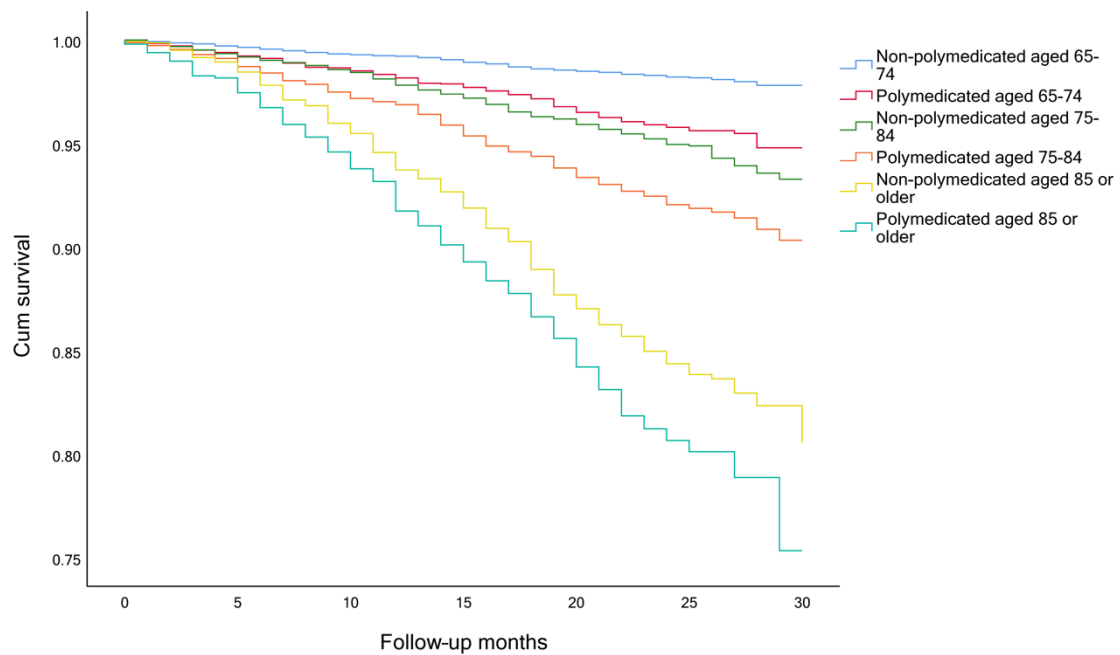


Figure 5 Survival curves non-polymedicated and polymedicated individuals split by age groups (Log rank: $p < 0.001$).

Given the multilevel structure of data, with individuals nested in each country, we used a multilevel binary logistic regression approach, considering death as the dependent variable. We performed multilevel, univariable logistic regression, considering each covariate in turn, to identify factors potentially associated with the outcome variable. Significant covariates from this first step were included in a multilevel, multivariable logistic regression model. Age (65–74 years, 75–84 years, ≥ 85 years), gender (female, male) were used as covariates, as well as a combination of polypharmacy with frailty (non-frail non-polymedicated individuals, non-frail polymedicated individuals, pre-frail non-polymedicated individuals, pre-frail polymedicated individuals, frail non-polymedicated individuals, frail polymedicated individuals).

The country was entered as a random effect. The final model was composed only of significant covariates, selected using a backward selection method. The odds ratio and 95% confidence intervals (CI) were reported. The significance level was set at 0.05. All analyses were performed using the software IBM SPSS Statistics (Version 26.0. Armonk, NY, USA).

Ethics Approval

The SHARE study is subjected to continuous ethics review, and from wave 4 onwards, it was reviewed and approved by the Ethics Council of the Max Planck Society. This study required no ethics approval once it was performed using publicly available data.

Results

Of the 24,693 participants included in this study, the mean age was 74.5 ± 6.9 years old, and 55.5% were female (Table 1). The overall prevalence of frailty status was 40.4% non-frail (between 26.6% in Poland to 52.7% in Denmark), 47.3% pre-frail (between 38.7% in Austria and Denmark to 57.7% in Estonia) and 12.3% frail (between 4.2% in Switzerland to 20.8% in Israel) (Table 1). Increasing age was associated with higher rates of pre-frailty and frailty; 43.4% and 6.4% for those aged 65–74, 51.7% and 15.8% for those aged 75–84, and 52.4% and 32.9% for those aged 85 years or older, of pre-frailty and frailty, respectively. Pre-frailty and frailty were found to be more common among females, comparing with males (49.1% and 14.8% vs. 45.0% and 9.3%) (data not shown).

The overall prevalence of polypharmacy was 31.3% (between 22.9% in Slovenia to 45.6% in Poland). Although males and females reported similar rates of polypharmacy (31.8% in female vs. 30.7% in males), along with age the prevalence of polypharmacy also increased (25.9%, 36.8% and 40.9%, for those age 65–74, 75–84 and 85+, respectively) (data not shown). Within the polymedicated individuals, 53.1% took medication for high blood cholesterol, 76.6% for high blood pressure, 28.5% for coronary diseases, 31.6% for other heart diseases, 33.1% diabetes, 35.3% for joint pain, 26.4% for other pain, 19.2% for sleep problems, 13.6% for anxiety or depression, 12.1% for osteoporosis, 20.6% for stomach burns, 7.8% for chronic bronchitis, 6.5% for suppressing inflammation (only glucocorticoids or steroids), and 29.0% for other conditions.

Polypharmacy was found to be almost 3 times more prevalent in frail individuals and 2 times in pre-frail individuals, when compared with non-frail ones (59.4%, 39.4%, 18.4%, respectively) (Table 1). Within non-frail individuals, polypharmacy prevalence was higher among males comparing (19.7% vs. 17.2%, in females). Within pre-frail and frail individuals, polypharmacy prevalence was higher in females (56.3% vs. 43.7%, among pre-frail individuals, and 66.9% vs. 59.4%, among frail individuals).

Median follow-up time was 25 months (23–26, IQR) for those who stayed alive, and 14 months (8–19, IQR) for those who deceased. Throughout follow-up, 94.8% (23 399) of the participants remained alive while 5.2% (1294) of the participants died from all-cause of mortality. The average age at baseline of the individuals who deceased is 80.1 ± 7.8 years, comparing with 74.2 ± 6.7 years for those alive at the end of the 30 months follow-up (Table 2).

Among frail and pre-frail individuals, the mortality rates were higher, comparing with non-frail ones (15.6%, 5.3% and 2.0%, respectively), and within each group, even higher for polymedicated participants (Table 3). Survival analysis showed significant differences between non-frail non-polymedicated and polymedicated individuals (Log rank: $\chi^2=4.470$, $p = 0.035$) (Figure 1) and between pre-frail non-polymedicated and polymedicated individuals (Figure 2) (Log rank: $\chi^2= 18.281$, $p < 0.001$). On the contrary, no significant differences were found between frail non-polymedicated and polymedicated individuals (Log rank: $\chi^2= 0.074$, $p = 0.785$) (Figure 3). Mortality rates were also higher in polymedicated individuals (7.8%), in male (6.7% vs. 4.1%, in female), in older participants (2.5%, 6.2%, 17.4%, for those age 65–74, 75–84 and 85+, respectively) (Table 3). Survival analysis showed significant differences between non-polymedicated and polymedicated individuals within gender (Figure 4) ((Log rank: $\chi^2= 240.729$, $p < 0.001$) and age (Figure 5) (Log rank: $\chi^2= 1045.855$, $p < 0.001$).

A significant association was found between mortality and gender, age, frailty status and polypharmacy, on both unadjusted and adjusted models (Table 4). Men were 2.1 times more prone to die within the 30 months follow up. The likelihood of death also increased with increasing age, comparing with those aged 65–74 years old ([OR = 2.051 (1.776–2.367)], for those aged 75–84 years old and [OR = 5.272 (4.477–6.207)], for those aged 85 or more years old). A significant association was also found between polypharmacy and frailty with mortality, except for the non-frail polymedicated individuals. Comparing with non-polymedicated non-frail individuals, polymedicated frail individuals are 7 times, non-polymedicated frail individuals are 6 times, polymedicated pre-frail individuals are 2.9 times and non-polymedicated pre-frail individuals are 2.1 times more prone to die with 30 months (Table 4).

Table 1 Detailed characteristics of the population included in the study, at baseline (wave 6–2015).

Country	Population N	Age Mean $\pm$ sd	Female %	Polypharmacy %	Frailty Status					
					Non-Frail		Pre-Frail		Frail	
					% Overall	% Polymedicated	% Overall	% Polymedicated	% Overall	% Polymedicated
Austria	1384	74.6 $\pm$ 6.7	58.7	30.0	50.1	16.0	38.7	39.8	11.3	58.3
Belgium	2065	74.6 $\pm$ 7.2	55.3	34.5	41.0	21.0	45.6	38.9	13.4	61.0
Croatia	770	73.1 $\pm$ 6.2	55.8	28.7	35.5	18.7	49.4	27.1	15.2	57.3
Czech Republic	2209	73.5 $\pm$ 6.2	58.0	40.2	46.9	27.1	44.2	47.7	8.9	71.9
Denmark	1207	74.3 $\pm$ 7.3	53.8	35.6	52.7	24.7	38.7	43.3	8.6	68.3
Estonia	2251	75.3 $\pm$ 6.7	65.3	28.2	28.5	16.7	57.7	29.2	13.9	47.4
France	1412	75.6 $\pm$ 7.6	58.4	33.5	34.6	15.6	50.1	36.7	15.3	63.4
Germany	1549	73.8 $\pm$ 6.4	48.8	28.6	49.9	17.5	43.0	36.3	7.1	60.0
Greece	1422	74.4 $\pm$ 6.6	52.6	23.5	38.0	12.4	49.4	24.5	12.6	53.1
Israel	742	74.9 $\pm$ 7.1	54.3	44.9	30.2	27.2	49.1	45.3	20.8	69.5
Italy	1817	73.9 $\pm$ 6.3	52.1	27.4	33.2	13.2	50.5	28.2	16.2	53.6
Luxembourg	404	72.9 $\pm$ 6.4	48.8	32.2	49.3	21.6	43.6	38.1	7.2	69.0
Poland	654	73.8 $\pm$ 6.9	57.0	45.6	26.6	29.3	54.1	46.3	19.3	65.9
Portugal	203	74.2 $\pm$ 6.6	56.2	44.3	33.0	25.4	46.3	41.5	20.7	81.0
Slovenia	1630	74.3 $\pm$ 6.7	57.2	22.9	47.1	11.3	41.8	29.2	11.1	48.6
Spain	2160	75.8 $\pm$ 7.2	53.9	29.1	29.1	12.9	52.1	27.6	18.8	58.5
Sweden	1715	75.1 $\pm$ 7.0	52.4	32.9	48.3	21.0	45.9	40.7	5.8	71.0
Switzerland	1099	74.9 $\pm$ 6.9	51.5	23.5	50.6	14.9	45.2	29.8	4.2	58.7
Total	24693	74.5 $\pm$ 6.9	55.5	31.3	40.4	18.4	47.3	34.9	12.3	59.4

Table 2 Characteristics, at baseline, for alive (IA) and deceased (ID) individuals, at the end of the follow-up period.

Country	N IA	N ID	Age IA Mean $\pm$ sd	Age ID Mean $\pm$ sd	% Female IA	% Female ID	% IA Polypharmacy	% ID Polypharmacy	Frailty Status					
									Non-Frail		Pre-Frail		Frail	
									% IA	% ID	% IA	% ID	% IA	% ID
Austria	1327	57	74.3 $\pm$ 6.5	80.1 $\pm$ 8.3	59.0	50.9	28.9	56.1	51.8	10.5	38.7	36.8	9.5	52.6
Belgium	1978	87	74.3 $\pm$ 7.1	81.3 $\pm$ 7.9	55.6	47.1	33.7	52.9	42.2	12.6	45.9	39.1	11.9	48.3
Croatia	714	56	72.7 $\pm$ 5.9	78.2 $\pm$ 8.0	57.6	33.9	28.4	32.1	37.1	14.3	49.3	50.0	13.6	35.7
Czech Republic	2098	111	73.3 $\pm$ 6.1	76.9 $\pm$ 7.3	58.8	43.2	39.2	58.6	48.1	23.4	43.9	50.5	8.0	26.1
Denmark	1127	80	73.8 $\pm$ 6.9	81.9 $\pm$ 9.1	53.8	53.8	34.3	53.8	55.1	18.8	38.6	40.0	6.3	41.3
Estonia	2118	133	75.0 $\pm$ 6.6	79.2 $\pm$ 7.5	66.4	47.4	27.9	32.3	29.4	14.3	58.3	48.1	12.4	37.6
France	1334	78	75.2 $\pm$ 7.4	82.4 $\pm$ 7.7	59.0	48.7	31.9	61.5	36.0	10.3	50.6	42.3	13.4	47.4
Germany	1499	50	73.6 $\pm$ 6.3	79.7 $\pm$ 7.5	49.2	36.0	28.1	44.0	50.9	20.0	42.8	48.0	6.3	32.0
Greece	1317	105	73.8 $\pm$ 6.4	81.4 $\pm$ 5.9	53.5	41.9	22.6	34.3	39.7	16.2	48.8	57.1	11.5	26.7
Israel	711	31	74.5 $\pm$ 6.8	83.7 $\pm$ 7.1	54.6	48.4	44.2	61.3	31.4	3.2	49.2	45.2	19.4	51.6
Italy	1727	90	73.6 $\pm$ 6.1	78.4 $\pm$ 7.0	53.0	35.6	26.6	42.2	34.2	14.4	50.4	52.2	15.3	33.3
Luxembourg	392	12	72.8 $\pm$ 6.3	75.3 $\pm$ 7.3	49.2	33.3	31.1	66.7	50.3	16.7	43.9	33.3	5.9	50.0
Poland	614	40	73.6 $\pm$ 6.9	76.8 $\pm$ 6.9	57.3	52.5	44.8	57.5	27.9	7.5	54.6	47.5	17.6	45.0
Portugal	192	11	73.8 $\pm$ 6.3	82.5 $\pm$ 7.4	57.8	27.3	43.2	63.6	34.9	0.0	46.4	45.5	18.8	54.5
Slovenia	1550	80	74.0 $\pm$ 6.6	79.9 $\pm$ 7.0	58.0	42.5	22.3	35.0	48.2	26.3	41.5	47.5	10.3	26.3
Spain	1998	162	75.4 $\pm$ 7.0	80.4 $\pm$ 7.8	55.1	40.1	28.1	42.0	30.3	14.2	52.7	44.4	17.0	41.4
Sweden	1643	72	74.8 $\pm$ 6.7	82.5 $\pm$ 8.8	52.9	41.7	32.2	50.0	49.5	20.8	45.4	56.9	5.1	22.2
Switzerland	1060	39	74.7 $\pm$ 6.8	80.6 $\pm$ 7.2	52.0	38.5	22.4	53.8	52.0	12.8	44.7	59.0	3.3	28.2
Total	23399	1294	74.2 $\pm$ 6.7	80.1 $\pm$ 7.8	56.2	43.4	30.4	46.4	41.8	15.7	47.3	47.5	11.0	36.8

Table 3 Detailed mortality rates within different groups (by gender, age, polymedicated, frailty status and polymedicated individuals by frailty status).

Country	Overall %	Gender		Age			Polypharmacy %	Frailty Status					
		Male %	Female %	65–74 %	75–84 %	85+ %		Non-Frail		Pre-Frail		Frail	
								Overall %	Polymedicated %	Overall %	Polymedicated %	Overall %	Polymedicated %
Austria	4.1	4.9	3.6	2.0	5.0	12.7	7.7	0.9	1.8	3.9	5.6	19.2	19.8
Belgium	4.2	5.0	3.6	1.9	4.5	14.8	6.5	1.3	0.0	3.6	5.8	15.2	12.1
Croatia	7.3	10.9	4.4	4.6	8.6	30.2	8.1	2.9	1.7	7.4	6.9	17.1	15.5
Czech Republic	5.0	6.8	3.7	3.3	6.4	16.0	7.3	2.5	7.4	5.7	6.8	14.8	17.2
Denmark	6.6	6.6	6.6	2.8	7.6	24.4	10.0	2.4	5.0	6.9	6.6	31.7	10.8
Estonia	5.9	9.0	4.3	3.5	6.0	16.5	6.8	3.0	3.9	4.9	6.9	16.0	19.7
France	5.5	6.8	4.6	1.8	5.9	17.2	10.1	1.6	2.5	4.7	6.9	17.1	35.2
Germany	3.2	4.0	2.4	1.3	4.2	13.5	5.0	1.3	4.5	3.6	9.3	14.5	17.9
Greece	7.4	9.1	5.9	1.8	9.7	32.5	10.8	3.1	0.0	8.5	10.8	15.6	18.5
Israel	4.2	4.7	3.7	0.5	4.5	19.8	5.7	0.4	1.1	3.8	4.9	10.4	15.4
Italy	5.0	6.7	3.4	2.6	6.7	15.4	7.6	2.2	0.0	5.1	4.2	10.2	11.2
Luxembourg	3.0	3.9	2.0	2.2	4.0	7.4	6.2	1.0	3.9	2.3	6.4	20.7	17.0
Poland	6.1	6.8	5.6	3.7	8.8	12.3	7.7	1.7	5.9	5.4	5.5	14.3	13.3
Portugal	5.4	9.0	2.6	0.8	9.5	18.2	7.8	0.0	2.3	5.3	4.5	14.3	20.0
Slovenia	4.9	6.6	3.6	2.2	6.6	15.9	7.5	2.7	0.0	5.6	7.7	11.6	11.8
Spain	7.5	9.7	5.6	3.8	8.0	18.9	10.8	3.7	2.3	6.4	8.5	16.5	10.2
Sweden	4.2	5.1	3.3	1.7	3.7	17.5	6.4	1.8	3.7	5.2	5.5	16.0	12.2
Switzerland	3.5	4.5	2.7	1.2	5.1	9.9	8.1	0.9	2.0	4.6	6.8	23.9	14.9
Total	5.2	6.7	4.1	2.5	6.2	17.4	7.8	2.0	2.7	5.3	6.5	15.6	15.8

Table 4 Association of age, gender, frailty status and polypharmacy with mortality: unadjusted and adjusted models.

	N	N Deceased (%)	Unadjusted Model			Adjusted Model		
			OR	CI 95	p	OR	CI 95	p
Age								
65–74 years	13451	330 (2.4)	1	-	-	1	-	-
75–84 years	8845	548 (6.2)	2.630	2.287–3.025	<0.001	2.051	1.776–2.367	<0.001
≥85 years	2397	416 (17.3)	8.487	7.279–9.896	<0.001	5.272	4.477–6.207	<0.001
Gender								
Female	13709	564 (4.1)	1	-	-	1	-	-
Male	10984	732 (6.7)	1.692	1.511–1.895	<0.001	2.134	1.894–2.405	<0.001
Frailty Status vs. Polypharmacy								
Non-frail non-polymedicated	8134	154 (1.9)	1	-	-	1	-	-
Non-frail polymedicated	1840	49 (2.7)	1.423	1.027–1.971	0.034	1.289	0.928–1.791	0.130
Pre-frail non-polymedicated	7598	350 (4.6)	2.472	2.038–2.999	<0.001	2.091	1.718–2.546	<0.001
Pre-frail polymedicated	4074	265 (6.5)	3.633	2.966–4.451	<0.001	2.874	2.335–3.539	<0.001
Frail non-polymedicated	1236	189 (15.3)	9.252	7.392–11.582	<0.001	5.973	4.711–7.573	<0.001
Frail polymedicated	1811	287 (15.8)	9.754	7.944–11.975	<0.001	6.981	5.624–8.664	<0.001

Polypharmacy and frailty are two very prevalent conditions in Europe and represent serious health issues that lead to lower quality of life, higher healthcare expenditures and a problem to society in general. Although polypharmacy is a universal and common term there is no universal definition [14,27]. There are numerical definitions that vary from two to 11 or more drugs taken, but there also descriptive definitions. The same happens to frailty as there are several tools to assess frailty since it is a multidimensional syndrome that includes a lot of variables. This makes it difficult to compare data from different studies of both conditions since it can lead to a wide range of results.

A previous study based on wave 6 of SHARE [14] showed a polypharmacy prevalence of 32.1%. It also showed that polypharmacy increases with age (26.7.1%, 37.5% and 43.1%, for those age 65–74, 75–84 and 85+, respectively) as well as it being more frequent in females than males (33.0% vs. 31.2%) [14], which agrees with the results of this work. Polypharmacy is known to be an independent predictor of mortality [26]. As the individual gets older, they are more likely to develop several diseases and comorbidities that lead to polypharmacy. With that being said, it is hard to determine whether polypharmacy is a cause of the increased risk of mortality or a consequence of ageing and multimorbidity. The intake of several drugs is associated with severe adverse drug reactions due to the different physiologic variations that are associated with ageing leading the body to be more sensitive to the medication, having a cumulative effect of several medications on the renal or hepatic systems that would lead to serious interactions [26,28]. With ageing, there is a decrease in liver mass, extending the half-life of several medications [29], and kidney's function also starts to decline, which has an impact on the elimination of many medications that are excreted through the kidneys [30]. The risk for falls, fractures and aspiration pneumonia is increased with medications affecting the central nervous system since they might cause adverse effects such as sleepiness, reduced memory, confusion, among others [31]. Assessing polypharmacy in older people may be valuable to determine the mortality risk but deprescribing approaches need to be studied to better know the improvements in health risks of these individuals [26,32]. Chronic pathologies associated with ageing, such as arterial hypertension, diabetes mellitus, dyslipidaemia, osteoarticular degenerative pathology, chronic obstructive pulmonary disease, atrial fibrillation, and dementia, potentiate polypharmacy, with a consequent increase in healthcare costs, falls and hospitalizations rates, adverse drug reactions, drug-drug reactions, medication nonadherence and

mortality [33,34,35]. In this study, within polymedicated individuals, cardiovascular diseases were the most common diseases, followed by diabetes, joint pain and other type of pain, sleep problems, anxiety, depression and osteoporosis, which are common conditions among the polymedicated older population [36]. A previous study on frailty status based on wave 6 from SHARE, showed a prevalence of pre-frailty and frailty of 42.9% and 7.7% respectively [27]. This study also showed that pre-frailty and frailty increase with age, which is in agreement with our study [27]. It also shows that pre-frailty and frailty are more common among females comparing to males (45.4% and 9.1% vs. 39.7% and 6.0%, respectively) which is also in line with our study (49.1% and 14.8% vs. 45.0% and 9.3%) [27]. In the present study, we found a higher prevalence of pre-frailty and frailty of 47.3% and 12.3% respectively, values slightly higher than those reported by Manfredi et al., which can be explained by the difference between the median age of both studies (67.45 ± 9.71 years vs. 74.5 ± 6.9 years). The development of frailty and its progression can have a lot of contributors and includes several aspects such as biological, sociodemographic, clinical and lifestyle [37]. Results from an overview of systematic reviews showed that 24/24 studies demonstrate an increased mortality risk for frail individuals while 7/7 showed a significant impact of pre-frailty in mortality [38]. The relation between frailty and mortality risk among other conditions in older adults was also studied, and it was found to increase the risk of death among diabetic patients [39], after hip fracture [40], after pelvic surgery [41], after mitral valve replacement [42], among others. Frailty is also associated with worse short term-term postoperative outcomes and mortality [43]. One of the risks associated with frailty appears to be multimorbidity. These different concepts may contribute to each other as a 2018 systematic review shows that most frail individuals have multimorbidity and a small fraction of multimorbid older people have frailty leading to an inconclusive association between the two, with a bidirectional association being the most plausible [37,44].

Studying the association between polypharmacy and frailty, we found that frail and pre-frail individuals have a higher prevalence of polypharmacy, with the pre-frail status being two times more polymedicated and frail status three times when comparing to polymedicated non-frail individuals. These results agree with previous publications [26,45,46,47,48]. A study from Singapore, using the Fried phenotype and the same definition of polypharmacy shows that (pre-)frail individuals are more prone to polypharmacy than robust individuals (41.5%, 29.8% and 18.1 in frail, pre-frail and robust, respectively) [20]. Besides this, it showed that for polymedicated individuals the mortality rates increase with the number of drugs, and the frail individuals showed even higher mortality rates. Moreover, the combination of frailty and excessive polypharmacy (polypharmacy being > 5 drugs and excessive polypharmacy > 10 or more) lead to a risk

of death by 6 times higher during the follow-up of 39 months [26]. Another Spanish study has similar conclusions regarding this topic [24]. When analysing both polymedicated and frail individuals our results are more in line with the French study. Concerning the polymedicated non-frail individuals, by the Spanish study, we found no significant association with mortality [OR = 1,289 (0.928–1.791), $p = 0.130$].

Kaplan-Meier curves for overall survival, (Figure 1 and Figure 2) showed that the cohort of participants with polypharmacy is at an increased risk of death (log-rank $p < 0.05$), except for of the frail polymedicated individuals when comparing to frail non-polymedicated individuals. Higher mortality risk within polymedicated participants along with age and for male agrees with previous studies [32,49]. Within frailty status, differences between polymedicated and non-polymedicated individuals also arose [2,26]. Multimorbidity associated with other factors may lead to polypharmacy and frailty which in turn may lead to a higher risk of mortality. This association further accentuates the need to have more consciousness regarding these conditions. With the high impact of polypharmacy on the health outcomes of patients, especially frail individuals, the potential harms of polypharmacy must be present for each new drug added to the patient's regimen should be well thought and review the current drugs. When reviewing the drug and deprescribing it should be considered the comprehensive health and medication list to reduce potentially inappropriate medications and pursue more personalized and individualized therapeutic plans for each patient. Life expectancy and care goals need to be taken into account when reviewing a patient's list with each medication's benefits and problems being weighed [30]. Suitable monitoring procedures must be applied including necessary laboratory testing and patient education about monitoring themselves for possible adverse events and what to do when it happens. It is important to mention that it might be hard to determine whether a higher risk of mortality and adverse outcomes are directly related to the numbers of drugs taken or the multiple chronic conditions that the individual might have. Therefore, interventions like deprescribing should be done with caution, as more studies need to be done to show how it affects long-term outcomes such as mortality [17,26].

Limitations in this study are the fact that all data on SHARE were self-reported, which might raise questions about the reliability of the data, as people might not recall correctly all the information they are being asked. People included in this type of research surveys are volunteers, who are asked if they want to participate. Healthier people might be more inclined to participate while a high number of older people with comorbidities might decline, which might reduce the number of people with disabilities in this study. Also, this survey is self-reported so the veracity of the answers might be questionable. The research based on this database is limited to the questions that exist in it since we cannot

change them to fit the type of research we want to do. Strengths are the high number of participants and the inclusion of 18 countries giving a close overview of these conditions in Europe. SHARE has some advantages when it comes to its survey since it is the same survey in each country with a direct translation. This makes for a strong comparison since we are comparing the same questions between countries. Other surveys like Eurostat also cover a wide range of countries but in each country the survey is different and adapted to the cultural differences of each country, making it difficult to make a comparison between them or have a reliable representation of the European people. Usually, it is different to compare studies and countries since they use different scales but since this study uses the same scale for frailty and polypharmacy, it allows us to make a comparison between those countries.

Conclusion

With this work, and through the use of a cohort of SHARE participants, it was possible to understand the trajectory of almost 25,000 people aged 65 or over, in Europe. This work reinforces the high prevalence of polypharmacy and frailty in the older population and clearly shows the prevalence of polypharmacy in non-frail, pre-frail and frail individuals, in 17 European countries, and Israel. At the same time, we were able to understand the 30-month mortality rates for the different groups. It becomes clear and evident that interventions are needed to decrease polypharmacy (especially if not necessary), and frailty, since it will impact society, health systems, caregivers, and older people, improving their quality of life, well-being, functional independence and their autonomy.

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Institutional Review Board Statement

Ethical review and approval were waived for this study, due to the fact that this work was performed using publicly available data.

Informed Consent Statement

Patient consent was waived due to the fact that this work was performed using publicly available data.

Data Availability Statement

The data presented in this study are openly available in <http://www.share-project.org/> (SHARE Wave 6 - DOI: 10.6103/SHARE.w6.710; SHARE Wave 7 - DOI: 10.6103/SHARE.w7.711)

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Brown G.C. Living too long: The current focus of medical research on increasing the quantity, rather than the quality, of life is damaging our health and harming the economy. *EMBO Rep.* 2015;16:137–141. doi: 10.15252/embr.201439518.
2. Eurostat . Ageing Europe—Looking at the Lives of Older People in EU. European Commision; Luxembourg: 2019.
3. Lunenfeld B., Stratton P. The clinical consequences of an ageing world and preventive strategies. *Best Pract. Res. Clin. Obstet. Gynaecol.* 2013;27:643–659. doi: 10.1016/j.bpobgyn.2013.02.005.
4. Divo M.J., Martinez C.H., Mannino D.M. Ageing and the epidemiology of multimorbidity. *Eur. Respir. J.* 2014;44:1055–1068. doi: 10.1183/09031936.00059814.
5. Clegg A., Young J., Iliffe S., Rikkert M.O., Rockwood K. Frailty in elderly people. *Lancet.* 2013;381:752–762. doi: 10.1016/S0140-6736(12)62167-9.
6. Schulz R., Eden J. Families Caring for an Aging America. National Academies Press (US); Washington, DC, USA: 2016. [(accessed on 27 October 2020)]. National Academies of Sciences, Engineering, and Medicine. Family Caregiving Roles and Impacts. Available online: <https://www.ncbi.nlm.nih.gov/books/NBK396398/>
7. Kojima G., Liljas A.E.M., Iliffe S. Frailty syndrome: Implications and challenges for health care policy. *Risk Manag. Healthc. Policy.* 2019;12:23–30. doi: 10.2147/RMHP.S168750.
8. Fried L.P., Tangen C.M., Walston J., Newman A.B., Hirsch C., Gottdiener J., Seeman T., Tracy R., Kop W.J., Burke G., et al. Frailty in older adults: Evidence for a phenotype. *J. Gerontol. A Biol. Sci. Med. Sci.* 2001;56:M146–M156. doi: 10.1093/gerona/56.3.M146.
9. Kojima G., Iliffe S., Walters K. Frailty index as a predictor of mortality: A systematic review and meta-analysis. *Age Ageing.* 2018;47:193–200. doi: 10.1093/ageing/afx162.
10. Kane R.L., Shamliyan T., Talley K., Pacala J. The association between geriatric syndromes and survival. *J. Am. Geriatr. Soc.* 2012;60:896–904. doi: 10.1111/j.1532-5415.2012.03942.x.
11. Grabovac I., Haider S., Mogg C., Majewska B., Drgac D., Oberndorfer M., Dorner T.E. Frailty Status Predicts All-Cause and Cause-Specific Mortality in Community Dwelling Older Adults. *J. Am. Med. Dir. Assoc.* 2019;20:1230–1235. doi: 10.1016/j.jamda.2019.06.007.

12. Shamliyan T., Talley K.M., Ramakrishnan R., Kane R.L. Association of frailty with survival: A systematic literature review. *Ageing Res. Rev.* 2013;12:719–736. doi: 10.1016/j.arr.2012.03.001.
13. Chang S.F., Lin P.L. Frail phenotype and mortality prediction: A systematic review and meta-analysis of prospective cohort studies. *Int. J. Nurs. Stud.* 2015;52:1362–1374. doi: 10.1016/j.ijnurstu.2015.04.005.
14. Midao L., Giardini A., Menditto E., Kardas P., Costa E. Polypharmacy prevalence among older adults based on the survey of health, ageing and retirement in Europe. *Arch. Gerontol. Geriatr.* 2018;78:213–220. doi: 10.1016/j.archger.2018.06.018.
15. Rambhade S., Chakarborty A., Shrivastava A., Patil U.K., Rambhade A. A Survey on Polypharmacy and Use of Inappropriate Medications. *Toxicol Int.* 2012;19:68–73. doi: 10.4103/0971-6580.94506.
16. Masnoon N., Shakib S., Kalisch-Ellett L., Caughey G.E. What is polypharmacy? A systematic review of definitions. *BMC Geriatr.* 2017;17:1–10. doi: 10.1186/s12877-017-0621-2.
17. Leelakanok N., Holcombe A.L., Lund B.C., Gu X., Schweizer M.L. Association between polypharmacy and death: A systematic review and meta-analysis. *J. Am. Pharm. Assoc. (2003)* 2017;57:729–738. doi: 10.1016/j.japh.2017.06.002.
18. Schottker B., Saum K.U., Muhlack D.C., Hoppe L.K., Holleczer B., Brenner H. Polypharmacy and mortality: New insights from a large cohort of older adults by detection of effect modification by multi-morbidity and comprehensive correction of confounding by indication. *Eur. J. Clin. Pharmacol.* 2017;73:1041–1048. doi: 10.1007/s00228-017-2266-7.
19. Veronese N., Stubbs B., Noale M., Solmi M., Pilotto A., Vaona A., Demurtas J., Mueller C., Huntley J., Crepaldi G., et al. Polypharmacy Is Associated With Higher Frailty Risk in Older People: An 8-Year Longitudinal Cohort Study. *J. Am. Med. Dir. Assoc.* 2017;18:624–628. doi: 10.1016/j.jamda.2017.02.009.
20. Merchant R.A., Chen M.Z., Tan L.W.L., Lim M.Y., Ho H.K., van Dam R.M. Singapore Healthy Older People Everyday (HOPE) Study: Prevalence of Frailty and Associated Factors in Older Adults. *J. Am. Med. Dir. Assoc.* 2017;18:734.e9–734.e14. doi: 10.1016/j.jamda.2017.04.020.
21. Saum K.U., Schottker B., Meid A.D., Holleczer B., Haefeli W.E., Hauer K., Brenner H. Is Polypharmacy Associated with Frailty in Older People? Results From the ESTHER Cohort Study. *J. Am. Geriatr. Soc.* 2017;65:e27–e32. doi: 10.1111/jgs.14718.

22. Yuki A., Otsuka R., Tange C., Nishita Y., Tomida M., Ando F., Shimokata H. Polypharmacy is associated with frailty in Japanese community-dwelling older adults. *Geriatr. Gerontol. Int.* 2018;18:1497–1500. doi: 10.1111/ggi.13507.
23. Gutiérrez-Valencia M., Izquierdo M., Cesari M., Casas-Herrero Á., Inzitari M., Martínez-Velilla N. The relationship between frailty and polypharmacy in older people: A systematic review. *Br. J. Clin. Pharmacol.* 2018;84:1432–1444. doi: 10.1111/bcp.13590.
24. Bonaga B., Sanchez-Jurado P.M., Martinez-Reig M., Ariza G., Rodriguez-Manas L., Gnjdic D., Salvador T., Abizanda P. Frailty, Polypharmacy, and Health Outcomes in Older Adults: The Frailty and Dependence in Albacete Study. *J. Am. Med. Dir. Assoc.* 2018;19:46–52. doi: 10.1016/j.jamda.2017.07.008.
25. Porter B., Arthur A., Savva G.M. How do potentially inappropriate medications and polypharmacy affect mortality in frail and non-frail cognitively impaired older adults? A cohort study. *BMJ Open.* 2019;9:e026171. doi: 10.1136/bmjopen-2018-026171.
26. Herr M., Robine J.M., Pinot J., Arvieu J.J., Ankri J. Polypharmacy and frailty: Prevalence, relationship, and impact on mortality in a French sample of 2350 old people. *Pharmacoepidemiol. Drug Saf.* 2015;24:637–646. doi: 10.1002/pds.3772.
27. Manfredi G., Midao L., Paul C., Cena C., Duarte M., Costa E. Prevalence of frailty status among the European elderly population: Findings from the Survey of Health, Aging and Retirement in Europe. *Geriatr. Gerontol. Int.* 2019;19:723–729. doi: 10.1111/ggi.13689.
28. Abrams W.B., Beers M.H. Clinical pharmacology in an aging population. *Clin. Pharmacol. Ther.* 1998;63:281–284. doi: 10.1016/S0009-9236(98)90159-X.
29. Andres T.M., McGrane T., McEvoy M.D., Allen B.F.S. Geriatric Pharmacology: An Update. *Anesthesiol. Clin.* 2019;37:475–492. doi: 10.1016/j.anclin.2019.04.007.
30. Kim J., Parish A.L. Polypharmacy and Medication Management in Older Adults. *Nurs. Clin. N. Am.* 2017;52:457–468. doi: 10.1016/j.cnur.2017.04.007.
31. Fick D.M., Cooper J.W., Wade W.E., Waller J.L., Maclean J.R., Beers M.H. Updating the Beers criteria for potentially inappropriate medication use in older adults: Results of a US consensus panel of experts. *Arch. Intern. Med.* 2003;163:2716–2724. doi: 10.1001/archinte.163.22.2716.
32. Gomez C., Vega-Quiroga S., Bermejo-Pareja F., Medrano M.J., Louis E.D., Benito-Leon J. Polypharmacy in the Elderly: A Marker of Increased Risk of Mortality in a Population-Based Prospective Study (NEDICES) *Gerontology.* 2015;61:301–309. doi: 10.1159/000365328.

33. Vrettos I., Voukelatou P., Katsoras A., Theotoka D., Kalliakmanis A. Diseases Linked to Polypharmacy in Elderly Patients. *Curr. Gerontol. Geriatr. Res.* 2017;2017:4276047. doi: 10.1155/2017/4276047.
34. Perez-Jover V., Mira J.J., Carratala-Munuera C., Gil-Guillen V.F., Basora J., Lopez-Pineda A., Orozco-Beltran D. Inappropriate Use of Medication by Elderly, Polymedicated, or Multipathological Patients with Chronic Diseases. *Int. J. Environ. Res. Public Health.* 2018;15:310. doi: 10.3390/ijerph15020310.
35. Hanlon P., Nicholl B.I., Jani B.D., McQueenie R., Lee D., Gallacher K.I., Mair F.S. Examining patterns of multimorbidity, polypharmacy and risk of adverse drug reactions in chronic obstructive pulmonary disease: A cross-sectional UK Biobank study. *BMJ Open.* 2018;8:e018404. doi: 10.1136/bmjopen-2017-018404.
36. Rieckert A., Trampisch U.S., Klaassen-Mielke R., Drewelow E., Esmail A., Johansson T., Keller S., Kunnamo I., Loffler C., Makinen J., et al. Polypharmacy in older patients with chronic diseases: A cross-sectional analysis of factors associated with excessive polypharmacy. *BMC Fam. Pract.* 2018;19:113. doi: 10.1186/s12875-018-0795-5.
37. Hoogendijk E.O., Afilalo J., Ensrud K.E., Kowal P., Onder G., Fried L.P. Frailty: Implications for clinical practice and public health. *Lancet.* 2019;394:1365–1375. doi: 10.1016/S0140-6736(19)31786-6.
38. Ofori-Asenso R., Chin K.L., Sahle B.W., Mazidi M., Zullo A.R., Liew D. Frailty Confers High Mortality Risk across Different Populations: Evidence from an Overview of Systematic Reviews and Meta-Analyses. *Geriatrics.* 2020;5:17. doi: 10.3390/geriatrics5010017.
39. Ferri-Guerra J., Aparicio-Ugarriza R., Salguero D., Baskaran D., Mohammed Y.N., Florez H., Ruiz J.G. The Association of Frailty with Hospitalizations and Mortality among Community Dwelling Older Adults with Diabetes. *J. Frailty Aging.* 2020;9:94–100. doi: 10.14283/jfa.2019.31.
40. Jorissen R.N., Lang C., Visvanathan R., Crotty M., Inacio M.C. The effect of frailty on outcomes of surgically treated hip fractures in older people. *Bone.* 2020:115327. doi: 10.1016/j.bone.2020.115327.
41. McChesney S.L., Canter D.J., Monlezun D.J., Green H., Margolin D.A. Modified Frailty Index Predicts Postoperative Outcomes in Patients Undergoing Radical Pelvic Surgery. *Am. Surg.* 2020;86:95–103. doi: 10.1177/000313482008600222.
42. Iyengar A., Goel N., Kelly J.J., Han J., Brown C.R., Khurshan F., Chen Z., Desai N. Effects of Frailty on Outcomes and 30-day Readmissions After Surgical Mitral Valve Replacement. *Ann. Thorac. Surg.* 2020;109:1120–1126. doi: 10.1016/j.athoracsur.2019.10.087.

43. Tse W., Newton D., Amendola M., George M., Pfeifer J. Frailty index predicts long-term mortality and postoperative complications in patients undergoing endovascular aortic aneurysm repair. *J. Vasc. Surg.* 2020 doi: 10.1016/j.jvs.2020.01.045.
44. Vetrano D.L., Palmer K., Marengoni A., Marzetti E., Lattanzio F., Roller-Wirnsberger R., Lopez Samaniego L., Rodriguez-Manas L., Bernabei R., Onder G., et al. Frailty and Multimorbidity: A Systematic Review and Meta-analysis. *J. Gerontol. A Biol. Sci. Med. Sci.* 2019;74:659–666. doi: 10.1093/gerona/gly110.
45. Bennett A., Gnjjidic D., Gillett M., Carroll P., Matthews S., Johnell K., Fastbom J., Hilmer S. Prevalence and impact of fall-risk-increasing drugs, polypharmacy, and drug-drug interactions in robust versus frail hospitalised falls patients: A prospective cohort study. *Drugs Aging.* 2014;31:225–232. doi: 10.1007/s40266-013-0151-3.
46. Drey M., Wehr H., Wehr G., Uter W., Lang F., Rupprecht R., Sieber C.C., Bauer J.M. The frailty syndrome in general practitioner care: A pilot study. *Z. Gerontol. Geriatr.* 2011;44:48–54. doi: 10.1007/s00391-010-0136-3.
47. Ernsth Bravell M., Westerlind B., Midlov P., Ostgren C.J., Borgquist L., Lannering C., Molstad S. How to assess frailty and the need for care? Report from the Study of Health and Drugs in the Elderly (SHADES) in community dwellings in Sweden. *Arch. Gerontol. Geriatr.* 2011;53:40–45. doi: 10.1016/j.archger.2010.06.011.
48. Ferrer A., Badia T., Formiga F., Sanz H., Megido M.J., Pujol R., Octabaiz Study G. Frailty in the oldest old: Prevalence and associated factors. *J. Am. Geriatr. Soc.* 2013;61:294–296. doi: 10.1111/jgs.12154.
49. Jyrkka J., Enlund H., Jkorhonen M., Sulkava R., Hartikainen S. Polypharmacy Status as an Indicator of Mortality in an Elderly Population. *Drugs Aging.* 2009;26:1048. doi: 10.2165/11319530-000000000-00000.

Manuscript III

Pre-Frailty and Frailty in Dialysis and Pre-Dialysis Patients: A
Systematic Review of Clinical and Biochemical Markers

Pereira A, Midão L, Almada M, Costa E.

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Patients under dialysis are known to be more vulnerable to frailty, a dynamic geriatric syndrome defined as a state of vulnerability to stressors, due to numerous metabolic changes. With rise of life expectancy globally, it is important to understand the complexity of the pathophysiology of frailty and identify possible markers that can help with the prognosis and diagnosis of frailty. The aim of this systematic review is to give an overview of the knowledge regarding clinical and biochemical markers associated with pre-frailty and frailty in dialysis and pre-dialysis patients. In November 2020, PubMed, Embase and Web of Science were searched. Studies regarding biomarkers associated with (pre-)frailty in (pre-)dialysis patients were included. This systematic review identified clinical and biochemical markers in pre-frail and frail patients under dialysis or pre-dialysis published in the literature. This study shows that more investigation is necessary to identify markers that can differentiate these processes to be used as a diagnostic and prognostic tool in routine care and management of geriatric needs. Interventions that can improve health outcomes in pre-frail and frail older adults under dialysis or pre-dialysis are essential to improve not only the individual's quality of life but also to reduce the burden to the health systems.

Keywords: Frailty, end-stage kidney disease, markers.

Frailty is a common clinical complication and a state of physical and biological vulnerability mostly diagnosed in the older population. This syndrome is of dynamic nature and is characterized by a progressive decline from robustness to pre-frailty and frailty [1]. The prevalence of frailty and pre-frailty tends to increase with age, and it affects more women compared to men. Frailty predicts more vulnerability to adverse outcomes such as falls, fractures, hospitalization, decreased health-related quality of life and significantly contributes to polypharmacy, increased multimorbidity and mortality [2,3]. In a study involving a vast number of participants with a final sample of 60,816 European community-dwelling individuals from 18 different countries aged 50 years old or over, with the mean age of 67.45 ± 9.71 years, the overall prevalence of pre-frailty was reported as 42.9% and frailty as 7.7%. Significant differences were identified between different countries regarding frailty status [4].

Although the pathophysiology of frailty is not yet clear, it has rather a complex multifactorial etiology characterized by dysregulation of different systems including reduced homeostasis and physiologic reserve, as well as increased vulnerability to poorer health outcomes and mortality. Chronic inflammation, marked by raised serum interleukin 6 (IL-6), C-reactive protein (CRP) and tumor necrosis factor alpha (TNF- α), anemia and lower hematocrit levels, immune activation, as well as obesity and other comorbidities have also been defined as etiologies of frailty [5,6].

Frailty is highly associated with aging, however its high prevalence is also seen in patients with all stages of kidney disease, regardless of their age. It is known that patients suffering from chronic kidney disease (CKD) have an increased predisposition to frailty [7]. Frailty is common in patients with end-stage renal disease (ESRD) and has been reported as affecting two-thirds of these patients [8]. Studies have been carried out to determine the prevalence of frailty amongst dialysis and pre-dialysis patients presenting CKD. In a cohort of 2275 adults undergoing dialysis, the prevalence of frailty was reported as an overall value of 67.7%, going from 44.4% in patients < 40 years old to 78.8% in patients aged 80 or older [9]. In 2012, a cohort studied 336 patients with non-dialysis-dependent CKD and reported prevalence as 14% [10]. A systematic review carried out in 2017 reported the prevalence of frailty from 7% in CKD community-dwellers to 73% in a cohort of patients undergoing hemodialysis. Frailty is an independent risk factor for a series of adverse events in all stages of CKD [11]. In an observational prospective longitudinal study carried out in 2019, a total of 277 patients in dialysis were studied for the presence of frailty. The results were reported as an initial prevalence of

29.6% of frail patients, which increased to 58.5% after a 29-month follow-up. In the same study, a higher risk of mortality was also identified in the frail group compared to the non-frail [12]. Frailty prevalence has also been reported as significantly higher (30–42%) among patients on hemodialysis when compared to the community-dwelling older population. In many other studies, frailty was related to an increased risk of hospitalization and mortality [13].

The literature supports that patients with CKD are, in general, more susceptible to suffering from frailty regardless of age and that the incidence increases with declining kidney function. CKD was classified as a state of accelerated metabolic aging where physiological and biochemical changes can be seen, such as anemia, sarcopenia, reduction of food intake, insulin resistance, persistent inflammation, oxidative stress and osteopenia. Although these changes can be associated with natural aging, it happens more rapidly in patients presenting CKD, leading to premature aging and an earlier manifestation of frailty [14]. Metabolic acidosis, impaired vitamin D metabolism, vascular dysfunction and hyperphosphatemia are other pathophysiological processes present in CKD that can lead to frailty. All these changes associated with the fact that CKD patients have a high prevalence of other comorbidities might be one of the reasons for the high prevalence of frailty in this group [15].

Due to the close association between aging and frailty syndrome, it is important to identify a comprehensive diagnostic tool that can give the information needed to distinguish frail and pre-frail individuals from non-frail. This systematic review aim is to consolidate the information available regarding biomarkers in frail and pre-frail CKD patients undergoing dialysis or in pre-dialysis to identify the biomarkers that can be used as tools to improve efficacy in geriatric medicine practice. The review aims to provide a high level of evidence and to support research groups, policymakers, funding bodies and even reviewers interested in this field by providing these professionals with rapid access to the latest information in patient healthcare management to support their practice and the design of future trials and research programs.

Materials and Methods

This systematic review was performed following the Cochrane Handbook for Systematic Reviews of Interventions [16]. To ensure that this systematic review addresses a relevant question in a way that benefits the scientific and healthcare community, input was obtained from three people with different and significant

backgrounds for the creation of this systematic review, from the identification of the review question until the selection of the final articles. The protocol for this systematic review is registered on PROSPERO under the registration number CRD42020215525.

Review Question

Although there are a few systematic reviews published covering biomarkers in frail patients, it is exceedingly rare to find these studies in ESRD patients. A lack of systematic reviews covering biomarkers in frail and pre-frail patients undergoing dialysis and in pre-dialysis was identified. Therefore, this review aimed to significantly contribute to cover the identified knowledge gap by creating a narrow review question.

The question for this review was created using PICO strategy, following Cochrane guidelines. Therefore, the aim was to gather data from primary articles published referring to biomarkers in pre-frail and frail patients undergoing dialysis and in pre-dialysis.

Inclusion and Exclusion Criteria

The inclusion criteria included primary studies covering clinical and biochemical markers identified in pre-frail and frail patients undergoing dialysis and pre-dialysis.

Articles fulfilling one or more of the exclusion criteria below were excluded during the data selection process for this systematic review:

- topics unrelated to frailty, dialysis and markers;
- not data-driven: editorials, letters to editors, opinions, discussion pieces, theoretical papers, reviews, hypothesis;
- no full text: conference abstracts;
- not published in English;
- subjects of the study were not humans;
- subjects of the study were not on dialysis, not assessed for frailty and no markers were studied.

Data Collection

In November 2020, two reviewers, A.P. and L.M., independently searched and extracted data from PubMed, Embase and Web of Science databases. The final search query was then constructed as: 'frail* OR geriatric assessment' AND 'dialys* OR hemodialys* OR haemodialys* OR 'end stage kidney disease' OR 'chronic kidney

disease' AND 'marker* OR biomarker*'. Language restrictions were applied to include only studies published in English. No limitations were used on the publication years in the search process.

A total number of 499 articles were found on the three separate databases, which were exported to an Excel spreadsheet and duplicates were removed using Excel tools, leaving a total of 366 articles. The same reviewers independently reviewed the titles and abstracts of all 366 articles and selected the articles with potential interest following the inclusion and exclusion criteria established. Twenty-four articles were selected, and the full text was reviewed for final eligibility evaluating against inclusion and exclusion criteria, selecting a final of five primary studies to be considered for this review (Figure 1). The quality of the final selected articles (n = 5) was assessed using a study quality assessment tool for observational cohort and cross-sectional studies from the National Heart, Lung and Blood Institute (NIH).

Interrater Reliability

The data selection process was conducted by two different reviewers, and a third reviewer (M.A.) was used to solve discrepancies. The level of agreement (interrater reliability) among the individuals was measured using SPSS software v.26 (IBM Corp. Armonk, NY, USA). Reliability of data collection is of extreme importance, especially for healthcare and clinical research studies, to ensure a high level of consistency when selecting articles for a systematic review, as well as selecting samples for a study. To measure the interrater reliability of the articles selected for this study, Cohen's kappa (κ) statistics were used [18].

The selection of articles for this systematic review was done in two phases—selection by title/summary and selection by full article and Cohen's kappa value obtained for both phases independently.

Ethics

The data used for this systematic review were data already published and publicly available, therefore no ethical approval was undertaken before data collection. Three independent people were part of different stages of the review and Cochrane guidelines were followed to minimize the risk of bias.

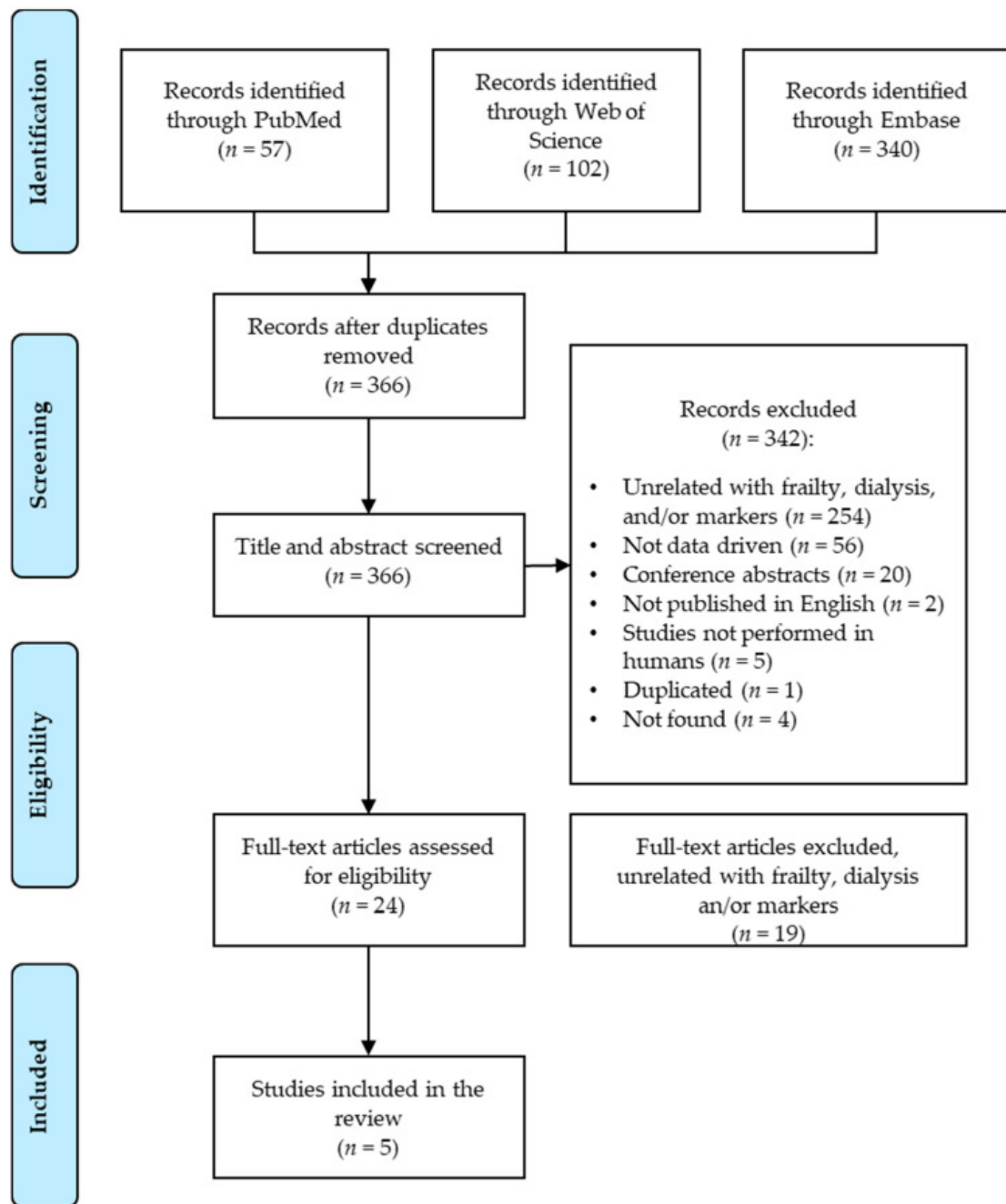


Figure 1 Literature search flowchart—PRISMA format [17].

Results

A total number of 499 articles were obtained using the initial search query. After removing 133 duplicates, titles and abstracts of the remaining articles were screened, for a total of 24 articles. Full-text reviews of these articles led to a final selection of five articles (Table 1) meeting the eligibility criteria to be included in the review (Figure 1).

All the studies included in this review were published in 2015 or after ($n = 5$, 100%) with data collected from 2009 onwards, and were carried out in five different countries, representing three continents: America ($n = 2$, 40%), Europe ($n = 2$, 40%) and Asia ($n = 1$, 20%). All the studies included in this review can be broadly classified as observational, however, cohort studies were performed by most of the groups ($n = 3$, 60%) and cross-sectional studies performed by the remaining two groups (40%). The follow-up period in the cohort study carried by one of the studies [19] was 1.1 years, in one other study [20] the population was followed up for 20 months, and 12 months was the follow-up time used by the third group [1]. Most of the studies ($n = 4$, 80%) recruited the population by convenience from the community, although one study [20] did not report the background of the population; contact with the author to obtain information was attempted but no answer was obtained.

Sample Characteristics

Data were collected from 2009 to 2016; all the studies included adults of both sexes, with a greater percentage of the male population, and a similar age range of >60 years old. Most of the studies ($n = 4$, 80%) had the data collected during the years 2015–2016. Samples size ranges varied from 61 to 605 participants. Three studies (60%) included in this systematic review have samples with more than 100 participants which can be considered significant, however, the studies are not consistent in sample size and there is a considerable gap between the 61-person sample [1] and the study with the biggest sample of 605 people [19]. Some of the studies ($n = 2$, 40%) did not report on ethnicity. In three studies ($n = 3$, 60%), ethnicity was reported as the percentage of non-Caucasian ($n = 1$, 20%), the percentage of African American and Hispanic ($n = 1$, 20%) and the percentage of European, Asian and African ($n = 1$, 20%). The sampling method used was primarily specific population-based cohorts ($n = 4$, 80%) but also convenience sampling ($n = 1$, 20%). A range between 61 to 605 patients, with 60% of the studies ($n = 3$) having a sample size >100, was observed. Regarding dialysis, two of the studies focused on the population undergoing dialysis (40%), two studies (40%) focused on pre-dialysis patients and one study (20%) included both groups.

Exclusion Criteria

Exclusion criteria was used in three studies (60%): patients suffering from specific health conditions were excluded ($n = 2$, 40%), as well as when they were not under dialysis for a specific period of time ($n = 2$, 40%).

Table 1 Description of reviewed studies.

First Author, Publication Year	Country, Data Collection Year(s)	Study Design	Sampling Method	Sample Characteristics: Size, Setting, Age, Sex	Exclusion Based on Health Conditions	Biomarkers Measured		Measurement of Frailty	Comparison	Outcome
						Clinical	Biochemical			
Mansur et al. (2015) [1]	Brazil (June 2011–September 2012)	Cohort study	Convenience sampling, CKD patients stages 3–5 on pre-dialysis	61, community, 60 ± 11.5 years old, biological sex: both (59% male)	Severe neuropathy, gout, amputation, severe physical sequelae caused by stroke, DVT, Parkinson's, pregnancy, COPD, neoplasia, HIV infection, cognitive impairment	BMI; Fat mass ^a ; Fat-free mass; Abdominal circumference; Osteopenia /Osteoporosis ^a	Creatinine; GFR; Glycemia; TSH; Total cholesterol; Ferritin; TSAT; Hb; TNF-α; IL-6; CRP; Ca; P; Ca × P product; Vitamin D; iPTH	Johansen et al. criteria	Non-Frail	Frail vs. Non-Frail: Higher fat-mass but not fat-free mass 100% incidence of osteoporosis
Poveda et al. (2017) [21]	Portugal (December 2014–June 2015) ^b	Cross-sectional study	ESRD patients under dialysis three times a week, for 3–5 h	83, community, average age: 64.3 ± 14.6 years old biological sex: both (53.0% male)	Acute inflammatory or infectious diseases, on dialysis < 3 months, <18 years old	BMI Interdialytic weight gain ^a	Hb ^a ; RBC; MCHC; Fe ^a ; Transferrin ^a ; Ferritin ^a ; Alb ^a	FRAIL scale score	Robust and Pre-Frail	Frail vs. Pre-Frail: . Lower interdialytic weight gain . Lower Hb . Lower transferrin . Lower ferritin . Lower Alb Frail vs Robust: . Lower Fe . Lower Alb
McAdams-DeMarco et al. (2018) [19]	US, (November 2009–May 2016)	Cohort study	ESRD on the KT waiting list, 67.7% in dialysis	605, community, ≥ 18 years old, biological sex: both ^d	None		CRP ^a ; IL-6 ^a ; sTNFR1 ^a	Fried criteria	Non-frail and intermediately frail	Frail vs non-frail and intermediately frail: . Higher IL-6; . Higher sTNFR1; . Higher CRP
Ali et al. (2018) [20]	UK (July 2015–July 2016)	Cohort study	Frail and non-frail on pre-dialysis, GFR ≤25 mL	104 ≥ 65 years old, average age 77.1 years (51% male) ^c	None		Hb; Alb; WBC; Ca; PTH; CRP	Combination of PRISMA questionnaire and Time up and Go test (TUGT)	Non-frail	Frail vs non-frail: No statistical significance found
Nakazato et al. (2020) [22]	Japan (June 2015–May 2016)	Cross-sectional study	HD patients for >6 months	109, community, average age 63.4 ± 11.3 b, biological sex: both (70.6% male)	Patients on HD for <6 months, patients who had completed <21 of 24 regular blood examinations		LDH ^a ; ALP ^a ; Na; AST; Cl; K; UA; ALT; Plat; WBC; LDL; P; HDL; Ca; TP; BUN; Cr ^a ; Hb; Alb ^a	Japanese version of the Cardiovascular Health Study criteria (J-CHS criteria)	Non-frail	Frail vs. non-frail: . Lower Alb . Lower Cr . Higher LDH . Higher ALP

^a $p < 0.05$ is statistically significant. ^b Information obtained by contacting author. ^c Average age obtained by calculation, as it was unable to be obtained from author. Information about population type was also unable to be obtained. ^d Unable to obtain information from author regarding average age. Abbreviations: CKD—chronic kidney disease, DVT—deep vein thrombosis, COPD—chronic obstructive pulmonary disease, HIV—human immunodeficiency virus, BMI—body mass index, GFR—glomerular filtration rate, TSH—thyroid-stimulating hormone, TSAT—transferrin saturation, Hb—hemoglobin, TNF-α—tumour necrosis factor alpha, sTNFR1—soluble tumour necrosis factor receptor-1, IL-6—interleukin 6, CRP—C-reactive protein, Ca—calcium, P—phosphorus, iPTH—intact parathyroid hormone, PTH—parathyroid hormone, ESRD—end-stage renal disease, RBC—red blood cells, MCHC—mean cell haemoglobin concentration, Fe—Iron, Alb—Albumin, WBC—white blood cells, LDH—lactate dehydrogenase, ALP—alkaline phosphatase, Na—sodium, AST—aspartic aminotransferase, Cl—chloride, K—potassium, UA—uric acid, ALT—alanine aminotransferase, Plat—platelets, LDL—LDL cholesterol, HDL—HDL cholesterol, TP—total protein, BUN—blood urea nitrogen, Cr—creatinine, HD—hemodialysis.

Excluding patients known to have inflammatory or infectious diseases is essential to avoid the risk of bias. Two studies (40%) did not evaluate sociodemographic parameters, one study (20%) reported on school education, and smoking population percentage was reported in two studies (40%). BMI was reported in two of the studies (40%), while time under dialysis was reported in two studies (40%). Mental state was evaluated in two studies (40%) by the Mini Mental State Examination Scale [23], the Lubben Social Network Scale was measured in one study (20%), while dementia was reported in another different study (20%). Charlson Comorbidity Index was assessed in three studies (60%), with comorbidities and diabetes diagnosis being reported in most of the studies (n = 4, 80%). Mansur et al. excluded patients with cognitive impairment from their study.

Biomarkers

In all the studies, biomarkers were measured as continuous variables, however different biomarkers were studied by different groups (Table 1). For easier reading, the biomarkers were grouped as clinical and biological markers in this review. Two studies (40%) reported clinical and biological markers, while the remaining three studies (60%) reported on biological markers only.

Mansur et al. reported a higher level of fat mass and 100% incidence of osteoporosis in frail individuals in pre-dialysis when compared to non-frail. Poveda et al. compared frail to the pre-frail group of patients under dialysis and obtained lower interdialytic weight gain, hemoglobin, transferrin, ferritin and Alb in the frail group. When comparing to the robust group, Poveda et al. obtained lower iron and Alb in the frail group. McAdams-DeMarco et al. studied ESRD patients on the KT list and obtained raised IL-6, sTNFR1 and CRP results in the frail group when comparing to both non-frail and intermediately frail individuals. Ali et al. did not obtain a statically significant difference when compared the results obtained for Hb, Alb, WBC, Ca, PTH and CRP in the frail and non-frail individuals in pre-dialysis. Nakazato et al. compared frail and non-frail groups of patients under dialysis and reported lower results for Alb, Cr and raised LDH and ALP results in the frail group.

Frailty Assessment

Frailty assessment was performed in all the studies included in this review (n = 5), however different approaches were taken and the measurement of frailty was performed using different criteria by each study: criteria proposed by Johansen et al. was used by Mansur et al., the FRAIL questionnaire was performed by Poveda et al. and Fried criteria

was used by McAdams-DeMarco et al., Ali et al. assessed frailty using a combination of PRISMA questionnaire and Timed Up and Go Test (TUGT) [24], and finally, Nakazato et al. used the Japanese version of the Cardiovascular Health Study Criteria (J-CHS criteria).

Comparison Groups

Regarding comparison groups, three of the studies (n = 3, 60%) compared the results of the frail group to a robust/non-frail group, one study (20%) compared the frail group to a robust and a pre-frail group, and the remaining study (n = 1, 20%) compared the frail group to a non-frail and intermediately frail group.

Discussion

Although frailty is a common condition in CKD patients, only recently has it become a topic of interest. No publication date restrictions were applied in this review, yet only five articles were found to meet the inclusion criteria. These were published over the last six years with data collected from 2009 to 2016. On one hand it shows very recent data, on the other hand, the limited number of published articles available hampers comparison and analysis of data from different studies but highlights the opportunity for further investigation. In this review, it was observed that sample characteristics were heterogeneous among articles, as Mansur et al. and Ali et al. reported on pre-dialysis patients and compared frail populations to non-frail; Poveda et al. studied ESRD patients under dialysis and compared frail populations to robust and pre-frail; Nakazato et al. studied dialysis patients and compared frail to non-frail; and McAdams-DeMarco et al. studied ESRD patients and did not differentiate the dialysis from pre-dialysis population and compared frail patients to non-frail and intermediately frail patients. Additionally, the aims of these studies were not specifically to identify biomarkers related to frail and pre-frail patients under dialysis or in pre-dialysis.

Populations from five different countries were studied, however no studies reported on the African or Australian population and most of the studies did not report on ethnicity. Previous studies have reported a higher prevalence of frailty in older persons from ethnic minority groups like African Americans when compared with European Americans, reporting an independent association between African American race and frailty [25]. A recent study performed in the Netherlands reported that older persons with a Turkish,

Moroccan and Surinamese background were frailer in comparison with their Dutch background counterparts [26]. Therefore, it is important to investigate differences in the prevalence of frailty between diverse ethnic groups. The majority of the groups carried out cohort studies [1,19,20] with similar follow-up times of 12 to 20 months. However, only mortality, the start of dialysis, hospitalization history and need for renal replacement therapy were variables accounted for at the different follow-ups. It would have been of high interest to measure the clinical and biological markers at the time of the follow-ups. Identification of the number of individuals who progressed from a pre-frail status to a frail status and its correlation with possible biomarker changes would have also been of interest.

All articles selected for this systematic review recruited their study population by convenience. However, it is known that frailty is more frequent among the female population [4]. Therefore, the sample recruiting method might lead to limitations since most of the studies included in this review reported a higher percentage of male population, which is not an accurate representation of the frail population [4] and might have been a source of bias.

McAdams-DeMarco et al. in 2018 reported findings in a population ≥ 18 years old, but no average age was reported or was able to be obtained by contacting the authors. However, the average age reported by the remaining studies was > 60 years old, which is aligned with the fact that frailty is often seen in older adults [4].

Two of the studies included in this review [1,20] reported markers in the pre-dialysis population, one study [19] focused on ESRD on the kidney transplant list without making a distinction between pre-dialysis and dialysis patients, and the remaining two studies [21,22] reported findings in the dialysis population. Poveda et al. studied the prevalence of frailty in ESRD patients under online-hemodiafiltration (OL-HDF) three times a week for 3–5 h, however no start date of dialysis was considered, and it is known that there are highly fluctuating parameter values during the hemodialysis (HD) initiation phase [27]. Studies have reported differences between CKD pre-dialysis and dialysis patients concerning frailty prevalence and also differences in GFR levels [11].

Making a distinction between pre-dialysis and dialysis patients allows for a more specific investigation and the possibility to analyze the differences independently between both populations. It would have been interesting to measure the biomarkers in a set time from pre-dialysis to dialysis to evaluate the possible changes in the specific markers and their association with frailty.

Poveda et al. reported an association between frailty and lower cognitive function and higher depressive symptoms, which is consistent with studies that found the same association in non-dialysis patients [28]. Poveda et al. have also reported that frail ESRD

patients are more susceptible to cognitive impairment and depression due to their exposure to specific factors associated with the dialysis treatment, such as oxidative, inflammatory and hemodynamic stress. A study from 2012 reported an association between frailty and worse cognitive performance and recommended that the frailty assessment should include a cognitive status investigation [29].

Mansur et al. observed a high frequency of frailty in pre-dialysis patients and an association with female gender, > 60 years old, endothelial dysfunction and obesity coincident with previous findings [30]. Osteoporosis was found to have an incident of 100% in the frail population in this study. Osteoporosis results in increased bone fragility and accumulated risk of fractures and its prevalence raises alongside with age. Sarcopenia and osteoporosis have been linked and associated with aging, often leading to frailty [31]. Patients with ESRD are more likely to develop osteoporosis and have a higher risk of fractures than their same-age counterparts [32].

Even though vitamin D, CRP, IL-6, TNF- α , Hb and GFR have previously been reported as related to frailty [33], Mansur et al. did not find an association between frailty and these markers, which could be explained by the great variability observed in the results, although the authors identified a strong association between endothelial function and frailty. Ali et al. also studied pre-dialysis patients with a frailty prevalence of 53.8% and did not find significant differences between frail and non-frail groups regarding age, gender, comorbidities, Hb, inflammatory markers or calcium levels. However, they were able to associate frailty with increased mortality, which has also been previously reported in the literature [34]. Peritoneal dialysis was reported by this research group as slightly better in terms of survival when compared to those patients who started on hemodialysis, which is consistent with several studies previously published [35].

Poveda et al. reported on patients under dialysis and hypertension was found to be the etiology of ESRD for the majority of the patients (32.5%), with diabetes for 10.8% and both diabetes and hypertension for 24.1% of the patients. Association was also found between frailty and advanced age, female gender and presence of diabetes and/or hypertension. These findings were expected and consistent with studies in community-dwelling patients [36]. Diabetes and hypertension are the main risk factors for CKD, which can quickly progress to ESRD in patients with uncontrolled diabetes and/or hypertension [37].

Lower interdialytic weight gain, Hb, transferrin and albumin (Alb), and an increase in ferritin serum levels were also reported by Poveda et al. when comparing frail to pre-frail patients. When comparing frail patients to robust patients, lower Fe and Alb was reported.

Hematologic alterations are often seen in ESRD patients under dialysis and a common complication is anemia, which is explained by reduced production of erythropoietin, a renal hormone essential to the production of hemoglobin. Anemia is associated with reduced quality of life, increases morbidity and mortality and accelerates CKD progression. Iron deficiency is also common among CKD patients [38,39]. Low Alb has also been identified to be associated with frailty and increased risk of mortality [40]. Poveda et al. found a correlation between frailty and lower cognitive function, higher prevalence of depression and comorbidities, which agrees with previous studies [28].

McAdams-DeMarco et al. studied ESRD patients on the kidney transplant (KT) waitlist and did not clearly distinguish dialysis from non-dialysis patients. Higher levels of inflammatory markers IL-6, sTNFR1 and CRP have been reported in frail ESRD patients when comparing to both groups of non-frail and intermediately frail individuals. Raised inflammatory markers in frailty are consistent with the literature and have been associated with the pathophysiology of frailty. Raised CRP and IL-6 are correlated with physical disability and muscle weakness. Raised TNF α is associated with mortality in older people [41].

McAdams-DeMarco et al.'s findings support previous studies which report that these inflammatory markers can be used to predict mortality and therefore support the decision to accelerate the care to the patients at greater risk [42].

Nakazato et al. studied patients on HD for longer than six months and found that the frail patients were generally older, had been under HD for a longer period and had lower levels of Alb and Cr and raised LDH and ALP when comparing to non-frail patients.

Lower serum Alb concentrations have been reported as a predictor of higher mortality in HD patients. Hypoalbuminemia has been associated with inflammation, poor nutrient intake and atherosclerotic disease [43]. Decrease in body weight and serum Alb levels have also been reported in HD patients in their final three months of life [44]. Lower Cr levels are common among the older population and have been linked to type 2 diabetes.

Both Mansur et al. and Ali et al. found a high prevalence of frailty among pre-dialysis patients. Mansur et al. reported these findings in 46% of the < 60 years old. However, while Mansur et al. found an association between frailty, gender, advanced age, obesity and endothelial dysfunction, Ali et al. reported no significant difference when comparing frail and non-frail groups regarding age, gender or any other studied variables. Both studies reported no association between frailty and inflammatory markers, calcium hemostasis and GFR. Ali et al. found no association between frailty and PTH or Alb, while Mansur et al. found no association between vitamin D and frailty. Mansur et al. and Ali et al. reported a link between frailty and pre-dialysis patients and increased risk of mortality.

Nakazato et al. and Poveda et al. both studied patients under dialysis and have both reported frailty as being associated with age. Poveda et al. found a higher prevalence of frail and pre-frail among ESRD under dialysis patients when compared to non-frail. Nakazato et al. also found an association between frailty and duration of HD, low Alb and Cr levels and higher LDH and ALP, while Poveda et al. reported higher prevalence of depressive symptoms, hypertension, lower iron levels, Hb, Alb and transferrin and raised ferritin among frail patients.

No association was found between frailty and Hb or Calcium by Nakazato et al. Despite McAdams-DeMarco et al. not differentiating dialysis from pre-dialysis patients, the group reported 67.7% of the population in study being under dialysis. Higher IL-6, sTNFR1, CRP and inflammatory index were found in frail patients. Inflammation was associated with frailty by this group.

To our knowledge, this is the first systematic review to summarize the information about biomarkers in pre-frail and frail patients in dialysis and pre-dialysis. We were able to identify the biomarkers studied and highlight the ones with statistical significance.

This systematic review was able to highlight the lack of studies in this area ($n = 5$) and the poor understanding of the etiology of the biomarker alterations due to the complexity of the health conditions presented by these patients. We were, therefore, unable to conclude on the associations between biomarker alterations and their association with frail and pre-frail patients undergoing dialysis or pre-dialysis. The majority of authors did not report on specific biomarkers and their significance but more on the prevalence and clinical outcomes of the conditions.

Despite the limitations of this review, it does fill a gap in the literature, and it shows the importance of continuing these studies to understand further the association between alteration in biomarkers in these specific patients to allow a better prognostic and care.

Conclusions

The ambiguities in defining frailty and the complex pathophysiology of this condition makes the development and identification of biomarkers a particularly challenging task. In fact, even the lack of guidelines for selecting a specific tool for assessing frailty is an obstacle.

However, the literature seems to reach consensus when reporting the inflammatory markers of CRP, IL-6 and TNF α . Other biomarkers reported as likely to be related to

frailty are Hb, GFR, Alb, hormones such as dehydroepiandrosterone (DHEA) sulfate, testosterone, insulin-like growth factor- α (IGF1) and vitamin D, as well as products of oxidative damage or antioxidants [33].

The inconsistency in approaches noted in the articles included in this review in terms of sample characteristics and biomarkers measured impacts its accuracy and does not offer a robust system able to predict frailty in dialysis patients. The relatively small sample sizes in these studies might have reduced the statistical significance of the biomarkers studied to detect differences between pre-frail and frail and pre-dialysis and dialysis groups.

After analyzing all the articles, it was common to find a high prevalence of frailty in patients under dialysis, particularly in female patients. The higher risk of mortality was also commonly associated with frail patients.

Early identification and intervention are crucial for a potential decrease or even reverse of frailty, especially in the early stages. Routine interventions to try and diminish polypharmacy and review adequacy of medication, nutritional guidance, psychological support and exercise in community-dwelling older adults, especially the ones suffering from CKD under dialysis or pre-dialysis, could be a good and relatively inexpensive strategy to decrease the raising cases of frailty and promote a better quality of life to these patients, improving geriatric care.

The implementation of this multidimensional approach could be done in the community and primary care centers to minimize poor outcomes such as falls and hospitalization, for example, to reduce the burden on the healthcare services.

A recent report has been published regarding a healthy aging program called 'HAPPY' in place in Singapore which aims to engage pre-frail and frail older adults in exercise in the community; an improvement in cognition, physical function, frailty status, reduction of social isolation and improving in perceived health has been reported [45].

Associations between exercise and improved health outcomes in patients suffering from CKD have been reported. A reduction of 22% of mortality among CKD patients under hemodialysis who engage in a 10 min/day physical activity has been reported [46]. Other studies have also reported the importance of light-intensity physical activity among patients suffering from CKD to reduce mortality [47].

Due to the complexity of frail syndrome and the comorbidities frequently related to these patients, including CKD, the identification of biomarkers that can differentiate between frailty and other comorbidities is still in its early stages of the investigation.

However, due to the high prevalence of frailty and the fact that an increase of prevalence is expected in the future as a result of improved life expectancy, it is essential that the assessment of frailty is done to identify the early stages of this syndrome and

that multidimensional strategies are applied to improve geriatric care, quality of life and reduction in mortality.

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Conflicts of Interest

The authors declare no conflict of interest.

References

1. Mansur H.N., Lovisi J.C.M., Colugnati F., Raposo N., Fernandes N., Bastos M.G. Association of Frailty With Endothelial Dysfunction and Its Possible Impact on Negative Outcomes in Brazilian Predialysis Patients With Chronic Kidney Disease. *BMC Nephrol.* 2015;16:1–9. doi: 10.1186/s12882-015-0150-1.
2. Almada M., Brochado P., Portela D. Prevalence of Falls and Associated Factors Among Community-Dwelling Older Adults: A Cross-Sectional Study. *J. Frailty Aging.* 2020;10:1–7. doi: 10.14283/jfa.2020.44.
3. Midão L., Brochado P., Almada M., Duarte M., Paúl C., Costa E. Frailty Status and Polypharmacy Predict All-Cause Mortality in Community Dwelling Older Adults in Europe. *Int. J. Environ. Res. Public Health.* 2021;18:3580. doi: 10.3390/ijerph18073580.
4. Manfredi G., Midão L., Paúl C., Cena C., Duarte M., Costa E. Prevalence of Frailty Status Among the European Elderly Population: Findings from the Survey of Health, Aging and Retirement in Europe. *Geriatr. Gerontol. Int.* 2019;19:723–729. doi: 10.1111/ggi.13689.
5. Leng S., Chen X., Mao G. Frailty Syndrome: An Overview. *Clin. Interv. Aging.* 2014;9:433–441. doi: 10.2147/CIA.S45300.
6. Leng S., Chaves P., Ms K.K., Walston J. Serum Interleukin-6 and Hemoglobin As Physiological Correlates in the Geriatric Syndrome of Frailty: A Pilot Study. *J. Am. Geriatr. Soc.* 2002;50:1268–1271. doi: 10.1046/j.1532-5415.2002.50315.x.
7. Nixon A.C., Bampouras T.M., Pendleton N., Woywodt A., Mitra S., Dhaygude A. Frailty and Chronic Kidney Disease: Current Evidence and Continuing Uncertainties. *Clin. Kidney J.* 2018;11:236–245. doi: 10.1093/ckj/sfx134.
8. Worthen G., Tennankore K. Frailty Screening in Chronic Kidney Disease: Current Perspectives. *Int. J. Nephrol. Renov. Dis.* 2019;ume 12:229–239. doi: 10.2147/IJNRD.S228956.
9. Johansen K.L., Chertow G.M., Jin C., Kutner N.G. Significance of Frailty Among Dialysis Patients. *J. Am. Soc. Nephrol.* 2007;18:2960–2967. doi: 10.1681/ASN.2007020221.
10. Roshanravan B., Khatri M., Robinson-Cohen C., Levin G., Patel K.V., de Boer I.H., Seliger S., Ruzinski J., Himmelfarb J., Kestenbaum B. A Prospective Study of Frailty in Nephrology-Referred Patients With CKD. *Am. J. Kidney Dis.* 2012;60:912–921. doi: 10.1053/j.ajkd.2012.05.017.

11. Chowdhury R., Peel N., Krosch M., Hubbard R. Frailty and Chronic Kidney Disease: A Systematic Review. *Arch. Gerontol. Geriatr.* 2017;68:135–142. doi: 10.1016/j.archger.2016.10.007.
12. Garcia-Canton C., Rodenas A., Lopez-Aperador C., Rivero Y., Anton G., Monzon T., Diaz N., Vega N., Loro J., Santana A., et al. Frailty in Hemodialysis and Prediction of Poor Short-Term Outcome: Mortality, Hospitalization and Visits to Hospital Emergency Services. *Ren. Fail.* 2019;41:567–575. doi: 10.1080/0886022X.2019.1628061.
13. Johansen K.L., Dalrymple L.S., Delgado C., Chertow G.M., Segal M.R., Chiang J., Grimes B., Kaysen G.A. Factors Associated With Frailty and Its Trajectory Among Patients on Hemodialysis. *Clin. J. Am. Soc. Nephrol.* 2017;12:1100–1108. doi: 10.2215/CJN.12131116.
14. Kuningas K., Inston N. Age Is Just a Number: Is Frailty Being Ignored in Vascular Access Planning for Dialysis? *J. Vasc. Access.* 2021 doi: 10.1177/1129729821989902.
15. Smith G., Avenell A., Band M.M., Hampson G., Lamb E.J., Littleford R.C., McNamee P., Soiza R.L., Sumukadas D., Witham M.D. Associations Between Frailty, Physical Performance, and Renal Biomarkers in Older People With Advanced Chronic Kidney Disease. *Eur. Geriatr. Med.* 2021;10:1–10. doi: 10.1007/s41999-021-00478-4.
16. Higgins J.P.T., Thomas J., Chandler J., Cumpston M., Li T., Page M.J., Welch V.A., editors. *Cochrane Handbook for Systematic Reviews of Interventions* version 6.2 (updated February 2021). Cochrane. 2021. [(accessed on 3 March 2021)]. Available online: www.training.cochrane.org/handbook
17. Cohen J. A Coefficient of Agreement for Nominal Scales. *Educ. Psychol. Meas.* 1960;20:37–46. doi: 10.1177/001316446002000104.
18. McAdams-DeMarco M.A., Ying H., Thomas A., Warsame F., Shaffer A., Haugen C.E., Garonzik-Wang J.M., Desai N.M., Varadhan R., Walston J., et al. Frailty, Inflammatory Markers, and Waitlist Mortality Among Patients With End-Stage Renal Disease in a Prospective Cohort Study. *Transplantation.* 2018;102:1740–1746. doi: 10.1097/TP.0000000000002213.
19. Baharani J., Ali H., Abdelaziz T., Abdelaal F. Assessment of Prevalence and Clinical Outcome of Frailty in an Elderly Predialysis Cohort Using Simple Tools. *Saudi J. Kidney Dis. Transplant.* 2018;29:63–70. doi: 10.4103/1319-2442.225175.

20. Folstein M.F., Folstein S.E., McHugh P.R. "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 1975;12:189–198. doi: 10.1016/0022-3956(75)90026-6.
21. Raïche M., Hébert R., Dubois M.-F. PRISMA-7: A Case-Finding Tool to Identify Older Adults With Moderate to Severe Disabilities. *Arch. Gerontol. Geriatr.* 2008;47:9–18. doi: 10.1016/j.archger.2007.06.004.
22. Moher D., Liberati A., Tetzlaff J., Altman D.G. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *BMJ.* 2009;339:332–336. doi: 10.1136/bmj.b2535.
23. Hirsch C., Anderson M.L., Newman A.B., Kop W., Jackson S., Gottdiener J., Tracy R., Fried L.P. The Association of Race With Frailty: The Cardiovascular Health Study. *Ann. Epidemiology.* 2006;16:545–553. doi: 10.1016/j.annepidem.2005.10.003.
24. Franse C.B., Van Grieken A., Qin L., Melis R.J.F., Rietjens J.A.C., Raat H. Ethnic Differences in Frailty: A Cross-Sectional Study of Pooled Data from Community-Dwelling Older Persons in the Netherlands. *BMJ Open.* 2018;8:e022241. doi: 10.1136/bmjopen-2018-022241.
25. Nakazato Y., Sugiyama T., Ohno R., Shimoyama H., Leung D.L., Cohen A.A., Kurane R., Hirose S., Watanabe A., Shimoyama H. Estimation of Homeostatic Dysregulation and Frailty Using Biomarker Variability: A Principal Component Analysis of Hemodialysis Patients. *Sci. Rep.* 2020;10:12.:1. doi: 10.1038/s41598-020-66861-6.
26. Poveda V., Filgueiras M., Miranda V., Santos-Silva A., Paúl C., Costa E. Frailty in End-Stage Renal Disease Patients under Dialysis and Its Association With Clinical and Biochemical Markers. *J Frailty Aging.* 2017;6:103–106.
27. Nakazato Y., Kurane R., Hirose S., Watanabe A., Shimoyama H. Aging and Death-Associated Changes in Serum Albumin Variability over the Course of Chronic Hemodialysis Treatment. *PLoS ONE.* 2017;12:e0185216. doi: 10.1371/journal.pone.0185216.
28. Searle S.D., Rockwood K. Frailty and the Risk of Cognitive Impairment. *Alzheimer's Res. Ther.* 2015;7:54. doi: 10.1186/s13195-015-0140-3.
29. Macuco C.R.M., Batistoni S., Lopes A., Cachioni M., Falcão D., Neri A.L., Yassuda M.S. Mini-Mental State Examination Performance in Frail, Pre-Frail, and Non-Frail Community Dwelling Older Adults in Ermelino Matarazzo, São Paulo, Brazil. *Int. Psychogeriatrics.* 2012;24:1725–1731. doi: 10.1017/S1041610212000907.

30. Blaum C.S., Xue Q.L., Michelon E., Semba R.D., Fried L.P. The Association Between Obesity and the Frailty Syndrome in Older Women: The Women's Health and Aging Studies. *J. Am. Geriatr. Soc.* 2005;53:927–934. doi: 10.1111/j.1532-5415.2005.53300.x.
31. Greco E.A., Pietschmann P., Migliaccio S. Osteoporosis and Sarcopenia Increase Frailty Syndrome in the Elderly. *Front. Endocrinol.* 2019;10:255. doi: 10.3389/fendo.2019.00255.
32. Alem A.M., Sherrard D.J., Gillen D.L., Weiss N.S., Beresford S.A., Heckbert S.R., Wong C., Stehman-Breen C. Increased Risk of Hip Fracture Among Patients With End-Stage Renal Disease. *Kidney Int.* 2000;58:396–399. doi: 10.1046/j.1523-1755.2000.00178.x.
33. Al Saedi A., Feehan J., Phu S., Duque G. Current and Emerging Biomarkers of Frailty in the Elderly. *Clin. Interv. Aging.* 2019;ume 14:389–398. doi: 10.2147/CIA.S168687.
34. Kojima G., Iliffe S., Walters K. Frailty Index As a Predictor of Mortality: A Systematic Review and Meta-Analysis. *Age Ageing.* 2018;47:193–200. doi: 10.1093/ageing/afx162.
35. Sachdeva B., Zulfiqar H., Aeddula N.R. Peritoneal Dialysis. [(accessed on 14 April 2021)]; Available online: <https://www.ncbi.nlm.nih.gov/books/NBK532979/>
36. Fried L.P., Tangen C.M., Walston J., Newman A.B., Hirsch C., Gottdiener J., Seeman T., Tracy R., Kop W.J., Burke G., et al. Frailty in Older Adults: Evidence for a Phenotype. *J. Gerontol. Ser. A Biol. Sci. Med. Sci.* 2001;56:M146–M157. doi: 10.1093/gerona/56.3.M146.
37. Kazancioğlu R. Risk Factors for Chronic Kidney Disease: An Update. *Kidney Int. Suppl.* 2013;3:368–371. doi: 10.1038/kisup.2013.79.
38. Gluba-Brzózka A., Franczyk B., Olszewski R., Rysz J. The Influence of Inflammation on Anemia in CKD Patients. *Int. J. Mol. Sci.* 2020;21:725. doi: 10.3390/ijms21030725.
39. Lankhorst C.E., Wish J.B. Anemia in Renal Disease: Diagnosis and Management. *Blood Rev.* 2010;24:39–47. doi: 10.1016/j.blre.2009.09.001.
40. Yanagita I., Fujihara Y., Iwaya C., Kitajima Y., Tajima M., Honda M., Teruya Y., Asakawa H., Ito T., Eda T., et al. Low Serum Albumin, Aspartate Aminotransferase, and Body Mass Are Risk Factors for Frailty in Elderly People With diabetes—a Cross-Sectional Study. *BMC Geriatr.* 2020;20:1–8. doi: 10.1186/s12877-020-01601-z.

41. Hubbard R.E., O'Mahony M.S., Savva G., Calver B.L., Woodhouse K.W. Inflammation and Frailty Measures in Older People. *J. Cell. Mol. Med.* 2009;13:3103–3109. doi: 10.1111/j.1582-4934.2009.00733.x.
42. Bao Y., Dalrymple L., Chertow G.M., Kaysen G.A., Johansen K.L. Frailty, Dialysis Initiation, and Mortality in End-Stage Renal Disease. *Arch. Intern. Med.* 2012;172:1071–1077. doi: 10.1001/archinternmed.2012.3020.
43. Leavey S.F., Strawderman R.L., Young E.W., Saran R., Roys E., Agodoa L.Y., Wolfe R.A., Port F.K. Cross-Sectional and Longitudinal Predictors of Serum Albumin in Hemodialysis Patients. *Kidney Int.* 2000;58:2119–2128. doi: 10.1111/j.1523-1755.2000.00385.x.
44. Kotanko P., Thijssen S., Usvyat L., Tashman A., Kruse A., Huber C., Levin N.W. Temporal Evolution of Clinical Parameters before Death in Dialysis Patients: A New Concept. *Blood Purif.* 2009;27:38–47. doi: 10.1159/000167007.
45. Merchant R.A., Tsoi C.T., Tan W.M., Lau W., Sandrasageran S., Arai H. Community-Based Peer-Led Intervention for Healthy Ageing and Evaluation of the 'HAPPY' Program. *J. Nutr. Heal. Aging.* 2021;25:520–527. doi: 10.1007/s12603-021-1606-6.
46. Matsuzawa R., Matsunaga A., Wang G., Kutsuna T., Ishii A., Abe Y., Takagi Y., Yoshida A., Takahira N. Habitual Physical Activity Measured by Accelerometer and Survival in Maintenance Hemodialysis Patients. *Clin. J. Am. Soc. Nephrol.* 2012;7:2010–2016. doi: 10.2215/CJN.03660412.
47. Beddhu S., Wei G., Marcus R.L., Chonchol M., Greene T. Light-Intensity Physical Activities and Mortality in the United States General Population and CKD Subpopulation. *Clin. J. Am. Soc. Nephrol.* 2015;10:1145–1153. doi: 10.2215/CJN.08410814.

Manuscript IV

Validation and reliability of a smartphone application for self-assessment of frailty based on the Groningen Frailty Indicator:
FRAILSURVEY

Midão L, Duarte M, Sampaio R, Almada M, Dias CC, Paúl C, Costa E.

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Background: Portugal is facing the challenge of population ageing, resulting in a notable increase in the proportion of older individuals. This has positioned the country among those in Europe with a high prevalence of frailty. Frailty, a geriatric syndrome characterized by diminished physiological reserve and heightened vulnerability to stressors, imposes a substantial burden on public health. It escalates the risks of adverse outcomes, including falls, hospitalization, disability, and mortality.

Objective: This exploratory research focuses on two primary objectives. First, it involves the translation and psychometric evaluation of the European Portuguese version of the Groningen Frailty Indicator (GFI). Second, it entails the development and evaluation of the FRAILSURVEY app, a novel assessment tool for frailty based on the GFI.

Methods: The study encompasses two major phases: the initial translation and validation of the GFI into European Portuguese and the development of the FRAILSURVEY app, followed by an examination of its validity and reliability compared to the conventional paper version of the GFI. For this, a randomized repeated crossover design was employed using the paper form of the Groningen Frailty Indicator and the smartphone application FRAILSURVEY.

Results: The meticulous translation process yields a final version of the GFI with robust psychometric properties, ensuring clarity and comprehensibility. The study includes 522 participants, predominantly women ($n=367$, 70.3%), with an average age of 73.7 ± 6.7 years. Psychometric evaluation of the European Portuguese GFI in paper form demonstrates good reliability (internal consistency: Cronbach's alpha 0.759; temporal stability: ICC 0.974) and construct validity (revealing a four-dimensional structure explaining 56.0% of variance). Evaluation of the app-based European Portuguese GFI indicates good reliability (inter-instrument reliability: Cohen's Kappa=0.790; temporal stability: ICC=0.800) and concurrent validity ($r=0.694$, $p<0.001$).

Conclusion: The study's main hypothesis proposed that participants would perceive both the smartphone application and paper version of the GFI as feasible and acceptable for use, with the smartphone app not being inferior to the standard paper version. The findings supported this hypothesis, as FRAILSURVEY exhibited comparable validity and reliability to its paper counterpart. FRAILSURVEY employs a standardized and validated assessment tool, offering objective and consistent measurements while eliminating subjective biases, enhancing accuracy, and ensuring reliability. This app holds promising potential for aiding healthcare professionals in identifying frailty in older individuals,

enabling early intervention, and improving the management of adverse health outcomes associated with this syndrome.

Keywords: frailty; mHealth; eHealth; Assessment; validation; GFI.

Portugal is currently confronting a significant population ageing phenomenon, placing it among the European countries with one of the highest percentages of older individuals. As of 2021, the ageing index reached 182, meaning there were 182 people aged 65 or above for every 100 individuals aged 0-14. This ageing trend results from various contributing factors, including a low birth rate, extended life expectancy, and emigration of young people. According to the 2011 census, 19.0% of the Portuguese population was 65 or older. A substantial increase was denoted in the 2021 census, to 23.4%. Projections indicate that this percentage will continue to rise in the upcoming years. In fact, estimations forecast that by 2080, the proportion of people aged 65 and over will escalate to 37.5% of the total population [1-4]. This demographic change has significant implications for the country's economy, social security system, and healthcare system. The increasing number of older people will require greater resources to provide for their care and support, including healthcare services, long-term care facilities, and home care services. At the same time, the working-age population will be under pressure to support the social security system as the number of retirees increases and the number of workers decreases. As the proportion of older people grows, so does the prevalence of age-related diseases, comorbidities, and geriatric syndromes. Portugal ranks among the European countries with the highest percentage of frailty (20.7%) [5, 6].

Frailty is characterized by a reduced physiologic reserve and increased susceptibility to stressors, leading to an elevated risk of adverse health outcomes like falls, hospitalization, disability, and death. Typically associated with ageing, frailty may encompass a blend of physical, cognitive, and psychosocial factors, making it a complex and multifaceted condition, and therefore, identifying and addressing frailty is essential for preventing comorbidities, optimizing health outcomes and improving the quality of life in older adults [7-11]. However, evaluating frailty poses challenges due to its multifactorial nature, resulting in various tools and methods commonly used for its assessment. It is crucial to recognize that every assessment tool is flawed, lacks standardization and different approaches may be more suitable for specific populations or settings [10, 12].

The Groningen Frailty Indicator (GFI) is a comprehensive assessment tool tailored for evaluating frailty in older adults. Covering physical, social, and cognitive aspects, the paper version of the GFI has undergone validation in diverse settings, confirming its accuracy and consistency. By encompassing a wide range of dimensions, the GFI thoroughly examines an individual's physical, social, and cognitive function, empowering

healthcare professionals to craft suitable care plans for their patients [13-16]. Distinguishing itself from other instruments, the GFI boasts a straightforward administration process, requiring no more than 10 minutes to complete. Furthermore, as a non-invasive instrument, individuals can complete it through self-reporting or seek guidance from a trained health professional if necessary [15, 16].

However, paper-based questionnaires have several disadvantages: manual data entry is time-consuming and leads to potential errors; accessibility is limited as they must be physically distributed and collected; data security may be compromised; as well as incomplete or illegible responses and reduced data analysis capabilities are common challenges. Furthermore, they lack interactive features that enhance engagement and data quality, such as in digital formats [17]. Smartphone-based assessments aim to develop a user-friendly tool that streamlines screening and monitoring by scoring data [18, 19]. Such an approach has the potential to increase health literacy resulting in cost savings. Nevertheless, it is crucial to validate the smartphone-based applications to ensure their accuracy and reliability compared to the original paper questionnaires, as there may be possible response bias between the two versions [20].

Given the burden of frailty in Portugal, this study aimed to, first, translate and validate the GFI into European Portuguese, and then examine the validity and reliability of the digital version of the GFI, the app FRAILSURVEY, compared to the conventional paper version of the GFI.

Methods

This is a quantitative, exploratory research that involves analysis of psychometric data and that was developed in two major phases: initially, the Groningen Frailty Indicator was translated and validated into European Portuguese, and; the application FRAILSURVEY was developed, and its validity and reliability studied as a mHealth tool for frailty assessment.

Frailty Screening Instrument

Groningen Frailty Indicator

The Groningen Frailty Indicator is a short, easy-to-use instrument which has proven to be a good alternative for assessing frailty in the population aged 65 or over [21]. The table 1 indicates the domains assessed in the GFI scale, as well as, scoring items. The

self-assessment version of the GFI published in 2013 was used, composed of 15 items and divided into four domains [22]. The physical domain has nine questions related to toileting, shopping, mobility functions, dressing, physical fitness, vision, hearing, unexplained weight loss, and medication use. The cognitive domain includes one item related to cognitive concerns. The social domain consists of three questions about emotional isolation, social relations, and social support. The psychological domain comprises two questions related to mood. Each item has a score of 0 or 1 attributed, with 1 indicating a dependency problem. For example, if the participant cannot dress or undress without help, he would score 1. The total score ranged from 0 to 15, and higher scores indicate greater levels of frailty. The originally proposed cutoff point is 4 or higher represents frailty [16].

Translation of the Groningen Frailty Indicator to European Portuguese

For the development of the European Portuguese version of the Groningen Frailty Indicator, the self-report instrument guidelines defined by the ISPOR Task Force for Translation and Cultural Adaptation were followed [23].

Table 1 Self-assessment version of the Groningen Frailty Indicator [22].

The Groningen Frailty Indicator (GFI)	
Physical domain	
Are you able to carry out these tasks single-handedly and without any help? (The use of help resources such as a walking stick, walking frame or wheelchair is considered independent.)	
1.	Shopping
2.	Walking around outside (around the house or to the neighbors)
3.	Dressing and undressing
4.	Going to the toilet
5.	What mark do you give yourself for physical fitness? (Scale 0 to 10)
6.	Do you experience problems in daily life due to poor vision?
7.	Do you experience problems in daily life due to being hard of hearing?
8.	During the last 6 months have you lost a lot of weight unwillingly? (3 kg in 1 month or 6 kg in 2 months)
9.	Do you take 4 or more different types of medicine?
Cognitive domain	
10.	Do you have any complaints about your memory?
Social domain	
11.	Do you sometimes experience emptiness around yourself?
12.	Do you sometimes miss people around yourself?
13.	Do you sometimes feel abandoned?
Psychological domain	
14.	Have you recently felt downhearted or sad?
15.	Have you recently felt nervous or anxious?
Scoring:	
Questions 1-4: Yes = 0; No = 1	
Question 5: 0-6 = 1; 7-10 = 0	
Questions 6-15: No = 0; Yes = 1	

Developing the smartphone application of the GFI

The smartphone application was developed for both Android (the operating system created by Google) and iOS (created by Apple) systems. FRAILSURVEY is a questionnaire that comprises two sets of questions: 19 questions about sociodemographic data, social resources, self-perception of health, nutrition, medication, psycho-social and cognitive status, and time occupation, plus a set of 15 questions used to assess frailty status, the Groningen Frailty Indicator.

FRAILSURVEY development was based on an accessibility principle for older adults, to guarantee greater autonomy to use it. Considerations such as vision, hearing, motor control and cognition were considered. In addition, the app features a typographic font designed for low-vision people, APHont, developed by the American Printing House for the Blind, and it also presents a way to increase or decrease the font size, as well as the possibility of listening to some audio information.

The results obtained classify the person as robust or frail. The app displays tailored recommendations if the person is classified as frail. The recommendations revolve around aspects such as physical exercise, a healthy diet, and social networks, among others (Figure 1). The app generates an anonymous database for research purposes.

Study design

A randomized repeated crossover design was employed using the paper form of the Groningen Frailty Indicator and the smartphone application FRAILSURVEY. This design entailed the dual administration of both assessment methods to each participant on distinct occasions, separated by a one-week interval. The order of presentation for the assessments was randomized to mitigate any potential sequence effects. In evaluating test-retest reliability, a subset of participants was randomly chosen from the larger cohort to participate in retest assessments approximately two weeks after their initial interaction. These retest assessments encompassed both the paper-based form and the application [24].

Ethics Approval

Ethical clearance for the research was granted by the Ethical Review Board of the Faculty of Pharmacy, University of Porto (Nº 33-11-2017). Before their involvement, the rights and responsibilities of participants were comprehensively elucidated, and written consent was obtained from all individuals. Throughout the process of data collection and entry, strict confidentiality measures were upheld.

Participants

Between February 2019 and February 2020, older adults living in the district of Porto, Portugal, were invited to take part in this study. A total of 522 participants were recruited for this study, employing a convenience sampling method. The sample included a diverse population of community-dwelling older individuals, residents of nursing homes, and older adults living in their own homes but availing daily care facilities. The inclusion criteria encompassed individuals aged 65 years and older, regardless of gender, who had the capacity to independently complete the assessments. The sample exceeded the sample size required to be ten times larger than the number of GFI items [25]. For test-retest reliability, 24 participants were included [24].

Statistical analysis

Categorical variables were summarized as absolute and relative frequencies. Descriptive statistics were used to report the subject characteristics of the study sample. Differences between different subgroups were studied, i.e., gender, age, marital status, education, and financial status. GFI scores (from 0 to 15) were presented as mean $\pm$ SD, and differences between subgroups were tested through the Kruskal-Wallis test. GFI classification (non-frail and frail) was presented as frequencies, and differences between different subgroups were tested through the Mann-Whitney U test.

The psychometric properties of the European Portuguese version of the GFI were assessed as follows: Internal consistency referred to the extent to which the items within a scale or questionnaire consistently measure the same construct and was assessed by Cronbach's alpha; The retest was conducted two weeks after the initial contact with the participant for assessing temporal stability. A two-week interval allows for a sufficient gap between the two administrations to minimize potential memory effects and recall bias while maintaining a relatively short timeframe. The most commonly used statistical measure to evaluate temporal stability is the Intraclass Correlation Coefficient (ICC), and therefore it was used in this study. The ICC value ranges between 0 and 1, with higher values indicating greater temporal stability. Values above 0.9 suggest excellent temporal stability, while values between 0.75 and 0.9 indicate good temporal stability and values between 0.5 and 0.75 show moderate temporal stability [26]; Construct validity was assessed by performing exploratory factor analysis with principal components and varimax rotation methods [27].



Figure 1 Screenshots of the FRAILSURVEY app interface.

The psychometric properties of the FRAILSURVEY were assessed as follows: Inter-instrument reliability refers to the consistency of GFI scores obtained by the same person between the paper and smartphone versions. Cohen's kappa was used to assess it. Cohen suggested the Kappa result be interpreted as follows: values ≤ 0 as indicating no agreement and 0.01–0.20 as none to slight (light), 0.21–0.40 as fair (fair), 0.41–0.60 as moderate (moderate), 0.61–0.80 as substantial (considerable), and 0.81–1.00 as almost perfect agreement [28]; Temporal stability was evaluated by the ICC, as described above, and; The concurrent validity was studied through Pearson's Correlation Coefficient, that was used to quantify the relationship between the scores obtained in the app and in paper and with the app, the scores from the established criterion measure and the scores from the instrument we intended to validate. Pearson's correlation coefficient assesses the strength and direction of the correlation, indicating the degree to which the two measures agree or disagree. The validity assessment in this study was based on demonstrating the absence of significant differences in the total score of the GFI and each item of the GFI. The significance level used was 0.05. Data were analyzed using IBM SPSS Statistics (Version 28.0. Armonk, NY, USA).

Results

European Portuguese Version of the Groningen Frailty Indicator

The English version of the GFI tool was translated into European Portuguese by two native Portuguese speakers. The back-translation was done by a professional service provider who knew nothing about the purpose of the research. A panel of experts assessed the similarity of the versions and reviewed and resolved all discrepancies and ambiguities by consensus. To assess the comprehensibility of the language and wording, the revised preliminary European Portuguese version was used with a pilot sample of 10 native Portuguese-speaking older adults. The final European Portuguese version of the GFI was defined and used in the validation process. No changes were made to the version used, as the items were judged to be clear and easy to understand. In the end, the final version was produced (Supplementary Table 1).

Participants

In this study, 522 participants were included, with an average age of 73.7 ± 6.7 years old and consisted mainly of women ($n=367$, 70.3%). Almost two-thirds of the sample were aged between 65 and 74 years old, most participants were married (59.6%), the majority only had primary school completed (54.2%) and 59.2% reported having moderate money to meet their needs (Table 2). Using the paper version of the European Portuguese version of the GFI, the average score was 4.57, significantly higher in women (5.05) than in men (3.43) ($p<0.001$). The score increases significantly with age, with higher scores being more present in older people (GFI=3.73 for participants aged between 65 and 74 years; GFI=5.58 for participants aged between 75 and 84 years old, and; GFI=7.77 for participants aged 85 years old or over, $p<0.001$). There are also significant differences in the mean GFI scores according to marital status, with married (3.67) and divorced people (4.62) having lower values while widowed (6.02) or single people (6.13) having higher values ($p<0.001$). Frailty is also related to education. We reported that higher frailty scores are associated with lower levels of education, and with the economic level, with greater scores of frailty in people with lower economic levels.

Table 2 Participants' sociodemographic characteristics and frailty status.

Variables	n (%)	Portuguese GFI Mean (SD)	p-value Kruskal-Wallis	Non-frailty n (%)	Frailty n (%)	p-value Mann-Whitney U
Gender						
Female	367 (70.3)	5.05 (3.04)	<0.001	127 (34,6)	240 (65.4)	<0.001
Male	155 (29.7)	3.43 (2.702)		89 (57.4)	66 (42.6)	
Age						
65-74	341 (65.3)	3.73 (2.68)	<0.001	181 (53.1)	160 (46.9)	<0.001
75-84	134 (25.7)	5.58 (2.91)		31 (23.1)	103 (76.9)	
85+	47 (9.0)	7.77 (2.86)		4 (8.5)	43 (91.5)	
Marital Status						
Single	32 (6.1)	6.13 (3.24)	<0.001	6 (18.8)	26 (81.3)	0.003
Married	311 (59.6)	3.67 (2.47)		161 (51.8)	150 (48.2)	
Widowed	158 (30.3)	6.02 (3.34)		38 (24.1)	120 (75.9)	
Divorced	21 (4.0)	4.62 (2.94)		11 (52.4)	10 (47.6)	
Education						
Illiterate	36 (6.9)	7.03 (3.11)	<0.001	5 (13.9)	31 (86.1)	<0.001
Unfinished primary school	80 (15.3)	5.90 (2.95)		19 (23.8)	61 (76.3)	
Primary school	283 (54.2)	4.29 (2.97)		128 (45.2)	155 (54.8)	
High school	92 (17.6)	3.52 (2.32)		47 (51.1)	45 (48.9)	
Higher education	31 (5.9)	4.00 (3.24)		17 (54.8)	14 (45.2)	
Do you think you have enough money to meet your needs?						
Nothing	12 (2.3)	5.00 (3.77)	<0.001	6 (50.0)	6 (50.0)	<0.001
Little	190 (36.4)	5.89 (3.20)		47 (24.7)	43 (75.3)	
Moderately	309 (59.2)	3.78 (2.63)		158 (51.1)	151 (48.9)	
Quite enough	11 (2.1)	(1.96)		4 (45.5)	6 (54.5)	

According to the GFI frailty classification, using the cutoff point of 4, 58.6% of the people included in this study are frail. Frailty is significantly greater in women (65.4% vs 42.6% in men, $p<0.001$), in older people (91.5% in people aged 85 and over vs. 76.9% in people aged 75 to 84 years vs. 46.9% in people aged 65 and 74, $p<0.001$), and in single people and widows (81.3% and 75.9% respectively vs 48.2% in married people and 47.6% in divorced people, $p<0.001$). The proportion of frail people is also significantly higher for people with the lowest level of education and at lower economic levels.

Item descriptive analysis and missing data

Of the 15 indicators, the most prevalent among all people are the items that assess nervousness and anxiety (present in 61.4% of participants), problems in daily life due to poor vision reported by 56% of participants, and polypharmacy reported by 53.6% (Table 3). The least prevalent items are mobility issues, more specifically, the inability to dress and undress alone (9.8%) and to use the bathroom without help (7.9%), and the feeling of abandonment (7.1%).

Table 3 Groningen Frailty Indicator: missing values and criteria fulfilments.

Question	Fulfil criteria (%)	n	Missing Values
1. Shopping	18.4	522	0
2. Walking around outside (around the house or to the neighbours)	13.0	522	0
3. Dressing and undressing	9.8	521	1
4. Going to the toilet	7.9	521	1
5. How do you rate your physical fitness? (Scale 0 to 10)	35.5	512	10
6. Do you experience problems in daily life due to poor vision?	56.0	520	2
7. Do you experience problems in daily life due to being hard of hearing?	35.1	522	0
8. During the last 6 months, did you lose a lot of weight unwillingly? (3 kg in 1 month or 6 kg in 2 months)	11.5	522	0
9. Do you take 4 or more different types of medicine?	53.6	520	2
10. Do you have any complaints about your memory?	35.2	522	0
11. Do you sometimes experience an emptiness around you?	39.1	522	0
12. Do you sometimes miss people around you?	28.0	522	0
13. Do you sometimes feel abandoned?	7.1	522	0
14. Did you felt downhearted or sad recently?	46.6	521	1
15. Did you felt nervous or anxious recently?	61.4	521	1

Of the 522 participants, there are only 18 missing values in 7 of the 15 GFI questions. The average of missing values per participant is 0.03. Only 1 participant has missing

values for two GFI questions, while the other 17 missing values come from 17 different participants. The question that has the most missing values (1.9%) is the question that asks the participant how he rates his physical fitness (from 0 to 10).

Psychometric Evaluation of the European Portuguese version of the GFI (paper)

Internal Consistency

The obtained Cronbach's alpha of 0.759 suggests a moderate level of internal consistency and no item was dropped (Table 4) [291].

Temporal stability

The values varied between 0.504 and 1.000, being an overall value of 0.974 (Table 4).

Construct Validity

The suitability of the factor analysis by checking the existence of significant correlations between the items was confirmed by Kaiser-Meyer-Olkin (KMO 0.799) and by Bartlett's sphericity test (QQ 2074.657; gl 105; and $p < 0.001$). Evaluation of the scree plot and the size of the eigenvalues strongly suggest that the GFI has a four-dimensional structure, explaining 56.0% of the variance (Table 5). This analysis produced four subscales: (1) Daily Activities and Physical Fitness (items 1–5), (2) Nourishment; (3) Health Problems (items 5,6,9,10), and (4) Psychosocial Functioning (items 11–15).

Table 4 Psychometric Evaluation of the European Portuguese version of the GFI - reliability analysis (internal consistency and temporal stability).

	Internal Consistency			Temporal stability
	Scale average if the item is removed	Scale variation if the item is removed	Cronbach's Alpha if the item is removed	ICC
1. Shopping	4.40	7.876	0.729	1.000
2. Walking around outside (around the house or to the neighbours)	4.46	8.189	0.737	0.947
3. Dressing and undressing	4.49	8.362	0.741	1.000
4. Going to the toilet	4.51	8.504	0.744	0.909
5. How do you rate your physical fitness? (Scale 0 to 10)	4.23	7.882	0.740	0.940

6. Do you experience problems in daily life due to poor vision?	4.02	8.438	0.764	1.000
7. Do you experience problems in daily life due to being hard of hearing?	4.24	8.381	0.759	1.000
8. During the last 6 months, did you lose a lot of weight unwillingly? (3 kg in 1 month or 6 kg in 2 months)	4.47	8.952	0.765	1.000
9. Do you take 4 or more different types of medicine?	4.05	8.087	0.751	1.000
10. Do you have any complaints about your memory?	4.24	8.257	0.755	0.911
11. Do you sometimes experience an emptiness around you?	4.20	7.795	0.737	0.958
12. Do you sometimes miss people around you?	4.30	8.014	0.742	0.727
13. Do you sometimes feel abandoned?	4.51	8.683	0.751	0.880
14. Did you felt downhearted or sad recently?	4.13	7.547	0.727	1.000
15. Did you felt nervous or anxious recently?	3.97	8.092	0.749	0.504
Total			0.759	0.974

Psychometric Evaluation of the FRAILSURVEY – a mHealth tool for frailty assessment

Inter-instrument reliability

The values varied between 0.100 and 0.634, being an overall value of 0.790 (Table 6). From the 15 items, 2 items had a substantial agreement, 5 had a moderate agreement, 6 had a fair agreement, 2 had none to a slight agreement, and the overall score had an almost perfect agreement.

Table 5 Psychometric Evaluation of the European Portuguese version of the GFI - validity analysis (construct validity): exploratory factor Analysis structure of the Portuguese version of the GFI: loading for each factor and each item in the model with four factors after an orthogonal varimax rotation and factor extraction using principal Components (n=502).

Items	Factors ^a			
	1	2	3	4
Daily Activities and Physical Fitness				
1. Shopping	0.822	0.167	0.165	-0.009
2. Walking around outside (around the house or to the neighbors)	0.863	0.084	0.087	-0.038
3. Dressing and undressing	0.880	0.076	0.002	0.018
4. Going to the toilet	0.872	0.028	-0.028	0.061
5. How do you rate your physical fitness? (Scale 0 to 10)	0.505	0.179	0.279	-0.034
Health Problems				
6. Do you experience problems in daily life due to poor vision?	-0.008	0.033	0.511	0.325
7. Do you experience problems in daily life due to being hard of hearing?	0.061	-0.073	0.705	0.094
9. Do you take 4 or more different types of medicine?	0.183	0.134	0.563	-0.172
10. Do you have any complaints about your memory?	0.062	0.206	0.465	0.073
Nourishment				
8. During the last 6 months, did you lose a lot of weight unwillingly? (3 kg in 1 month or 6 kg in 2 months)	-0.053	0.041	0.153	0.832

Psychosocial functioning				
11. Do you sometimes experience an emptiness around you?	0.092	0.817	0.058	-0.007
12. Do you sometimes miss people around you?	0.029	0.778	0.042	0.152
13. Do you sometimes feel abandoned?	0.270	0.432	-0.092	0.368
14. Did you felt downhearted or sad recently?	0.258	0.676	0.190	-0.005
15. Did you felt nervous or anxious recently?	-0.008	0.497	0.389	-0.214
Percentage of total variance explained for each factor	27.11	13.50	8.66	6.67

* Percentage of total variance explained for the four extracted factors = 56%; KMO=0.799 and Bartlett's Test of Sphericity < 0.001

Temporal stability

The retest was administered two weeks after the initial contact with the participant to evaluate the temporal stability of the measurements. The ICC values varied between 0.589 and 0.958, being an overall value of 0.800 (Table 6).

Table 6 Psychometric Evaluation of the FRAILSURVEY - reliability analysis (inter-instrument reliability and temporal stability).

	Inter-instrument reliability				Temporal stability
	Standard Error	Observed Kappa	Lower Limit .95 Confidence Interval	Upper Limit .95 Confidence Interval	ICC
1. Shopping	0.045	0.634	0.546	0.722	0.793
2. Walking around outside (around the house or to the neighbors)	0.053	0.608	0.503	0.712	0.867
3. Dressing and undressing	0.069	0.522	0.387	0.657	0.958
4. Going to the toilet	0.079	0.468	0.314	0.622	0.875
5. How do you rate your physical fitness? (Scale 0 to 10)	0.043	0.419	0.335	0.503	0.788
6. Do you experience problems in daily life due to poor vision?	0.042	0.266	0.182	0.349	0.958
7. Do you experience problems in daily life due to being hard of hearing?	0.045	0.289	0.201	0.378	0.798
8. During the last 6 months, did you lose a lot of weight unwillingly? (3 kg in 1 month or 6 kg in 2 months)	0.086	0.100	0.000	0.270	0.958
9. Do you take 4 or more different types of medicine?	0.042	0.337	0.256	0.419	0.913
10. Do you have any complaints about your memory?	0.045	0.236	0.147	0.324	0.724
11. Do you sometimes experience an emptiness around you?	0.041	0.454	0.374	0.533	0.857
12. Do you sometimes miss people around you?	0.047	0.336	0.245	0.428	0.667
13. Do you sometimes feel abandoned?	0.099	0.188	0.000	0.381	0.793
14. Did you felt downhearted or sad recently?	0.039	0.443	0.366	0.520	0.718

15. Did you felt nervous or anxious recently?	0.043	0.328	0.243	0.413	0.589
GFI SCORE	0.027	0.790	0.737	0.844	0.800

Concurrent Validity

All values were positive, ranging from 0.101 to 0.634, and the total score was 0.694 (Table 7). These results demonstrate a positive correlation between responses in both formats, paper, and app.

Table 7 Psychometric Evaluation of the FRAILSURVEY - validity analysis (concurrent validity).

	N	FRAILSURVEY mean	Paper mean	r	p- value
1. Shopping	522	0.20	0.18	0.634	<.001
2. Walking around outside (around the house or to the neighbours)	522	0.15	0.13	0.609	<.001
3. Dressing and undressing	521	0.10	0.1	0.522	<.001
4. Going to the toilet	521	0.09	0.08	0.468	<.001
5. How do you rate your physical fitness? (Scale 0 to 10)	512	0.35	0.36	0.419	<.001
6. Do you experience problems in daily life due to poor vision?	520	0.52	0.56	0.266	<.001
7. Do you experience problems in daily life due to being hard of hearing?	522	0.33	0.35	0.290	<.001
8. During the last 6 months, did you lose a lot of weight unwillingly? (3 kg in 1 month or 6 kg in 2 months)	522	0.10	0.11	0.101	0.021
9. Do you take 4 or more different types of medicine?	520	0.55	0.54	0.337	<.001
10. Do you have any complaints about your memory?	522	0.38	0.35	0.236	<.001
11. Do you sometimes experience an emptiness around you?	522	0.38	0.39	0.454	<.001
12. Do you sometimes miss people around you?	522	0.32	0.28	0.338	<.001
13. Do you sometimes feel abandoned?	522	0.08	0.07	0.189	<.001
14. Did you felt downhearted or sad recently?	521	0.50	0.47	0.444	<.001
15. Did you felt nervous or anxious recently?	521	0.64	0.61	0.329	<.001
Total score	522	4.67	4.57	0.694	<.001

Discussion

Translating and validating frailty assessment tools is vital for cross-cultural research, ensuring inclusivity and diversity, and allowing researchers and healthcare professionals to identify frailty in older adults independently/irrespective of linguistic and cultural backgrounds [30]. Translated versions enhance measurement accuracy and consistency by retaining the psychometric properties and measurement validity. This facilitates the development of comprehensive public health policies and targeted interventions, improving care and quality of life for ageing populations worldwide [31]. Overall,

translating and validating frailty assessment tools is crucial in advancing research, clinical practice, and public health initiatives related to frailty [32]. In this study, the translation of the GFI into European Portuguese underwent rigorous processes, resulting in a final version with strong psychometric properties. The translated version proved to be clear and easily understandable.

Among the 522 participants in the study, the majority were women, which aligns with typical demographic patterns in this type of research. Additionally, most participants were 65 to 74 years old, were either married or widowed, had completed only primary education, and had moderate money to meet their needs.

The mean GFI score was 4.57 in this study, whereas validation studies conducted in China, Romania and Lebanon were 4.60, 5.68 and 6.80, respectively [33-35]. Consistent with previous research, the average score was significantly higher in women compared to men [5, 12, 33, 34]. As anticipated, there was a significant positive correlation between age and GFI score, and additionally, marital status showed significant differences, with singles and widowers having higher scores [36]. Frailty also demonstrated significant associations with lower education levels and lower economic statuses, as already shown [37].

The GFI comprises 15 frailty indicators, and the most prevalent were polypharmacy, vision problems, and feelings of anxiety or nervousness, all reported by more than 50% of the participants. Indeed, the link between polypharmacy and frailty has been established through a study utilizing SHARE data, which explored the connection between mortality, frailty, and polypharmacy across 18 countries. According to these findings, 59.4% of the identified frail population was found to be taking multiple medications, a percentage that closely aligns with the results obtained in the current study, where 53.6% of the population were under polypharmacy [5]. Frailty and poor vision are interconnected conditions with a bidirectional relationship, as already described [38]. Poor vision can contribute to frailty by impairing balance, mobility, and daily functioning, increasing the risk of falls and social isolation. It has already been described that people with visual impairment have 3.7 greater odds of being frail [38]. Anxiety symptoms, reported by 61.4% of participants of this study, were reported to be notably more prevalent among older adults with frailty, compared to those who are robust, which has also been reported elsewhere [39].

The psychometric evaluation of the European Portuguese version of the GFI demonstrated good reliability and validity. In previous psychometric studies assessing the internal consistency of the GFI, Cronbach's α values ranged from 0.680 to 0.810. Nevertheless, in this study, the obtained value was 0.759, which is similar to Cronbach's α value of the original scale [21]. Internal consistency maintained the same value even

if any item was deleted. The assessment of reliability over time involved a retest conducted two weeks after the initial contact, and the Intraclass Correlation Coefficient (ICC) was used for calculation. The ICC values ranged from 0.504 to 1.000, with an overall value of 0.974. This value surpassed the reliability values obtained in two comparable studies conducted on the Chinese population (0.950 and 0.939) [35, 40]. These results demonstrate that the European Portuguese version of the GFI exhibits excellent reliability over time, confirming its consistency as a measurement tool. The factor analysis yielded the same number of factors as the original scale, indicating that the translated version maintains a similar underlying factor structure to the original scale, suggesting that it measures the same fundamental constructs or dimensions as the items in the original version [41]. This encouraging finding indicates that the translation process effectively retained the core structure of the scale. Moreover, this confirmation of reliability and validity further demonstrates that the translated version of the GFI effectively preserves the essential elements of the original instrument.

The general hypothesis of this study was that a smartphone GFI app would show the same validity and reliability as the paper version, and it was proved in this study. The inter-instrument reliability was studied to investigate the agreement and consistency between the two instruments, thereby ensuring the robustness of the results. High inter-instrument reliability strengthens the credibility and accuracy of research outcomes, contributing to the overall quality and validity of assessments and evaluations. In this study, high levels of agreement were recorded between the instruments, proving that the digital format of the questionnaire is as reliable as the paper version. The reliability assessment over time was done in the same way as for the paper version of the GFI. The ICC values ranged from 0.589 to 0.958, with an overall value of 0.800, evidencing that, just like on paper, the digital version of the GFI remained reliable over time. The validity of the application was assessed by comparing the answers and total scores of the same individuals in the paper format (conventional) and the application (the new format to be validated). The results revealed a robust, positive, and statistically significant relationship between the responses in both forms. These findings not only establish the reliability of the application but also demonstrate its validation.

Health apps are vital in modern healthcare, providing easy access to health information, monitoring tools, and personalised advice [42]. However, the proliferation of health apps on smartphone app stores is still on the rise due to the ease of app development, the absence of regulation and the direct marketing to users, leading to an overcrowded scenario, which lack reliability and accuracy. However, the ability of health stakeholders to discern the quality of these apps still lags significantly. This challenge largely stems from the lack of validation, which hinders app reliability and validity

assurance of [43]. Some potential benefits of validating health apps include improved accuracy and reliability of the app, increased user confidence in the app, and improved safety and effectiveness [44, 45].

Assessing frailty is crucial as it helps identify individuals at higher risk of adverse health outcomes and enables timely interventions to mitigate these risks. Moreover, frailty assessments may guide treatment decisions, leading to tailored healthcare approaches focused on maintaining independence and managing chronic conditions. The impact of frailty in individuals and communities is profound, increasing healthcare utilization, decreasing quality of life, and adding strain on families and caregivers. Understanding these effects allows for prioritized interventions, effective resource allocation, and appropriate support, ultimately improving the well-being and outcomes of frail individuals. The advantages of using apps for frailty assessment include their ease of use, ability to provide real-time feedback to the user, and their potential for improving the accuracy and reliability of frailty assessment [46, 47]. An app designed to assess frailty offers numerous advantages and can revolutionize how frailty is identified. Its accessibility on smartphones and digital devices ensures easy and convenient frailty assessment, even in remote areas, while enabling early detection of an individual's physical and cognitive abilities, allowing for timely interventions.

In overall, FRAILSURVEY employs a standardized and validated assessment tool, providing objective and consistent measurements, eliminating subjective biases, and enhancing accuracy and reliability. Compared to traditional in-person assessments, its cost-effectiveness can reduce healthcare expenses and increase accessibility. The future integration with electronic health records and other health-related data could enable personalized interventions tailored to an individual's specific needs and medical history, ultimately leading to more effective frailty management and improved overall health outcomes for at-risk individuals.

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References

1. Costa, A., et al., Active aging awareness and well-being among older adults in Portugal. *Front Public Health*, 2023. 11: p. 1149731.
2. Instituto Nacional de Estatística, I. Censos de 2011. 2012; Available from: https://censos.ine.pt/xportal/xmain?xpid=CENSOS&xpgid=censos2011_apresentacao.
3. Instituto Nacional de Estatística, I., Projeções de População Residente. 2020.
4. Instituto Nacional de Estatística, I. Censos de 2021. 2022; Available from: https://www.pordata.pt/censos/resultados/emdestaque-portugal-361?gclid=Cj0KCQjw8NilBhDOARIsAHzpbLDWvmQg3s1BI4KANch169fs_R-2tOq8AvfLUNEvCOMx8pkG3PvpO2kaAtsvEALw_wcB.
5. Midão, L., et al., Frailty Status and Polypharmacy Predict All-Cause Mortality in Community Dwelling Older Adults in Europe. *Int J Environ Res Public Health*, 2021. 18(7).
6. Tessier, L., N. De Wulf, and Y. Momose. Long-term care in the context of population ageing: a rights-based approach to universal coverage. 2023; Available from: <https://www.ilo.org/static/english/intserv/working-papers/wp082/index.html>.
7. Cesari, M., et al., Frailty: An Emerging Public Health Priority. *J Am Med Dir Assoc*, 2016. 17(3): p. 188-92.
8. de Souto Barreto, P., et al., Recommendations on Physical Activity and Exercise for Older Adults Living in Long-Term Care Facilities: A Taskforce Report. *J Am Med Dir Assoc*, 2016. 17(5): p. 381-92.
9. Fried, L.P., et al., Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*, 2001. 56(3): p. M146-56.
10. Kojima, G., Frailty as a Predictor of Future Falls Among Community-Dwelling Older People: A Systematic Review and Meta-Analysis. *J Am Med Dir Assoc*, 2015. 16(12): p. 1027-33.
11. Vermeiren, S., et al., Frailty and the Prediction of Negative Health Outcomes: A Meta-Analysis. *J Am Med Dir Assoc*, 2016. 17(12): p. 1163 e1-1163 e17.

12. Manfredi, G., et al., Prevalence of frailty status among the European elderly population: Findings from the Survey of Health, Aging and Retirement in Europe. *Geriatrics & Gerontology International*, 2019. 19(8): p. 723-729.
13. Daniels, R., et al., Interventions to prevent disability in frail community-dwelling elderly: a systematic review. *BMC Health Serv Res*, 2008. 8: p. 278.
14. de Vries, N.M., et al., Outcome instruments to measure frailty: A systematic review. *Ageing Research Reviews*, 2011. 10(1): p. 104-114.
15. Peters, L.L., et al., Measurement properties of the Groningen Frailty Indicator in home-dwelling and institutionalized elderly people. *J Am Med Dir Assoc*, 2012. 13(6): p. 546-51.
16. Steverink, N., et al., Measuring frailty: Developing and testing the GFI (Groningen frailty indicator). *Gerontologist*, 2001. 41: p. 236-237.
17. Smith, M.J., et al., Improving Patient Satisfaction Through Computer-Based Questionnaires. *Orthopedics*, 2016. 39(1): p. e31-e35.
18. Ahn, D.T., Benefits and risks of apps for patients. *Curr Opin Endocrinol Diabetes Obes*, 2022. 29(1): p. 17-22.
19. Lecomte, T., et al., Mobile Apps for Mental Health Issues: Meta-Review of Meta-Analyses. *JMIR Mhealth Uhealth*, 2020. 8(5): p. e17458.
20. Pagliari, C., et al., What is eHealth (4): a scoping exercise to map the field. *J Med Internet Res*, 2005. 7(1): p. e9.
21. Schuurmans, H., et al., Old or frail: what tells us more? *J Gerontol A Biol Sci Med Sci*, 2004. 59(9): p. M962-5.
22. Bielderman, A., et al., Multidimensional structure of the Groningen Frailty Indicator in community-dwelling older people. *BMC Geriatr*, 2013. 13: p. 86.
23. Wild, D., et al., Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. *Value Health*, 2005. 8(2): p. 94-104.
24. Streiner, D.L., G.R. Norman, and J. Cairney, Health measurement scales: a practical guide to their development and use. 5th ed. 2015, Oxford, United Kingdom: Oxford University Press. 294-5.
25. Cappelleri, J.C., et al., Patient-Reported Outcomes: Measurement, Implementation and Interpretation. 1st ed. 2014, New York: Chapman and Hall/CRC.
26. Koo, T.K. and M.Y. Li, A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. *J Chiropr Med*, 2016. 15(2): p. 155-63.

27. Kaiser, H.F., Computer Program for Varimax Rotation in Factor Analysis. Educational and Psychological Measurement, 1959. 19(3): p. 413-420.
28. Introductory Statistics for Health and Nursing Using SPSS. 2009, Sage: London.
29. Bielderma, A., et al., Multidimensional structure of the Groningen Frailty Indicator in community-dwelling older people. BMC Geriatrics, 2013. 13(1): p. 86.
30. Sperber, A.D., Translation and validation of study instruments for cross-cultural research. Gastroenterology, 2004. 126: p. S124-S128.
31. Dambi, J.M., et al., A systematic review of the psychometric properties of the cross-cultural translations and adaptations of the Multidimensional Perceived Social Support Scale (MSPSS). Health Qual Life Outcomes, 2018. 16(1): p. 80.
32. Donoghue, O.A., et al., Translating Frailty Assessment Methodologies and Research-based Evidence to Clinical Education and Practice. Journal of Aging & Social Policy, 2022. 34(4): p. 537-551.
33. Khamis, R., et al., Evaluating the psychometric properties of the Arabic version of the Groningen Frailty Indicator among Lebanese elderly people. J Egypt Public Health Assoc, 2019. 94(1): p. 28.
34. Olariu, M., et al., The psychometric qualities of the Groningen Frailty Indicator in Romanian community-dwelling old citizens. Fam Pract, 2014. 31(4): p. 490-5.
35. Xiang, W., et al., Cross-cultural adaptation and validation of the Groningen Frailty Indicator in Chinese nursing home residents. Aging Clin Exp Res, 2020. 32(6): p. 1035-1042.
36. Garre-Olmo, J., et al., Prevalence of frailty phenotypes and risk of mortality in a community-dwelling elderly cohort. Age Ageing, 2013. 42(1): p. 46-51.
37. Wang, J. and C. Hulme, Frailty and socioeconomic status: a systematic review. J Public Health Res, 2021. 10(3).
38. Varadaraj, V., et al., Near Vision Impairment and Frailty: Evidence of an Association. Am J Ophthalmol, 2019. 208: p. 234-241.
39. Tan, M., C. Bhanu, and R. Frost, The association between frailty and anxiety: A systematic review. Int J Geriatr Psychiatry, 2023. 38(5): p. e5918.
40. Luh, R.-L., S.-Y. Yu, and C.H. Yang. Chinese Version of Groningen Frailty Index: Validation in a Chinese Elderly Population. 2018.
41. Krabbe, P.F.M., Chapter 7 - Validity, in The Measurement of Health and Health Status, P.F.M. Krabbe, Editor. 2017, Academic Press: San Diego. p. 113-134.
42. Maaß, L., et al., The Definitions of Health Apps and Medical Apps From the Perspective of Public Health and Law: Qualitative Analysis of an Interdisciplinary Literature Overview. JMIR Mhealth Uhealth, 2022. 10(10): p. e37980.

43. Akbar, S., Coiera, Enrico, and F. Magrabi, Safety concerns with consumer-facing mobile health applications and their consequences: a scoping review. *Journal of the American Medical Informatics Association*, 2019. 27(2): p. 330-340.
44. Gordon, W.J., et al., Beyond validation: getting health apps into clinical practice. *npj Digital Medicine*, 2020. 3(1): p. 14.
45. Sarah, L., S. Lev, and T. John, Evaluating evaluation frameworks: a scoping review of frameworks for assessing health apps. *BMJ Open*, 2021. 11(3): p. e047001.
46. Chang, R., et al., Web-based software applications for frailty assessment in older adults: a scoping review of current status with insights into future development. *BMC Geriatr*, 2021. 21(1): p. 723.
47. Morley, J.E., et al., Frailty consensus: a call to action. *J Am Med Dir Assoc*, 2013. 14(6): p. 392-7.

CHAPTER III

General Discussion and Final Remarks

Discussion and general conclusions

The global demographic landscape is undergoing a profound transformation characterised by a substantial increase in the ageing population. This demographic shift has raised significant concerns regarding the sustainability of healthcare systems worldwide. Among the myriad challenges this ageing population poses, frailty stands out prominently [394, 395]. Frailty is a complex geriatric syndrome characterised by increased vulnerability resulting from age-related declines in physical, cognitive, and psychological capacities. It has garnered increasing attention due to its far-reaching impact on clinical outcomes, quality of life, and the economic burden associated with ageing.

One of the primary challenges in addressing frailty on a global scale lies in its diverse definitions and assessment tools. This diversity has led to a wide-ranging reported prevalence of frailty, varying from as low as 4.0% to as high as 59.1%. A study was conducted in 18 European countries using a standardised methodology to facilitate meaningful cross-country comparisons [396]. This study adopted an operationalised version of Fried's Phenotype criteria, widely recognised as the 'gold standard' for frailty assessment. The findings of this study revealed that frailty prevalence increases significantly with age, with women being more susceptible to frailty than men. Comparing data from earlier waves of the study, it was observed that while frailty prevalence has increased among the older population, there has been a decrease in frailty prevalence in some countries within the 50–64 age group. This suggests a growing awareness of frailty among healthcare professionals and policymakers, leading to initiatives to prevent and postpone frailty in older adults. Furthermore, the study highlighted substantial variations in frailty prevalence across European countries, with Northern European nations exhibiting lower prevalence rates than Southern European countries. This disparity aligns with broader health indicators in the region, indicating worsening health conditions as one moves from Northern to Southern Europe.

Recognising the significance of frailty in Europe's ageing population, it is crucial to emphasise that frailty should not be viewed as an inevitable consequence of ageing. Instead, it is a dynamic process with intermediate stages that can be modified. Early identification of frailty is paramount for healthcare professionals and policymakers to take timely action, improve outcomes, and reduce unnecessary healthcare costs. With approximately 43% of the European population aged 50 or more experiencing pre-frailty and nearly 8% facing frailty, interventions to mitigate and postpone frailty's progression are essential to enhance the well-being and quality of life of older adults and ensure the sustainability of healthcare systems.

Another significant health issue facing the ageing population in Europe is polypharmacy, characterised by the concurrent use of multiple medications. Like frailty, polypharmacy lacks a standardised definition, contributing to variations in reported prevalence rates across studies. A previous study reported a polypharmacy prevalence of 32.1% in Europe, with higher rates observed in older individuals, particularly those aged 85 and older, and among females. Polypharmacy is an independent predictor of mortality, although questions persist regarding its causal relationship with ageing and multimorbidity.

Interestingly, there is a significant interplay between polypharmacy and frailty. Polypharmacy is one of the criteria used to assess frailty in some tools. Polypharmacy and frailty share a complex and interconnected relationship, especially among older adults. Medications may contribute to frailty by increasing the risk of falls, cognitive impairment, muscle weakness, and overall functional decline. Moreover, frail individuals may have altered pharmacokinetics and pharmacodynamics, making them more susceptible to the adverse effects of medications. Therefore, addressing polypharmacy is vital in managing frailty, as deprescribing unnecessary medications and optimising drug regimens can help mitigate the negative impact of polypharmacy on frail individuals and improve their overall well-being.

However, frail and pre-frail individuals exhibited a higher polypharmacy prevalence than their non-frail counterparts [397]. This association underscores the importance of recognising and addressing polypharmacy and frailty in older populations. Kaplan-Meier survival curves further demonstrated that individuals with polypharmacy have an increased mortality risk, especially with advancing age and among males. These findings highlight the need for a comprehensive approach when assessing mortality risk in older adults, considering both polypharmacy and frailty.

Frailty is a significant concern in chronic kidney disease patients, as this population faces a high risk of developing and experiencing the negative consequences of frailty due to their underlying health conditions and the demands of the haemodialysis treatment itself [398, 399]. Haemodialysis patients typically have advanced chronic kidney disease or end-stage renal disease, which can lead to complications, including anaemia, malnutrition, and inflammation, contributing to frailty. The process of haemodialysis, which involves frequent visits to dialysis centres and the physical stress of the treatment, can lead to fatigue and muscle wasting, which are associated with frailty.

Despite frailty being a common condition in chronic kidney disease patients, our work noted the limited availability of studies, with only five articles meeting inclusion criteria published in the last six years. This underscores the recent interest in this area and

emphasises the need for further investigation into the relationship between frailty and chronic kidney disease, particularly in patients undergoing dialysis or pre-dialysis.

One notable challenge in studying CKD's frailty is the research's heterogeneous nature. Studies included in our review exhibited variations in sample characteristics, with some focusing on pre-dialysis patients and others on individuals undergoing dialysis [400]. Moreover, the primary aims of these studies were only sometimes centred on identifying biomarkers related to frailty, potentially limiting the depth of their findings. This heterogeneity highlights the complexity of studying frailty in chronic kidney disease patients and the need for standardised research approaches.

Diversity in geographic representation is another aspect addressed in the article. While the studies covered populations from five different countries, the absence of studies from African or Australian people is mentioned. Given that frailty may vary among diverse ethnic groups, this gap in representation could limit the generalizability of findings. Our work also discussed gender imbalance in sample recruitment. Frailty is found to be more common among females, yet sample recruitment methods often resulted in a higher percentage of male participants, introducing potential bias into the studies. This gender disparity highlights the importance of more inclusive recruitment strategies.

Variability in findings regarding the association between biomarkers and frailty is another challenge mentioned in the article. Some studies found significant correlations with markers such as endothelial function, cognitive function, and depressive symptoms. In contrast, others did not find significant associations with inflammatory markers, calcium levels, or kidney function. This variability underscores the complexity of health conditions in chronic kidney disease patients, suggesting that many factors influence frailty.

Translating and validating psychometric scales in Portuguese or any other language is a meticulous process to ensure that the scale maintains its reliability and validity when used in a new linguistic and cultural context [401, 402]. Within this work, we translated and validated a frailty assessment tool into European Portuguese, the Groningen Frailty Indicator. This article underscores the critical role of standardised assessment tools in advancing research and healthcare for older adults. Our work emphasised the significance of translating and validating frailty assessment tools for cross-cultural research. These tools are pivotal in ensuring inclusivity and diversity, allowing researchers and healthcare professionals to identify frailty independently of linguistic and cultural backgrounds. The translation and validation process enhances measurement accuracy and consistency while retaining psychometric properties and measurement validity.

The study involved 522 participants, primarily women in the 65 to 74 age group, married or widowed, with primary education and moderate financial resources. The mean GFI score in this study was 4.57, with variations observed when compared to validation studies conducted in different populations. The article notes that women generally had higher GFI scores than men, and various demographic factors, including age, marital status, education levels, and economic status, were associated with differences in GFI scores.

Among the 15 frailty indicators in the GFI, the most prevalent were polypharmacy, vision problems, and feelings of anxiety or nervousness, reported by more than 50% of the participants. The article highlights the interconnected nature of these indicators, particularly the link between polypharmacy and frailty.

Psychometric properties of the European Portuguese version of the GFI were robust, with good reliability and validity. The Cronbach's α value indicated high internal consistency, and the Intraclass Correlation Coefficient (ICC) demonstrated reliability over time. Factor analysis confirmed the scale's underlying structure, maintaining similarity to the original scale.

Using apps for frailty assessment offers several advantages. These include ease of use, real-time feedback, and the potential to enhance the accuracy and reliability of frailty assessment. Such apps can revolutionise the identification of frailty by being easily accessible on smartphones and digital devices, making frailty assessment convenient, even in remote areas. This accessibility facilitates the early detection of an individual's physical and cognitive abilities, enabling timely interventions [375, 403]. In our work, we discussed the validation and reliability of a smartphone application version of the GFI, FRAILSURVEY, highlighting its high inter-instrument reliability, reliability over time, and validity. Health apps, like the one validated in this study, offer ease of use, real-time feedback, and improved accuracy and reliability in frailty assessment. The potential integration of FRAILSURVEY with electronic health records and other health-related data holds promise for personalised interventions tailored to an individual's specific needs and medical history. This integration could lead to more effective frailty management and improved overall health outcomes for individuals at risk of frailty.

Final Remarks

This PhD thesis has embarked on a remarkable journey to unravel the intricacies of frailty among older adults. This journey has been driven by a passion for understanding the challenges and opportunities of an ageing global population. By harnessing data-driven analyses, embracing cross-cultural considerations, and leveraging cutting-edge health technology, our mission has been to contribute not only to the theoretical foundations of gerontology and geriatrics but also to the practical enhancement of the lives of older individuals.

Throughout this thesis, we have pursued several key objectives, each aimed at shedding light on different facets of frailty and its management. As we bring this journey to a close, we reflect on the insights gained and their implications for ageing research and healthcare.

First and foremost, our exploration of frailty has highlighted the critical importance of standardised assessment tools and definitions. Frailty is a complex syndrome with diverse manifestations, and this diversity has led to varying prevalence rates and challenges in cross-country comparisons. Adopting standardised criteria, such as an operationalised version of Fried's Phenotype, has facilitated meaningful comparisons and illuminated the increasing prevalence of frailty with age, particularly among women.

We reinforced that frailty should not be seen as an inevitable consequence of ageing. It is a dynamic process with intermediate stages that can be modified through timely interventions. With a substantial portion of the European population experiencing pre-frailty and frailty, there is a pressing need for healthcare professionals and policymakers to identify and address frailty early, thereby enhancing the well-being and quality of life of older adults while ensuring the sustainability of healthcare systems.

Polypharmacy, another critical issue facing the ageing population, has been intricately woven into our exploration of frailty. The interplay between polypharmacy and frailty is undeniable, with medications contributing to the vulnerability of older individuals and frailty increasing the risk of adverse medication effects. Addressing polypharmacy is vital in managing frailty, underscoring the need for deprescribing unnecessary medications and optimising drug regimens.

Our journey also led us to chronic kidney disease and its relationship with frailty. While frailty is prevalent among CKD patients, the limited availability of research in this area underscores the need for further investigation, particularly among those undergoing dialysis or in the pre-dialysis stage. The heterogeneity of CKD research, along with geographic and gender disparities, poses unique challenges that demand standardised approaches and more inclusive recruitment strategies.

Furthermore, our work delved into the translation and validation of psychometric scales, emphasising their critical role in cross-cultural research. Translating the Groningen Frailty Indicator into European Portuguese exemplifies the significance of ensuring that assessment tools maintain their reliability and validity when used in new linguistic and cultural contexts.

In our quest for innovation, we explored the potential of smartphone applications for frailty assessment, exemplified by the FRAILSURVEY app. These technologies offer convenience, real-time feedback, and improved accuracy, revolutionising frailty identification and management. Integrating such apps with electronic health records holds promise for personalised interventions tailored to individual needs and medical histories.

In summary, this thesis has profoundly explored frailty, transcending boundaries and embracing diverse ageing research and healthcare dimensions. By adopting a multidisciplinary approach, we have uncovered valuable insights and laid the groundwork for future advancements in gerontology and geriatrics. As we conclude this journey, we hope that the knowledge gained will inform academia and translate into tangible improvements in the lives of older individuals, fostering a future where ageing is synonymous with vitality and well-being.

CHAPTER IV

References and Annexes

1. Khan, H.T.A., *Population ageing in a globalized world: Risks and dilemmas?* Journal of evaluation in clinical practice, 2018.
2. Rudnicka, E., et al., *The World Health Organization (WHO) approach to healthy ageing*. Maturitas, 2020. **139**: p. 6-11.
3. Wang, X.Q. and P.J. Chen, *Population ageing challenges health care in China*. Lancet, 2014. **383**(9920): p. 870.
4. Briggs, A.M., et al., *System strengthening to support value-based care and healthy ageing for people with chronic pain*. Pain, 2019. **160**(6): p. 1240-1244.
5. North, M.S. and S.T. Fiske, *Modern Attitudes Toward Older Adults in the Aging World: A Cross-Cultural Meta-Analysis*. Psychol Bull, 2015. **141**(5): p. 993-1021.
6. Chang, E.S., et al., *Global reach of ageism on older persons' health: A systematic review*. PLOS ONE, 2020. **15**(1): p. e0220857.
7. Olivari, B.S., et al., *CDC Grand Rounds: Promoting Well-Being and Independence in Older Adults*. MMWR Morb Mortal Wkly Rep, 2018. **67**(37): p. 1036-1039.
8. Vlandas, T., D. McArthur, and M. Ganslmeier, *Ageing and the economy: a literature review of political and policy mechanisms*. Political Research Exchange, 2021. **3**(1): p. 1932532.
9. Zhao, S., J. He, and H. Yang, *Population Ageing, Financial Deepening and Economic Growth: Evidence from China*. Sustainability, 2018. **10**(12): p. 4627.
10. Carta, F., F. D'Amuri, and T.M. Wachter, *Workforce Aging, Pension Reforms, and Firm Outcomes*. International Corporate Finance eJournal.
11. Taylor, P., et al., *Managing older workers during a period of tight labour supply*. Ageing & Society, 2013. **33**(1): p. 16-43.
12. Jansen, A., *Work-retirement cultures: a further piece of the puzzle to explain differences in the labour market participation of older people in Europe?* Ageing & Society, 2018. **38**(8): p. 1527-1555.
13. Syse, A., et al., *Changes in Health and Health Behavior Associated With Retirement*. Journal of Aging and Health, 2015. **29**(1): p. 99-127.
14. Li, C., et al., *Health Care Utilization and Unmet Needs in Chinese Older Adults With Multimorbidity and Functional Impairment*. J Am Med Dir Assoc, 2020. **21**(6): p. 806-810.
15. Liotta, G., et al., *Active Ageing in Europe: Adding Healthy Life to Years*. Frontiers in Medicine, 2018. **5**.
16. Polder, J.J., et al., *Age-specific increases in health care costs*. Eur J Public Health, 2002. **12**(1): p. 57-62.
17. Philp, I., *The contribution of geriatric medicine to integrated care for older people*. Age Ageing, 2015. **44**(1): p. 11-5.
18. Williams, G.R., et al., *Capacity to Provide Geriatric Specialty Care for Older Adults in Community Oncology Practices*. Oncologist, 2020. **25**(12): p. 1032-1038.
19. Witham, M.D., et al., *Growing research in geriatric medicine*. Age Ageing, 2019. **48**(3): p. 316-319.
20. Cerami, A., *Ageing and the politics of pension reforms in Central Europe, South-Eastern Europe and the Baltic States*. International Journal of Social Welfare, 2011. **20**(4): p. 331-343.
21. D'Addio, A.C., M. Keese, and E. Whitehouse, *Population ageing and labour markets*. Oxford Review of Economic Policy, 2010. **26**(4): p. 613-635.
22. Dovie, D.A., *The Status of Older Adult Care in Contemporary Ghana: A Profile of Some Emerging Issues*. Frontiers in Sociology, 2019. **4**.
23. Finkenzeller, T., et al., *Aging in high functioning elderly persons: study design and analyses of behavioral and psychological factors*. Scandinavian Journal of Medicine & Science in Sports, 2019. **29**(S1): p. 7-16.
24. Maldonado Briegas, J.J., et al., *The Well-Being of the Elderly: Memory and Aging*. Frontiers in Psychology, 2020. **11**.

25. Birditt, K.S., et al., *Daily interpersonal tensions and well-being among older adults: The role of emotion regulation strategies*. Psychology and Aging, 2020. **35**(4): p. 578-590.
26. Steptoe, A. and S.E. Jackson, *The Life Skills of Older Americans: Association with Economic, Psychological, Social, and Health Outcomes*. Scientific Reports, 2018. **8**(1): p. 9669.
27. Czaja, S.J., J.H. Moxley, and W.A. Rogers, *Social Support, Isolation, Loneliness, and Health Among Older Adults in the PRISM Randomized Controlled Trial*. Frontiers in Psychology, 2021. **12**.
28. Neville, S., et al., *Loneliness in Men 60 Years and Over: The Association With Purpose in Life*. American Journal of Men's Health, 2018. **12**(4): p. 730-739.
29. Tomaz, S.A., et al., *Loneliness, Wellbeing, and Social Activity in Scottish Older Adults Resulting from Social Distancing during the COVID-19 Pandemic*. International Journal of Environmental Research and Public Health, 2021. **18**(9): p. 4517.
30. Economic, U.N.D.o. and S. Affairs, *World Social Report 2023*. 2023: United Nations.
31. Preston, S.H. and A. Stokes, *Sources of Population Aging in More and Less Developed Countries*. Popul Dev Rev, 2012. **38**(2): p. 221-236.
32. Bai, C. and X. Lei, *New trends in population aging and challenges for China's sustainable development*. China Economic Journal, 2020. **13**(1): p. 3-23.
33. Lee, H.-H. and K. Shin, *Nonlinear effects of population aging on economic growth*. Japan and the World Economy, 2019. **51**: p. 100963.
34. Xu, X., et al., *Identifying the Impacts of Social, Economic, and Environmental Factors on Population Aging in the Yangtze River Delta Using the Geographical Detector Technique*. Sustainability, 2018. **10**(5): p. 1528.
35. Bal, P. and D. Rousseau, *Idiosyncratic Deals between Employees and Organizations : Conceptual i ssues, applications and the role of co-workers*.
36. Bhasin, S., et al., *The Implications of Reproductive Aging for the Health, Vitality, and Economic Welfare of Human Societies*. The Journal of Clinical Endocrinology & Metabolism, 2019. **104**(9): p. 3821-3825.
37. Trask, B.S. *Migration, Urbanization, and the Family Dimension*. 2022.
38. Permanyer, I. and N. Scholl, *Global trends in lifespan inequality: 1950-2015*. PLOS ONE, 2019. **14**(5): p. e0215742.
39. Yongze, L., G. Chenxi, and C. Yanli, *Secular incidence trends and effect of population aging on mortality due to type 1 and type 2 diabetes mellitus in China from 1990 to 2019: findings from the Global Burden of Disease Study 2019*. BMJ Open Diabetes Research & Care, 2021. **9**(2): p. e002529.
40. Tang, B., et al., *Economic Implications of Health Care Burden for Elderly Population*. Inquiry, 2022. **59**: p. 469580221121511.
41. Eurostat. *More than a fifth of the EU population are aged 65 or over*. 2021 [cited 26 September 2023; Available from: <https://ec.europa.eu/eurostat/web/products-eurostat-news/-/ddn-20210316-1>].
42. Eurostat. *Population projections in the EU*. 2023 [26 September 2023].
43. Margaras, V., *Demographic trends in EU regions* E.-E.P.R. Service, Editor. 2019.
44. Martinez, C., et al. *Demographic change and local development: shrinkage, regeneration and social dynamics*. 2012.
45. Union, S.O.o.t.E., *Ageing Europe: Looking at the Lives of Older People in the EU : 2020 Edition*. 2020: Publications Office of the European Union.
46. Costa, A., et al., *Active aging awareness and well-being among older adults in Portugal*. Front Public Health, 2023. **11**: p. 1149731.
47. Instituto Nacional de Estatística, I. *Censos de 2011*. 2012; Available from: https://censos.ine.pt/xportal/xmain?xpid=CENSOS&xpgid=censos2011_apresentacao.
48. Instituto Nacional de Estatística, I., *Projeções de População Residente*. 2020.

49. Instituto Nacional de Estatística, I. *Censos de 2021*. 2022; Available from: https://www.pordata.pt/censos/resultados/emdestaque-portugal-361?gclid=Cj0KCQjw8NilBhDOARIsAHZpbLDWvmQg3s1BI4KANch169fs_R-2tOq8AvfLUNEvCOMx8pkG3PvpO2kaAtsvEALw_wcB.
50. Banco de Portugal, B., *Portuguese Economic Growth - A View on Structural Features, Blockages and Reforms*, E.a.R. Development, Editor. 2019, Banco de Portugal: Portugal.
51. Marques, S.R., S.F. Casaca, and M. Arcanjo, *Work–Family Articulation Policies in Portugal and Gender Equality: Advances and Challenges*. Social Sciences, 2021. **10**(4): p. 119.
52. Van Hoof, J., et al., *The Challenges of Urban Ageing: Making Cities Age-Friendly in Europe*. International Journal of Environmental Research and Public Health, 2018. **15**(11): p. 2473.
53. Del Barrio, E., et al., *From Active Aging to Active Citizenship: The Role of (Age) Friendliness*. Social Sciences, 2018. **7**(8): p. 134.
54. Partridge, L., J. Deelen, and P.E. Slagboom, *Facing up to the global challenges of ageing*. Nature, 2018. **561**(7721): p. 45-56.
55. Guerchet, M.M., et al., *A cohort study of the effects of older adult care dependence upon household economic functioning, in Peru, Mexico and China*. PLOS ONE, 2018. **13**(4): p. e0195567.
56. Högberg, B., et al., *Ageing, health inequalities and the welfare state: A multilevel analysis*. Journal of European Social Policy, 2018. **28**(4): p. 311-325.
57. Li, L., T. Du, and Y. Hu, *The Effect of Population Aging on Healthcare Expenditure from a Healthcare Demand Perspective Among Different Age Groups: Evidence from Beijing City in the People's Republic of China*. Risk Manag Healthc Policy, 2020. **13**: p. 1403-1412.
58. Bongaarts, J., *Population Aging and the Rising Cost of Public Pensions*. Population and Development Review, 2004. **30**(1): p. 1-23.
59. Rouzet, D., et al., *Fiscal challenges and inclusive growth in ageing societies*. 2019.
60. Kim, H., et al., *A comparative study to identify factors of caregiver burden between baby boomers and post baby boomers: a secondary analysis of a US online caregiver survey*. BMC Public Health, 2018. **18**(1): p. 579.
61. The, L., *Population ageing in China: crisis or opportunity?* Lancet, 2022. **400**(10366): p. 1821.
62. Gadomska-Lila, K., *Effectiveness of reverse mentoring in creating intergenerational relationships*. Journal of Organizational Change Management, 2020. **33**(7): p. 1313-1328.
63. O'Connor, J.P., et al., *Intergenerational understandings of personal, social and community assets for health*. Health & Place, 2019. **57**: p. 218-227.
64. Parisi, J.M., et al., *Can the Wisdom of Aging be Activated and Make a Difference Societally?* Educ Gerontol, 2009. **35**(10): p. 867-879.
65. Dommaraju, P. and S. Wong, *Chapter 1 - The concept of productive aging, in Assessments, Treatments and Modeling in Aging and Neurological Disease*, C.R. Martin, V.R. Preedy, and R. Rajendram, Editors. 2021, Academic Press. p. 3-11.
66. Lee, S.M. and D. Lee, *Healthcare wearable devices: an analysis of key factors for continuous use intention*. Service Business, 2020. **14**(4): p. 503-531.
67. Malwade, S., et al., *Mobile and wearable technologies in healthcare for the ageing population*. Comput Methods Programs Biomed, 2018. **161**: p. 233-237.
68. Leśna-Wierszółowicz, E., *Silver economy as a response to demographic changes*, in *Srebrna gospodarka jako odpowiedź na zmiany demograficzne*. Wydawnictwo Uniwersytetu Ekonomicznego we Wrocławiu: Wrocław.
69. Zhu, H. and A. Walker, *Why China needs an active social policy on ageing*. Asian Population Studies, 2022. **18**(2): p. 190-205.

70. Bokhour, B.G., et al., *How can healthcare organizations implement patient-centered care? Examining a large-scale cultural transformation*. BMC Health Services Research, 2018. **18**(1): p. 168.
71. Kim, Y.-S., et al., *Unmet healthcare needs of elderly people in Korea*. BMC Geriatrics, 2018. **18**(1): p. 98.
72. Wang, Y.C., et al., *Post-Acute Care as a Key Component in a Healthcare System for Older Adults*. Ann Geriatr Med Res, 2019. **23**(2): p. 54-62.
73. Snoswell, C.L., et al., *An overview of the effect of telehealth on mortality: A systematic review of meta-analyses*. Journal of Telemedicine and Telecare, 2023. **29**(9): p. 659-668.
74. Bratt, C., D. Abrams, and H.J. Swift. *Supporting the old but neglecting the young? The two faces of ageism*. American Psychological Association [doi:10.1037/dev0000903]. 2020.
75. Choi, Y.J., *Age-Friendly Features in Home and Community and the Self-Reported Health and Functional Limitation of Older Adults: the Role of Supportive Environments*. Journal of Urban Health, 2020. **97**(4): p. 471-485.
76. Fraser, H.C., et al., *Biological mechanisms of aging predict age-related disease co-occurrence in patients*. Aging Cell, 2022. **21**(4): p. e13524.
77. Jaul, E. and J. Barron, *Characterizing the Heterogeneity of Aging: A Vision for a Staging System for Aging*. Frontiers in Public Health, 2021. **9**.
78. Midão, L., et al., *Polypharmacy prevalence among older adults based on the survey of health, ageing and retirement in Europe*. Arch Gerontol Geriatr, 2018. **78**: p. 213-220.
79. Aïdoud, A., et al., *High Prevalence of Geriatric Conditions Among Older Adults With Cardiovascular Disease*. Journal of the American Heart Association, 2023. **12**(2): p. e026850.
80. MacNee, W., R.A. Rabinovich, and G. Choudhury, *Ageing and the border between health and disease*. Eur Respir J, 2014. **44**(5): p. 1332-52.
81. Shilpa, A., S. Kalyani, and S. Manisha, *Ageing Process and Physiological Changes*, in *Gerontology*, D.O. Grazia, G. Antonio, and S. Daniele, Editors. 2018, IntechOpen: Rijeka. p. Ch. 1.
82. Kassis, A., et al., *Nutritional and lifestyle management of the aging journey: A narrative review*. Front Nutr, 2022. **9**: p. 1087505.
83. López-Otín, C., et al., *The hallmarks of aging*. Cell, 2013. **153**(6): p. 1194-217.
84. Maldonado, E., et al., *Aging Hallmarks and the Role of Oxidative Stress*. Antioxidants (Basel), 2023. **12**(3).
85. Ferrucci, L. and E. Fabbri, *Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty*. Nat Rev Cardiol, 2018. **15**(9): p. 505-522.
86. Saavedra, D., et al., *Aging and chronic inflammation: highlights from a multidisciplinary workshop*. Immunity & Ageing, 2023. **20**(1): p. 25.
87. Roberts, S., et al., *Ageing in the musculoskeletal system*. Acta Orthop, 2016. **87**(sup363): p. 15-25.
88. Heavener, K.S. and E.M. Bradshaw, *The aging immune system in Alzheimer's and Parkinson's diseases*. Semin Immunopathol, 2022. **44**(5): p. 649-657.
89. van den Beld, A.W., et al., *The physiology of endocrine systems with ageing*. Lancet Diabetes Endocrinol, 2018. **6**(8): p. 647-658.
90. Lian, J., et al., *Immunosenescence: a key player in cancer development*. J Hematol Oncol, 2020. **13**(1): p. 151.
91. Roman, M.A., H.B. Rossiter, and R. Casaburi, *Exercise, ageing and the lung*. Eur Respir J, 2016. **48**(5): p. 1471-1486.
92. Dumic, I., et al., *Gastrointestinal Tract Disorders in Older Age*. Can J Gastroenterol Hepatol, 2019. **2019**: p. 6757524.
93. Dybiec, J., et al., *Structural and Functional Changes in Aging Kidneys*. International Journal of Molecular Sciences, 2022. **23**(23): p. 15435.

94. Fabbri, E., et al., *Aging and Multimorbidity: New Tasks, Priorities, and Frontiers for Integrated Gerontological and Clinical Research*. J Am Med Dir Assoc, 2015. **16**(8): p. 640-7.
95. Bernell, S. and S.W. Howard, *Use Your Words Carefully: What Is a Chronic Disease?* Front Public Health, 2016. **4**: p. 159.
96. Goodman, R.A., et al., *Defining and Measuring Chronic Conditions: Imperatives for Research, Policy, Program, and Practice*. Preventing Chronic Disease, 2013. **10**: p. E66.
97. Megari, K., *Quality of Life in Chronic Disease Patients*. Health Psychol Res, 2013. **1**(3): p. e27.
98. Costa, E., et al., *Aging and Cardiovascular Risk*. BioMed Research International, 2015. **2015**: p. 871656.
99. Petersen, K.S. and P.M. Kris-Etherton, *Diet Quality Assessment and the Relationship between Diet Quality and Cardiovascular Disease Risk*. Nutrients, 2021. **13**.
100. Perez, A. and J. Fleury, *Wellness motivation theory in practice*. Geriatr Nurs, 2009. **30**(2 Suppl): p. 15-20.
101. Lloyd-Jones, D., et al., *Heart disease and stroke statistics--2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee*. Circulation, 2009. **119**(3): p. e21-181.
102. Dai, X., et al., *Cardiovascular physiology in the older adults*. J Geriatr Cardiol, 2015. **12**(3): p. 196-201.
103. Damluji, A.A., et al., *Older Adults in the Cardiac Intensive Care Unit: Factoring Geriatric Syndromes in the Management, Prognosis, and Process of Care: A Scientific Statement From the American Heart Association*. Circulation, 2020. **141**(2): p. e6-e32.
104. Head, T., S. Daunert, and P.J. Goldschmidt-Clermont, *The Aging Risk and Atherosclerosis: A Fresh Look at Arterial Homeostasis*. Front Genet, 2017. **8**: p. 216.
105. Strait, J.B. and E.G. Lakatta, *Aging-associated cardiovascular changes and their relationship to heart failure*. Heart Fail Clin, 2012. **8**(1): p. 143-64.
106. Bhatia, N., et al., *Aortic valve disease in the older adult*. J Geriatr Cardiol, 2016. **13**(12): p. 941-944.
107. Bellary, S., et al., *Type 2 diabetes mellitus in older adults: clinical considerations and management*. Nat Rev Endocrinol, 2021. **17**(9): p. 534-548.
108. Laiteerapong, N. and E.S. Huang, *Diabetes in Older Adults*, in *Diabetes in America*, C.C. Cowie, et al., Editors. 2018, National Institute of Diabetes and Digestive and Kidney Diseases (US): Bethesda (MD).
109. Chia, C.W., J.M. Egan, and L. Ferrucci, *Age-Related Changes in Glucose Metabolism, Hyperglycemia, and Cardiovascular Risk*. Circ Res, 2018. **123**(7): p. 886-904.
110. Batsis, J.A. and D.T. Villareal, *Sarcopenic obesity in older adults: aetiology, epidemiology and treatment strategies*. Nat Rev Endocrinol, 2018. **14**(9): p. 513-537.
111. Wang, M., et al., *Diabetes and Sarcopenic Obesity: Pathogenesis, Diagnosis, and Treatments*. Front Endocrinol (Lausanne), 2020. **11**: p. 568.
112. Spinelli, R., et al., *Molecular basis of ageing in chronic metabolic diseases*. J Endocrinol Invest, 2020. **43**(10): p. 1373-1389.
113. Park, J.H., et al., *Sedentary Lifestyle: Overview of Updated Evidence of Potential Health Risks*. Korean J Fam Med, 2020. **41**(6): p. 365-373.
114. Fejer, R. and A. Ruhe, *What is the prevalence of musculoskeletal problems in the elderly population in developed countries? A systematic critical literature review*. Chiropr Man Therap, 2012. **20**(1): p. 31.
115. Aspray, T.J. and T.R. Hill, *Osteoporosis and the Ageing Skeleton*. Subcell Biochem, 2019. **91**: p. 453-476.

116. Padilla Colón, C.J., et al., *Muscle and Bone Mass Loss in the Elderly Population: Advances in diagnosis and treatment*. J Biomed (Syd), 2018. **3**: p. 40-49.
 117. Poursmaeili, F., et al., *A comprehensive overview on osteoporosis and its risk factors*. Ther Clin Risk Manag, 2018. **14**: p. 2029-2049.
 118. Loeser, R.F., *Age-related changes in the musculoskeletal system and the development of osteoarthritis*. Clin Geriatr Med, 2010. **26**(3): p. 371-86.
 119. Ferreira, M.L. and K. de Luca, *Spinal pain and its impact on older people*. Best Pract Res Clin Rheumatol, 2017. **31**(2): p. 192-202.
 120. Wong, A.Y.L., J. Karppinen, and D. Samartzis, *Low back pain in older adults: risk factors, management options and future directions*. Scoliosis Spinal Disord, 2017. **12**: p. 14.
 121. Cho, S.J. and H.W. Stout-Delgado, *Aging and Lung Disease*. Annual Review of Physiology, 2020. **82**(1): p. 433-459.
 122. Janssens, J.P., J.C. Pache, and L.P. Nicod, *Physiological changes in respiratory function associated with ageing*. Eur Respir J, 1999. **13**(1): p. 197-205.
 123. Eckhardt, C.M. and H. Wu, *Environmental Exposures and Lung Aging: Molecular Mechanisms and Implications for Improving Respiratory Health*. Curr Environ Health Rep, 2021. **8**(4): p. 281-293.
 124. Jiang, X.-Q., X.-D. Mei, and D. Feng, *Air pollution and chronic airway diseases: what should people know and do?* Journal of Thoracic Disease, 2015. **8**(1): p. E31-E40.
 125. Vaz Fragoso, C.A., et al., *Chronic obstructive pulmonary disease in older persons: A comparison of two spirometric definitions*. Respir Med, 2010. **104**(8): p. 1189-96.
 126. Warwick, M., et al., *Self-management and symptom monitoring among older adults with chronic obstructive pulmonary disease*. J Adv Nurs, 2010. **66**(4): p. 784-93.
 127. Agarwal, A.K., A. Raja, and B.D. Brown, *Chronic Obstructive Pulmonary Disease*, in *StatPearls*. 2023, StatPearls Publishing
- Copyright © 2023, StatPearls Publishing LLC.: Treasure Island (FL).
128. Weinstein, J.R. and S. Anderson, *The aging kidney: physiological changes*. Adv Chronic Kidney Dis, 2010. **17**(4): p. 302-7.
 129. Denic, A., R.J. Glasscock, and A.D. Rule, *Structural and Functional Changes With the Aging Kidney*. Adv Chronic Kidney Dis, 2016. **23**(1): p. 19-28.
 130. Peter, J.B., *Mechanisms of development of multimorbidity in the elderly*. European Respiratory Journal, 2015. **45**(3): p. 790.
 131. Zhang, J., et al., *Ageing and the telomere connection: An intimate relationship with inflammation*. Ageing Research Reviews, 2016. **25**: p. 55-69.
 132. Dai, L., et al., *Early vascular ageing in chronic kidney disease: impact of inflammation, vitamin K, senescence and genomic damage*. Nephrology Dialysis Transplantation, 2020. **35**(Supplement_2): p. ii31-ii37.
 133. Nowak, K.L., et al., *Strategies for Achieving Healthy Vascular Aging. Hypertension*, 2018. **71**(3): p. 389-402.
 134. Czarkowska-Pączek, B., K. Mucha, and L. Pączek, *Age-Related Decline in Renal Blood Flow Could Be a Beneficial and Compensatory Mechanism*. Med Sci Monit, 2020. **26**: p. e918643.
 135. Dalal, R., Z.S. Bruss, and J.S. Sehdev, *Physiology, Renal Blood Flow and Filtration*, in *StatPearls*. 2023, StatPearls Publishing
- Copyright © 2023, StatPearls Publishing LLC.: Treasure Island (FL).
136. Yang, H.C. and A.B. Fogo, *Fibrosis and renal aging*. Kidney Int Suppl (2011), 2014. **4**(1): p. 75-78.
 137. Mallappallil, M., et al., *Chronic kidney disease in the elderly: evaluation and management*. Clin Pract (Lond), 2014. **11**(5): p. 525-535.

138. Barbosa, R., et al., *Cognitive performance in older adults across Europe based on the SHARE database*. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn, 2021. **28**(4): p. 584-599.
139. Madreiter-Sokolowski, C.T., C. Thomas, and M. Ristow, *Interrelation between ROS and Ca(2+) in aging and age-related diseases*. Redox Biol, 2020. **36**: p. 101678.
140. Sumien, N., et al., *Neurodegenerative Disease: Roles for Sex, Hormones, and Oxidative Stress*. Endocrinology, 2021. **162**(11).
141. Takalo, M., et al., *Protein aggregation and degradation mechanisms in neurodegenerative diseases*. Am J Neurodegener Dis, 2013. **2**(1): p. 1-14.
142. Sehar, U., et al., *Amyloid Beta in Aging and Alzheimer's Disease*. International Journal of Molecular Sciences, 2022. **23**(21): p. 12924.
143. Zhao, Y., et al., *Molecular Mechanism of Autophagy: Its Role in the Therapy of Alzheimer's Disease*. Curr Neuropharmacol, 2020. **18**(8): p. 720-739.
144. Niu, H., et al., *Prevalence and incidence of Alzheimer's disease in Europe: A meta-analysis*. Neurología (English Edition), 2017. **32**(8): p. 523-532.
145. Gasiorowska, A., et al., *The Biology and Pathobiology of Glutamatergic, Cholinergic, and Dopaminergic Signaling in the Aging Brain*. Frontiers in Aging Neuroscience, 2021. **13**.
146. Tysnes, O.B. and A. Storstein, *Epidemiology of Parkinson's disease*. J Neural Transm (Vienna), 2017. **124**(8): p. 901-905.
147. Guzman-Martinez, L., et al., *Neuroinflammation as a Common Feature of Neurodegenerative Disorders*. Front Pharmacol, 2019. **10**: p. 1008.
148. Zhang, W., et al., *Role of neuroinflammation in neurodegeneration development*. Signal Transduction and Targeted Therapy, 2023. **8**(1): p. 267.
149. Rajeev, V., et al., *Pathophysiology of blood brain barrier dysfunction during chronic cerebral hypoperfusion in vascular cognitive impairment*. Theranostics, 2022. **12**(4): p. 1639-1658.
150. Pilleron, S., et al., *Global cancer incidence in older adults, 2012 and 2035: A population-based study*. Int J Cancer, 2019. **144**(1): p. 49-58.
151. Xiang, D., et al., *Worldwide cancer statistics of adults over 75 years old in 2019: a systematic analysis of the global burden of disease study 2019*. BMC Public Health, 2022. **22**(1): p. 1979.
152. Berben, L., et al., *Cancer and Aging: Two Tightly Interconnected Biological Processes*. Cancers (Basel), 2021. **13**(6).
153. Stead, E.R. and I. Bjedov, *Balancing DNA repair to prevent ageing and cancer*. Exp Cell Res, 2021. **405**(2): p. 112679.
154. Cheong, A. and Z.D. Nagel, *Human Variation in DNA Repair, Immune Function, and Cancer Risk*. Frontiers in Immunology, 2022. **13**.
155. Hoeijmakers, J.H., *DNA damage, aging, and cancer*. N Engl J Med, 2009. **361**(15): p. 1475-85.
156. White, M.C., et al., *Age and cancer risk: a potentially modifiable relationship*. Am J Prev Med, 2014. **46**(3 Suppl 1): p. S7-15.
157. Henderson, B.E. and H.S. Feigelson, *Hormonal carcinogenesis*. Carcinogenesis, 2000. **21**(3): p. 427-433.
158. Orzolek, I., J. Sobieraj, and J. Domagała-Kulawik, *Estrogens, Cancer and Immunity*. Cancers (Basel), 2022. **14**(9).
159. Flores, R., et al., *Age-Related Macular Degeneration: Pathophysiology, Management, and Future Perspectives*. Ophthalmologica, 2021. **244**(6): p. 495-511.
160. Thomas, C.J., R.G. Mirza, and M.K. Gill, *Age-Related Macular Degeneration*. Med Clin North Am, 2021. **105**(3): p. 473-491.
161. Somasundaran, S., et al., *Retinal pigment epithelium and age-related macular degeneration: A review of major disease mechanisms*. Clin Exp Ophthalmol, 2020. **48**(8): p. 1043-1056.

162. Wong, J.H.C., et al., *Exploring the pathogenesis of age-related macular degeneration: A review of the interplay between retinal pigment epithelium dysfunction and the innate immune system*. Frontiers in Neuroscience, 2022. **16**.
 163. Chew, M., et al., *The Impact of Cataract, Cataract Types, and Cataract Grades on Vision-Specific Functioning Using Rasch Analysis*. American Journal of Ophthalmology, 2012. **154**(1): p. 29-38.e2.
 164. Nizami, A.A. and A.C. Gulani, *Cataract*, in *StatPearls*. 2023, StatPearls Publishing
- Copyright © 2023, StatPearls Publishing LLC.: Treasure Island (FL).
165. Asbell, P.A., et al., *Age-related cataract*. Lancet, 2005. **365**(9459): p. 599-609.
 166. Li, J., et al., *Molecular genetics of congenital cataracts*. Exp Eye Res, 2020. **191**: p. 107872.
 167. Bowl, M.R. and S.J. Dawson, *Age-Related Hearing Loss*. Cold Spring Harb Perspect Med, 2019. **9**(8).
 168. Wang, J. and J.L. Puel, *Presbycusis: An Update on Cochlear Mechanisms and Therapies*. J Clin Med, 2020. **9**(1).
 169. Frisina, R.D. and J.P. Walton, *Age-related structural and functional changes in the cochlear nucleus*. Hear Res, 2006. **216-217**: p. 216-23.
 170. Löhler, J., et al., *Hearing Impairment in Old Age*. Dtsch Arztebl Int, 2019. **116**(17): p. 301-310.
 171. Baiduc, R.R., et al., *Clinical measures of auditory function: the cochlea and beyond*. Dis Mon, 2013. **59**(4): p. 147-56.
 172. Powell, D.S., et al., *Hearing Impairment and Cognition in an Aging World*. J Assoc Res Otolaryngol, 2021. **22**(4): p. 387-403.
 173. Meghani, S.H., et al., *The conceptualization and measurement of comorbidity: a review of the interprofessional discourse*. Nurs Res Pract, 2013. **2013**: p. 192782.
 174. Valderas, J.M., et al., *Defining comorbidity: implications for understanding health and health services*. Ann Fam Med, 2009. **7**(4): p. 357-63.
 175. Rodrigues, L.P., et al., *Association between multimorbidity and hospitalization in older adults: systematic review and meta-analysis*. Age Ageing, 2022. **51**(7).
 176. Kadambi, S., M. Abdallah, and K.P. Loh, *Multimorbidity, Function, and Cognition in Aging*. Clin Geriatr Med, 2020. **36**(4): p. 569-584.
 177. Rizzuto, D. and L. Fratiglioni, *Lifestyle Factors Related to Mortality and Survival: A Mini-Review*. Gerontology, 2014. **60**(4): p. 327-335.
 178. Nobili, A., S. Garattini, and P.M. Mannucci, *Multiple Diseases and Polypharmacy in the Elderly: Challenges for the Internist of the Third Millennium*. Journal of Comorbidity, 2011. **1**(1): p. 28-44.
 179. Calderón-Larrañaga, A., et al., *Multimorbidity and functional impairment-bidirectional interplay, synergistic effects and common pathways*. J Intern Med, 2019. **285**(3): p. 255-271.
 180. Maresova, P., et al., *Consequences of chronic diseases and other limitations associated with old age – a scoping review*. BMC Public Health, 2019. **19**(1): p. 1431.
 181. Byers, A.L., et al., *High occurrence of mood and anxiety disorders among older adults: The National Comorbidity Survey Replication*. Arch Gen Psychiatry, 2010. **67**(5): p. 489-96.
 182. Almada, M., et al., *Prevalence of Falls and Associated Factors among Community-Dwelling Older Adults: A Cross-Sectional Study*. J Frailty Aging, 2021. **10**(1): p. 10-16.
 183. Molokhia, M. and A. Majeed, *Current and future perspectives on the management of polypharmacy*. BMC Fam Pract, 2017. **18**(1): p. 70.
 184. Baqir, W., et al., *Impact of medication review, within a shared decision-making framework, on deprescribing in people living in care homes*. Eur J Hosp Pharm, 2017. **24**(1): p. 30-33.

185. Radcliffe, E., et al., *What makes a multidisciplinary medication review and deprescribing intervention for older people work well in primary care? A realist review and synthesis*. BMC Geriatrics, 2023. **23**(1): p. 591.
186. Dartigues, J.F., et al., *Co-Occurrence of Geriatric Syndromes and Diseases in the General Population: Assessment of the Dimensions of Aging*. The journal of nutrition, health & aging, 2022. **26**(1): p. 37-45.
187. Hefny, A.F., A.K. Abbas, and F.M. Abu-Zidan, *Geriatric fall-related injuries*. Afr Health Sci, 2016. **16**(2): p. 554-9.
188. Liu, S.W., et al., *Frequency of ED revisits and death among older adults after a fall*. Am J Emerg Med, 2015. **33**(8): p. 1012-8.
189. Giovannini, S., et al., *Falls among Older Adults: Screening, Identification, Rehabilitation, and Management*. Applied Sciences, 2022. **12**(15): p. 7934.
190. Xing, L., et al., *Falls caused by balance disorders in the elderly with multiple systems involved: Pathogenic mechanisms and treatment strategies*. Front Neurol, 2023. **14**: p. 1128092.
191. Demaagd, G.A. and T.C. Davenport, *Management of urinary incontinence*. P t, 2012. **37**(6): p. 345-361h.
192. Ranson, R.N. and M.J. Saffrey, *Neurogenic mechanisms in bladder and bowel ageing*. Biogerontology, 2015. **16**(2): p. 265-84.
193. Bellelli, G., J.S. Brathwaite, and P. Mazzola, *Delirium: A Marker of Vulnerability in Older People*. Frontiers in Aging Neuroscience, 2021. **13**.
194. Iglseider, B., T. Frühwald, and C. Jagsch, *Delirium in geriatric patients*. Wien Med Wochenschr, 2022. **172**(5-6): p. 114-121.
195. Wilson, J.E., et al., *Delirium*. Nat Rev Dis Primers, 2020. **6**(1): p. 90.
196. Santilli, V., et al., *Clinical definition of sarcopenia*. Clin Cases Miner Bone Metab, 2014. **11**(3): p. 177-80.
197. Wilson, D., et al., *Frailty and sarcopenia: The potential role of an aged immune system*. Ageing Research Reviews, 2017. **36**: p. 1-10.
198. Rolland, Y., et al., *Sarcopenia: its assessment, etiology, pathogenesis, consequences and future perspectives*. J Nutr Health Aging, 2008. **12**(7): p. 433-50.
199. Wleklík, M., et al., *Multidimensional Approach to Frailty*. Front Psychol, 2020. **11**: p. 564.
200. Xue, Q.L., *The frailty syndrome: definition and natural history*. Clin Geriatr Med, 2011. **27**(1): p. 1-15.
201. Brown, I., R. Renwick, and D. Raphael, *Frailty: constructing a common meaning, definition, and conceptual framework*. Int J Rehabil Res, 1995. **18**(2): p. 93-102.
202. Clegg, A., et al., *Frailty in elderly people*. Lancet, 2013. **381**(9868): p. 752-62.
203. Walston, J.D. and K. Bandeen-Roche, *Frailty: a tale of two concepts*. BMC Medicine, 2015. **13**(1): p. 185.
204. Buckinx, F., et al., *Burden of frailty in the elderly population: perspectives for a public health challenge*. Archives of Public Health, 2015. **73**(1): p. 19.
205. Lekan, D.A., S.K. Collins, and A.A. Hayajneh, *Definitions of Frailty in Qualitative Research: A Qualitative Systematic Review*. J Aging Res, 2021. **2021**: p. 6285058.
206. Gobbens, R.J.J., et al., *In Search of an Integral Conceptual Definition of Frailty: Opinions of Experts*. Journal of the American Medical Directors Association, 2010. **11**(5): p. 338-343.
207. Abbasi, M., et al., *Identification and management of frailty in the primary care setting*. Cmaj, 2018. **190**(38): p. E1134-e1140.
208. Rockwood, K. and S.E. Howlett, *Fifteen years of progress in understanding frailty and health in aging*. BMC Medicine, 2018. **16**(1): p. 220.
209. Kwak, D. and L.V. Thompson, *Frailty: Past, present, and future?* Sports Med Health Sci, 2021. **3**(1): p. 1-10.

210. Sara, P., *Frailty, Vulnerability, and Plasticity: Towards a New Medicine of Complexity*, in *Frailty in the Elderly*, P. Sara, Editor. 2021, IntechOpen: Rijeka. p. Ch. 1.
211. Chen, X., G. Mao, and S.X. Leng, *Frailty syndrome: an overview*. Clin Interv Aging, 2014. **9**: p. 433-41.
212. Sobhani, A., et al., *The conceptual and practical definitions of frailty in older adults: a systematic review*. J Diabetes Metab Disord, 2021. **20**(2): p. 1975-2013.
213. Pilotto, A., et al., *A multidimensional approach to frailty in older people*. Ageing Res Rev, 2020. **60**: p. 101047.
214. Taylor, J.A., et al., *Multisystem physiological perspective of human frailty and its modulation by physical activity*. Physiological Reviews, 2023. **103**(2): p. 1137-1191.
215. Walston, J., B. Buta, and Q.L. Xue, *Frailty Screening and Interventions: Considerations for Clinical Practice*. Clin Geriatr Med, 2018. **34**(1): p. 25-38.
216. Dodds, R. and A.A. Sayer, *Sarcopenia and frailty: new challenges for clinical practice*. Clin Med (Lond), 2016. **16**(5): p. 455-458.
217. Gielen, E., et al., *Sarcopenia, osteoporosis and frailty*. Metabolism, 2023. **145**: p. 155638.
218. Greco, E.A., P. Pietschmann, and S. Migliaccio, *Osteoporosis and Sarcopenia Increase Frailty Syndrome in the Elderly*. Front Endocrinol (Lausanne), 2019. **10**: p. 255.
219. Li, H., B. Manwani, and S.X. Leng, *Frailty, inflammation, and immunity*. Aging Dis, 2011. **2**(6): p. 466-73.
220. Salaffi, F., et al., *Inflammaging and Frailty in Immune-Mediated Rheumatic Diseases: How to Address and Score the Issue*. Clinical Reviews in Allergy & Immunology, 2023. **64**(2): p. 206-221.
221. Baechle, J.J., et al., *Chronic inflammation and the hallmarks of aging*. Molecular Metabolism, 2023. **74**: p. 101755.
222. Brünsgaard, H. and B.K. Pedersen, *Age-related inflammatory cytokines and disease*. Immunol Allergy Clin North Am, 2003. **23**(1): p. 15-39.
223. Gómez-Rubio, P., et al., *Salivary IL-6 Concentration Is Associated with Frailty Syndrome in Older Individuals*. Diagnostics (Basel), 2022. **12**(1).
224. Nascimento, C.M.C., et al., *Higher levels of tumor necrosis factor β are associated with frailty in socially vulnerable community-dwelling older adults*. BMC Geriatr, 2018. **18**(1): p. 268.
225. Rea, I.M., et al., *Age and Age-Related Diseases: Role of Inflammation Triggers and Cytokines*. Frontiers in Immunology, 2018. **9**.
226. Clegg, A. and Z. Hassan-Smith, *Frailty and the endocrine system*. Lancet Diabetes Endocrinol, 2018. **6**(9): p. 743-752.
227. Gupta, D. and J.E. Morley, *Hypothalamic-Pituitary-Adrenal (HPA) Axis and Aging*, in *Comprehensive Physiology*. p. 1495-1510.
228. Ricci Bitti, S., et al., *GH Replacement in the Elderly: Is It Worth It?* Frontiers in Endocrinology, 2021. **12**.
229. Borges, M.K., et al., *Frailty as a Predictor of Cognitive Disorders: A Systematic Review and Meta-Analysis*. Front Med (Lausanne), 2019. **6**: p. 26.
230. Searle, S.D. and K. Rockwood, *Frailty and the risk of cognitive impairment*. Alzheimer's Research & Therapy, 2015. **7**(1): p. 54.
231. Li, Y., et al., *Diabetic vascular diseases: molecular mechanisms and therapeutic strategies*. Signal Transduction and Targeted Therapy, 2023. **8**(1): p. 152.
232. Kosmas, C.E., et al., *Insulin resistance and cardiovascular disease*. J Int Med Res, 2023. **51**(3): p. 3000605231164548.
233. Perazza, L.R., H.M. Brown-Borg, and L.V. Thompson, *Physiological Systems in Promoting Frailty*. Compr Physiol, 2022. **12**(3): p. 3575-3620.
234. Zazzara, M.B., et al., *Frailty and chronic disease*. Panminerva Med, 2019. **61**(4): p. 486-492.

235. Adja, K.Y.C., et al., *The Importance of Taking a Patient-Centered, Community-Based Approach to Preventing and Managing Frailty: A Public Health Perspective*. *Frontiers in Public Health*, 2020. **8**.
236. Fried, L.P., et al., *The physical frailty syndrome as a transition from homeostatic symphony to cacophony*. *Nat Aging*, 2021. **1**(1): p. 36-46.
237. Cadore, E.L., et al., *Effects of different exercise interventions on risk of falls, gait ability, and balance in physically frail older adults: a systematic review*. *Rejuvenation Res*, 2013. **16**(2): p. 105-14.
238. Alves, S., et al., *Examining Frailty Phenotype Dimensions in the Oldest Old*. *Frontiers in Psychology*, 2020. **11**.
239. Fried, L.P., et al., *Frailty in older adults: evidence for a phenotype*. *J Gerontol A Biol Sci Med Sci*, 2001. **56**(3): p. M146-56.
240. Romero-Ortuno, R., *The Frailty Instrument for primary care of the Survey of Health, Ageing and Retirement in Europe predicts mortality similarly to a frailty index based on comprehensive geriatric assessment*. *Geriatr Gerontol Int*, 2013. **13**(2): p. 497-504.
241. Romero-Ortuno, R., et al., *A frailty instrument for primary care: findings from the Survey of Health, Ageing and Retirement in Europe (SHARE)*. *BMC Geriatr*, 2010. **10**: p. 57.
242. Gagesch, M., et al., *Prevalence of Physical Frailty: Results from the DO-HEALTH Study*. *J Frailty Aging*, 2022. **11**(1): p. 18-25.
243. Portela, D., et al., *Instrumental Activities of Daily Living (iADL) Limitations in Europe: An Assessment of SHARE Data*. *Int J Environ Res Public Health*, 2020. **17**(20).
244. Chittrakul, J., et al., *Physical Frailty and Fall Risk in Community-Dwelling Older Adults: A Cross-Sectional Study*. *J Aging Res*, 2020. **2020**: p. 3964973.
245. Hu, K., et al., *Association between Frailty and Mortality, Falls, and Hospitalization among Patients with Hypertension: A Systematic Review and Meta-Analysis*. *Biomed Res Int*, 2021. **2021**: p. 2690296.
246. Lan, X., et al., *Frailty as a predictor of future falls in hospitalized patients: A systematic review and meta-analysis*. *Geriatric Nursing*, 2020. **41**(2): p. 69-74.
247. Middleton, R., et al., *Mortality, Falls, and Fracture Risk Are Positively Associated With Frailty: A SIDIAP Cohort Study of 890 000 Patients*. *The Journals of Gerontology: Series A*, 2021. **77**(1): p. 148-154.
248. Angulo, J., et al., *Physical activity and exercise: Strategies to manage frailty*. *Redox Biology*, 2020. **35**: p. 101513.
249. Kojima, G., R. Aoyama, and M. Tanabe, *Associations Between Social Isolation and Physical Frailty in Older Adults: A Systematic Review and Meta-Analysis*. *J Am Med Dir Assoc*, 2022. **23**(11): p. e3-e6.
250. Quach, L.T., et al., *The Intersection of Physical and Social Frailty in Older Adults*. *R I Med J* (2013), 2021. **104**(4): p. 16-19.
251. Liu, C.K. and R.A. Fielding, *Exercise as an intervention for frailty*. *Clin Geriatr Med*, 2011. **27**(1): p. 101-10.
252. Coelho-Junior, H.J., et al., *Protein Intake and Frailty in Older Adults: A Systematic Review and Meta-Analysis of Observational Studies*. *Nutrients*, 2022. **14**(13).
253. Nwadiugwu, M.C., *Frailty and the Risk of Polypharmacy in the Older Person: Enabling and Preventative Approaches*. *J Aging Res*, 2020. **2020**: p. 6759521.
254. Bunt, S., et al., *Social frailty in older adults: a scoping review*. *Eur J Ageing*, 2017. **14**(3): p. 323-334.
255. Makizako, H., et al., *Social Frailty Among Community-Dwelling Older Adults: Recommended Assessments and Implications*. *Ann Geriatr Med Res*, 2018. **22**(1): p. 3-8.
256. Pek, K., et al., *Social Frailty Is Independently Associated with Mood, Nutrition, Physical Performance, and Physical Activity: Insights from a Theory-Guided Approach*. *Int J Environ Res Public Health*, 2020. **17**(12).

257. Wu, K.-Y., et al., *Fear of falling as a mediator in the association between social frailty and health-related quality of life in community-dwelling older adults*. BMC Geriatrics, 2023. **23**(1): p. 421.
258. Zhang, X.M., et al., *The Prevalence of Social Frailty Among Older Adults: A Systematic Review and Meta-Analysis*. J Am Med Dir Assoc, 2023. **24**(1): p. 29-37.e9.
259. Qi, X., et al., *Prevalence of social frailty and its associated factors in the older Chinese population: a national cross-sectional study*. BMC Geriatrics, 2023. **23**(1): p. 532.
260. Mehrabi, F. and F. Béland, *Effects of social isolation, loneliness and frailty on health outcomes and their possible mediators and moderators in community-dwelling older adults: A scoping review*. Archives of Gerontology and Geriatrics, 2020. **90**: p. 104119.
261. Lozupone, M., et al., *Social Frailty in the COVID-19 Pandemic Era*. Front Psychiatry, 2020. **11**: p. 577113.
262. Andrew, M.K., A.B. Mitnitski, and K. Rockwood, *Social Vulnerability, Frailty and Mortality in Elderly People*. PLOS ONE, 2008. **3**(5): p. e2232.
263. Mazo, G.Z., et al., *Impact of Social Isolation on Physical Activity and Factors Associated With Sedentary Behavior in Older Adults During the COVID-19 Pandemic*. J Aging Phys Act, 2022. **30**(1): p. 148-152.
264. Schrempft, S., et al., *Associations between social isolation, loneliness, and objective physical activity in older men and women*. BMC Public Health, 2019. **19**(1): p. 74.
265. Duppen Rn, D., et al., *Meaning in Life for Socially Frail Older Adults*. Journal of Community Health Nursing, 2019. **36**(2): p. 65-77.
266. Fujiwara, Y., et al., *Social frailty as social aspects of frailty: Research, practical activities, and prospects*. Geriatr Gerontol Int, 2022. **22**(12): p. 991-996.
267. Hülür, G. and B. Macdonald, *Rethinking social relationships in old age: Digitalization and the social lives of older adults*. Am Psychol, 2020. **75**(4): p. 554-566.
268. Yip, O., et al., *Health and social care of home-dwelling frail older adults in Switzerland: a mixed methods study*. BMC Geriatrics, 2022. **22**(1): p. 857.
269. Gilmore, N., et al., *The Relationship Between Frailty and Emotional Health in Older Patients with Advanced Cancer*. Oncologist, 2021. **26**(12): p. e2181-e2191.
270. Jinlong, Z., et al., *Psychological frailty in older adults: a systematic scoping review*. medRxiv, 2022: p. 2022.08.01.22278302.
271. Coker, J.F., et al., *Frailty: an in-depth qualitative study exploring the views of community care staff*. BMC Geriatrics, 2019. **19**(1): p. 47.
272. Borges, M.K., et al., *Frailty and affective disorders throughout adult life: A 5-year follow-up of the Lifelines Cohort Study*. J Am Geriatr Soc, 2022. **70**(12): p. 3424-3435.
273. Gaspar, P.M., et al., *Cognitive reserve and mental health in cognitive frailty phenotypes: Insights from a study with a Portuguese sample*. Frontiers in Psychology, 2022. **13**.
274. Mulasso, A., et al., *Associations of frailty and psychosocial factors with autonomy in daily activities: a cross-sectional study in Italian community-dwelling older adults*. Clin Interv Aging, 2016. **11**: p. 37-45.
275. Mutz, J., et al., *Frailty in individuals with depression, bipolar disorder and anxiety disorders: longitudinal analyses of all-cause mortality*. BMC Medicine, 2022. **20**(1): p. 274.
276. Zhao, J., et al., *Exploring the concept of psychological frailty in older adults: a systematic scoping review*. Journal of Clinical Epidemiology, 2023. **159**: p. 300-308.

277. Furtado, G.E., et al., *Emotional Well-Being and Cognitive Function Have Robust Relationship With Physical Frailty in Institutionalized Older Women*. Front Psychol, 2020. **11**: p. 1568.
278. Henry, J.D., et al., *Social Frailty in Late Adulthood: Social Cognitive and Psychological Well-Being Correlates*. J Gerontol B Psychol Sci Soc Sci, 2023. **78**(1): p. 87-96.
279. Salem, B.E., et al., *Correlates of physical, psychological, and social frailty among formerly incarcerated, homeless women*. Health Care Women Int, 2019. **40**(7-9): p. 788-812.
280. Pinheiro, I.M., et al., *Biopsychosocial factors associated with the frailty and pre-frailty among older adults*. Geriatr Nurs, 2019. **40**(6): p. 597-602.
281. Gobbens, R.J., et al., *The Tilburg Frailty Indicator: psychometric properties*. J Am Med Dir Assoc, 2010. **11**(5): p. 344-55.
282. Peters, L.L., et al., *Measurement Properties of the Groningen Frailty Indicator in Home-Dwelling and Institutionalized Elderly People*. Journal of the American Medical Directors Association, 2012. **13**(6): p. 546-551.
283. Faria, A., et al., *Multidimensional Frailty and Lifestyles of Community-Dwelling Older Portuguese Adults*. Int J Environ Res Public Health, 2022. **19**(22).
284. Cesari, M., et al., *The frailty phenotype and the frailty index: different instruments for different purposes*. Age and Ageing, 2013. **43**(1): p. 10-12.
285. Melvin, R.L., et al., *A review of frailty instruments in human medicine and proposal of a frailty instrument for dogs*. Frontiers in Veterinary Science, 2023. **10**.
286. Boreskie, K.F., et al., *Frailty-aware care: giving value to frailty assessment across different healthcare settings*. BMC Geriatrics, 2022. **22**(1): p. 13.
287. Kyriakou, E., et al., *Implementing frailty assessment into a healthcare system: a clinical opinion paper*. J Frailty Sarcopenia Falls, 2019. **4**(4): p. 111-115.
288. Rockwood, K., et al., *A global clinical measure of fitness and frailty in elderly people*. Cmaj, 2005. **173**(5): p. 489-95.
289. Mitnitski, A.B., A.J. Mogilner, and K. Rockwood, *Accumulation of Deficits as a Proxy Measure of Aging*. TheScientificWorldJOURNAL, 2001. **1**: p. 321027.
290. Hébert, R., et al., *PRISMA: a new model of integrated service delivery for the frail older people in Canada*. Int J Integr Care, 2003. **3**: p. e08.
291. Bielderman, A., et al., *Multidimensional structure of the Groningen Frailty Indicator in community-dwelling older people*. BMC Geriatrics, 2013. **13**(1): p. 86.
292. Rolfson, D.B., et al., *Validity and reliability of the Edmonton Frail Scale*. Age and Ageing, 2006. **35**(5): p. 526-529.
293. Checa-López, M., et al., *FRAILTOOLS study protocol: a comprehensive validation of frailty assessment tools to screen and diagnose frailty in different clinical and social settings and to provide instruments for integrated care in older adults*. BMC Geriatr, 2019. **19**(1): p. 86.
294. Castro, M.L., et al., *Reproducibility and validity of the Portuguese Edmonton Frail Scale version in cardiac surgery patients*. Rev Port Cardiol, 2023. **42**(4): p. 295-304.
295. Coelho, T., et al., *Portuguese version of the Tilburg Frailty Indicator: Transcultural adaptation and psychometric validation*. Geriatr Gerontol Int, 2015. **15**(8): p. 951-60.
296. Duarte, M. and C. Paúl, *Prevalência de fragilidade fenotípica em pessoas em processo de envelhecimento numa comunidade portuguesa*. Revista Brasileira de Geriatria e Gerontologia, 2015. **18**(4): p. 871-880.
297. Pereira Pinto, M., et al., *European Portuguese Version of the Clinical Frailty Scale: Translation, Cultural Adaptation and Validation Study*. Acta Med Port, 2021. **34**(11): p. 749-760.

298. Santiago, L.M., et al., *Cross-cultural adaptation and validation of the PRISMA-7 scale for European Portuguese*. Family Medicine & Primary Care Review, 2020. **22**(1): p. 59-66.
299. Laukli, I., L. Sandvik, and H. Ormstad, *Frailty assessment of older adults, first-time applicants of public home care service in Norway*. Scand J Prim Health Care, 2021. **39**(1): p. 3-9.
300. Werner, C., et al., *A multifactorial interdisciplinary intervention to prevent functional and mobility decline for more participation in (pre-)frail community-dwelling older adults (Prometheus): study protocol for a multicenter randomized controlled trial*. BMC Geriatrics, 2022. **22**(1): p. 124.
301. Strojnik, V. and B. Gabrovec, *Management of Frailty at Individual Level: Narrative Review of Physical Activity from the European Perspective of Joint Action on Frailty - JA Advantage*. Zdr Varst, 2019. **58**(2): p. 84-90.
302. Kime, N., et al., *Implementing personalised care planning for older people with frailty: a process evaluation of the PROSPER feasibility trial*. BMC Geriatrics, 2022. **22**(1): p. 760.
303. Byrne, A.L., A. Baldwin, and C. Harvey, *Whose centre is it anyway? Defining person-centred care in nursing: An integrative review*. PLoS One, 2020. **15**(3): p. e0229923.
304. Kouroubali, A., et al., *Developing an AI-Enabled Integrated Care Platform for Frailty*. Healthcare (Basel), 2022. **10**(3).
305. Zou, Y., et al., *Predictive value of frailty in the mortality of hospitalized patients with COVID-19: a systematic review and meta-analysis*. Ann Transl Med, 2022. **10**(4): p. 166.
306. Cameron, I.D., et al., *Interventions for preventing falls in older people in care facilities and hospitals*. Cochrane Database Syst Rev, 2018. **9**(9): p. Cd005465.
307. Montero-Odasso, M., et al., *World guidelines for falls prevention and management for older adults: a global initiative*. Age and Ageing, 2022. **51**(9).
308. Fairhall, N., et al., *Economic evaluation of a multifactorial, interdisciplinary intervention versus usual care to reduce frailty in frail older people*. J Am Med Dir Assoc, 2015. **16**(1): p. 41-8.
309. Coelho, T., et al., *Determinants of frailty: the added value of assessing medication*. Frontiers in Aging Neuroscience, 2015. **7**.
310. Liao, S.J., et al., *Medication Management in Frail Older People: Consensus Principles for Clinical Practice, Research, and Education*. Journal of the American Medical Directors Association, 2021. **22**(1): p. 43-49.
311. Salahudeen, M.S., *Deprescribing medications in older people: a narrative review*. Drugs Today (Barc), 2018. **54**(8): p. 489-498.
312. Yang, Z.C., et al., *Frailty Is a Risk Factor for Falls in the Older Adults: A Systematic Review and Meta-Analysis*. J Nutr Health Aging, 2023. **27**(6): p. 487-595.
313. Istepanian, R.S.H., *Mobile Health (m-Health) in Retrospect: The Known Unknowns*. Int J Environ Res Public Health, 2022. **19**(7).
314. Merrell, R.C. and C.R. Doarn, *m-Health*. Telemed J E Health, 2014. **20**(2): p. 99-101.
315. Park, Y.T., *Emerging New Era of Mobile Health Technologies*. Healthc Inform Res, 2016. **22**(4): p. 253-254.
316. Meskó, B., et al., *Digital health is a cultural transformation of traditional healthcare*. mHealth, 2017. **3**(9).
317. Steinhubl, S.R., E.D. Muse, and E.J. Topol, *The emerging field of mobile health*. Sci Transl Med, 2015. **7**(283): p. 283rv3.
318. Zakerabasali, S., et al., *Mobile Health Technology and Healthcare Providers: Systemic Barriers to Adoption*. Healthc Inform Res, 2021. **27**(4): p. 267-278.

319. Abaza, H. and M. Marschollek, *mHealth Application Areas and Technology Combinations*. A Comparison of Literature from High and Low/Middle Income Countries*. *Methods Inf Med*, 2017. **56**(7): p. e105-e122.
320. Crico, C., et al., *mHealth and telemedicine apps: in search of a common regulation*. *Ecancermedicallscience*, 2018. **12**: p. 853.
321. Allida, S., et al., *mHealth education interventions in heart failure*. *Cochrane Database Syst Rev*, 2020. **7**(7): p. Cd011845.
322. Badawy, S.M., et al., *Habit Strength, Medication Adherence, and Habit-Based Mobile Health Interventions Across Chronic Medical Conditions: Systematic Review*. *J Med Internet Res*, 2020. **22**(4): p. e17883.
323. Emerson, M.R., et al., *Addressing and evaluating health literacy in mHealth: a scoping review*. *Mhealth*, 2022. **8**: p. 33.
324. Gandapur, Y., et al., *The role of mHealth for improving medication adherence in patients with cardiovascular disease: a systematic review*. *Eur Heart J Qual Care Clin Outcomes*, 2016. **2**(4): p. 237-244.
325. Heneghan, M.B., et al., *Access to Technology and Preferences for an mHealth Intervention to Promote Medication Adherence in Pediatric Acute Lymphoblastic Leukemia: Approach Leveraging Behavior Change Techniques*. *J Med Internet Res*, 2021. **23**(2): p. e24893.
326. Mason, M., et al., *Technologies for Medication Adherence Monitoring and Technology Assessment Criteria: Narrative Review*. *JMIR Mhealth Uhealth*, 2022. **10**(3): p. e35157.
327. Pouls, B.P.H., et al., *Effect of Interactive eHealth Interventions on Improving Medication Adherence in Adults With Long-Term Medication: Systematic Review*. *J Med Internet Res*, 2021. **23**(1): p. e18901.
328. Mallow, J.A., et al., *Using mHealth Tools to Improve Rural Diabetes Care Guided by the Chronic Care Model*. *Online J Rural Nurs Health Care*, 2014. **14**(1): p. 43-65.
329. Wilson, K., *Mobile cell phone technology puts the future of health care in our hands*. *Cmaj*, 2018. **190**(13): p. E378-e379.
330. Rehman, H., et al., *Mobile Health (mHealth) Technology for the Management of Hypertension and Hyperlipidemia: Slow Start but Loads of Potential*. *Current Atherosclerosis Reports*, 2017. **19**(3): p. 12.
331. Rowland, S.P., et al., *What is the clinical value of mHealth for patients? NPJ Digit Med*, 2020. **3**: p. 4.
332. Kang, H.S. and M. Exworthy, *Wearing the Future-Wearables to Empower Users to Take Greater Responsibility for Their Health and Care: Scoping Review*. *JMIR Mhealth Uhealth*, 2022. **10**(7): p. e35684.
333. Amjad, A., P. Kordel, and G. Fernandes, *A Review on Innovation in Healthcare Sector (Telehealth) through Artificial Intelligence*. *Sustainability*, 2023. **15**(8): p. 6655.
334. Haleem, A., et al., *Telemedicine for healthcare: Capabilities, features, barriers, and applications*. *Sens Int*, 2021. **2**: p. 100117.
335. Gajarawala, S.N. and J.N. Pelkowski, *Telehealth Benefits and Barriers*. *J Nurse Pract*, 2021. **17**(2): p. 218-221.
336. Kim, Y.K. and S. Ang, *Older Adults With Functional Limitations and Their Use of Telehealth During COVID-19*. *Res Aging*, 2023. **45**(9-10): p. 609-619.
337. Casariego-Vales, E., et al., *Efficacy of Telemedicine and Telemonitoring in At-Home Monitoring of Patients with COVID-19*. *J Clin Med*, 2021. **10**(13).
338. Ji, W., et al., *Evaluation of the Effectiveness of Remote Monitoring to Establish a Community Health Intervention During COVID-19: A Community Intervention Trial*. *Telemedicine and e-Health*, 2022. **29**(2): p. 253-260.
339. Kuan, P.X., et al., *Efficacy of telemedicine for the management of cardiovascular disease: a systematic review and meta-analysis*. *The Lancet Digital Health*, 2022. **4**(9): p. e676-e691.

340. Suárez-Gil, R., et al., *Efficacy of Telemedicine and At-Home Telemonitoring following Hospital Discharge in Patients with COVID-19*. Journal of Personalized Medicine, 2022. **12**(4): p. 609.
341. Oliosi, E., F. Guede-Fernández, and A. Londral, *Machine Learning Approaches for the Frailty Screening: A Narrative Review*. Int J Environ Res Public Health, 2022. **19**(14).
342. Saedi, A.A., et al., *Current and emerging biomarkers of frailty in the elderly*. Clin Interv Aging, 2019. **14**: p. 389-398.
343. Sykoutris, A., et al., *iCompanion: A Serious Games App for the Management of Frailty*. Stud Health Technol Inform, 2022. **294**: p. 624-628.
344. Pedrolí, E., et al., *Brain M-App's Structure and Usability: A New Application for Cognitive Rehabilitation at Home*. Front Hum Neurosci, 2022. **16**: p. 898633.
345. Merchant, R.A., et al., *Rapid Geriatric Assessment Using Mobile App in Primary Care: Prevalence of Geriatric Syndromes and Review of Its Feasibility*. Front Med (Lausanne), 2020. **7**: p. 261.
346. Tan, L.F., et al., *Practicality and Reliability of Self Vs Administered Rapid Geriatric Assessment Mobile App*. J Nutr Health Aging, 2021. **25**(9): p. 1064-1069.
347. Singer, J.P., et al., *A mobile health technology enabled home-based intervention to treat frailty in adult lung transplant candidates: A pilot study*. Clin Transplant, 2018. **32**(6): p. e13274.
348. Madureira, P., et al., *My-AHA: Software Platform to Promote Active and Healthy Ageing*. Information, 2020. **11**(9): p. 438.
349. Zolnowski-Kolp, V., et al., *Assessment of Frailty by the French Version of the Vulnerable Elders Survey-13 on Digital Tablet: Validation Study*. J Med Internet Res, 2023. **25**: p. e42017.
350. Zacharaki, E.I., et al., *FrailSafe: An ICT Platform for Unobtrusive Sensing of Multi-Domain Frailty for Personalized Interventions*. IEEE Journal of Biomedical and Health Informatics, 2020. **24**(6): p. 1557-1568.
351. Okpara, C., et al., *The Geras virtual frailty rehabilitation program to build resilience in older adults with frailty during COVID-19: a randomized feasibility trial*. Pilot Feasibility Stud, 2023. **9**(1): p. 124.
352. Stefanicka-Wojtas, D. and D. Kurpas, *eHealth and mHealth in Chronic Diseases-Identification of Barriers, Existing Solutions, and Promoters Based on a Survey of EU Stakeholders Involved in Regions4PerMed (H2020)*. J Pers Med, 2022. **12**(3).
353. O'Connell, M.L., T. Coppinger, and A.L. McCarthy, *The role of nutrition and physical activity in frailty: A review*. Clinical Nutrition ESPEN, 2020. **35**: p. 1-11.
354. Takemoto, M., et al., *Diet and Activity Assessments and Interventions Using Technology in Older Adults*. Am J Prev Med, 2018. **55**(4): p. e105-e115.
355. Calvillo-Arbizu, J., et al., *A Sensor-Based mHealth Platform for Remote Monitoring and Intervention of Frailty Patients at Home*. Int J Environ Res Public Health, 2021. **18**(21).
356. García-Fernández, J., et al., *The Promotion of Physical Activity from Digital Services: Influence of E-Lifestyles on Intention to Use Fitness Apps*. International Journal of Environmental Research and Public Health, 2020. **17**(18): p. 6839.
357. Lee, M., et al., *Mobile App-Based Health Promotion Programs: A Systematic Review of the Literature*. International Journal of Environmental Research and Public Health, 2018. **15**(12): p. 2838.
358. Petersen, J.M., et al., *Promoting physical activity during the COVID-19 lockdown in Australia: The roles of psychological predictors and commercial physical activity apps*. Psychology of Sport and Exercise, 2021. **56**: p. 102002.
359. Petersen, J.M., I. Prichard, and E. Kemps, *A Comparison of Physical Activity Mobile Apps With and Without Existing Web-Based Social Networking Platforms: Systematic Review*. J Med Internet Res, 2019. **21**(8): p. e12687.

360. Wang, Q., et al., *Diet and Physical Activity Apps: Perceived Effectiveness by App Users*. JMIR Mhealth Uhealth, 2016. **4**(2): p. e33.
361. West, J.H., et al., *Controlling Your "App"etite: How Diet and Nutrition-Related Mobile Apps Lead to Behavior Change*. JMIR Mhealth Uhealth, 2017. **5**(7): p. e95.
362. Knight, E., et al., *Public health guidelines for physical activity: is there an app for that? A review of android and apple app stores*. JMIR Mhealth Uhealth, 2015. **3**(2): p. e43.
363. Bonnechère, B., et al., *Brain training using cognitive apps can improve cognitive performance and processing speed in older adults*. Sci Rep, 2021. **11**(1): p. 12313.
364. Al-Thaqib, A., et al., *Brain Training Games Enhance Cognitive Function in Healthy Subjects*. Med Sci Monit Basic Res, 2018. **24**: p. 63-69.
365. Chan, J.Y.C., et al., *Cognitive training interventions and depression in mild cognitive impairment and dementia: a systematic review and meta-analysis of randomized controlled trials*. Age and Ageing, 2020. **49**(5): p. 738-747.
366. Ledbetter, C., A.L. Moore, and T. Mitchell, *Cognitive Effects of ThinkRx Cognitive Rehabilitation Training for Eleven Soldiers with Brain Injury: A Retrospective Chart Review*. Frontiers in Psychology, 2017. **8**.
367. Ledreux, A., et al., *Differential Effects of Physical Exercise, Cognitive Training, and Mindfulness Practice on Serum BDNF Levels in Healthy Older Adults: A Randomized Controlled Intervention Study*. Journal of Alzheimer's Disease, 2019. **71**: p. 1245-1261.
368. Wright, J.H., et al., *Computer-Assisted Cognitive-Behavior Therapy and Mobile Apps for Depression and Anxiety*. Current Psychiatry Reports, 2019. **21**(7): p. 62.
369. Zhang, H., et al., *Computerized multi-domain cognitive training reduces brain atrophy in patients with amnesic mild cognitive impairment*. Translational Psychiatry, 2019. **9**(1): p. 48.
370. Zhang, M., et al., *Attention and Cognitive Bias Modification Apps: Review of the Literature and of Commercially Available Apps*. JMIR Mhealth Uhealth, 2018. **6**(5): p. e10034.
371. Gurupur, V.P. and T.T.H. Wan, *Challenges in implementing mHealth interventions: a technical perspective*. Mhealth, 2017. **3**: p. 32.
372. Ratanawong, J.P., et al., *Achieving the potential of mHealth in medicine requires challenging the ethos of care delivery*. Prim Health Care Res Dev, 2022. **23**: p. e18.
373. Cosco, T.D., et al., *Mobilizing mHealth Data Collection in Older Adults: Challenges and Opportunities*. JMIR Aging, 2019. **2**(1): p. e10019.
374. Kokorelias, K.M., et al., *Inclusion of Older Adults in Digital Health Technologies to Support Hospital-to-Home Transitions: Secondary Analysis of a Rapid Review and Equity-Informed Recommendations*. JMIR Aging, 2022. **5**(2): p. e35925.
375. Mugueta-Aguinaga, I. and B. Garcia-Zapirain, *Is Technology Present in Frailty? Technology a Back-up Tool for Dealing with Frailty in the Elderly: A Systematic Review*. Aging Dis, 2017. **8**(2): p. 176-195.
376. Brall, C., P. Schröder-Bäck, and E. Maeckelberghe, *Ethical aspects of digital health from a justice point of view*. Eur J Public Health, 2019. **29**(Supplement_3): p. 18-22.
377. Cheraghi-Sohi, S., et al., *A study to explore the usefulness of a mobile health application to support people with mild cognitive and/or communication impairment due to dementia and their carers*. DIGITAL HEALTH, 2023. **9**: p. 20552076231173560.
378. Tajudeen, F.P., et al., *Understanding User Requirements for a Senior-Friendly Mobile Health Application*. Geriatrics (Basel), 2022. **7**(5).
379. Paul, M., et al., *Digitization of healthcare sector: A study on privacy and security concerns*. ICT Express, 2023. **9**(4): p. 571-588.

380. Schroeder, T., M. Haug, and H. Gewald, *Data Privacy Concerns Using mHealth Apps and Smart Speakers: Comparative Interview Study Among Mature Adults*. JMIR Form Res, 2022. **6**(6): p. e28025.
381. Wang, R.H., et al., *Proactive and Ongoing Analysis and Management of Ethical Concerns in the Development, Evaluation, and Implementation of Smart Homes for Older Adults With Frailty*. JMIR Aging, 2023. **6**: p. e41322.
382. De Sutter, E., et al., *Implementation of Electronic Informed Consent in Biomedical Research and Stakeholders' Perspectives: Systematic Review*. J Med Internet Res, 2020. **22**(10): p. e19129.
383. Delgado, J., et al., *Bias in algorithms of AI systems developed for COVID-19: A scoping review*. J Bioeth Inq, 2022. **19**(3): p. 407-419.
384. Abernethy, A., et al., *The Promise of Digital Health: Then, Now, and the Future*. NAM Perspect, 2022. **2022**.
385. Bhatt, P., et al., *Emerging Artificial Intelligence-Empowered mHealth: Scoping Review*. JMIR Mhealth Uhealth, 2022. **10**(6): p. e35053.
386. Chen, C., S. Ding, and J. Wang, *Digital health for aging populations*. Nature Medicine, 2023. **29**(7): p. 1623-1630.
387. Lavalley, D.C., et al., *mHealth and patient generated health data: stakeholder perspectives on opportunities and barriers for transforming healthcare*. mHealth, 2019. **6**.
388. Dinh-Le, C., et al., *Wearable Health Technology and Electronic Health Record Integration: Scoping Review and Future Directions*. JMIR Mhealth Uhealth, 2019. **7**(9): p. e12861.
389. Zhang, X. and R. Saltman, *Impact of Electronic Health Record Interoperability on Telehealth Service Outcomes*. JMIR Med Inform, 2022. **10**(1): p. e31837.
390. Torab-Miandoab, A., et al., *Interoperability of heterogeneous health information systems: a systematic literature review*. BMC Med Inform Decis Mak, 2023. **23**(1): p. 18.
391. Liu, N., et al., *Mobile health applications for older adults: a systematic review of interface and persuasive feature design*. J Am Med Inform Assoc, 2021. **28**(11): p. 2483-2501.
392. Gerke, S., T. Minssen, and G. Cohen, *Chapter 12 - Ethical and legal challenges of artificial intelligence-driven healthcare*, in *Artificial Intelligence in Healthcare*, A. Bohr and K. Memarzadeh, Editors. 2020, Academic Press. p. 295-336.
393. Jacobson, N.C., et al., *Ethical dilemmas posed by mobile health and machine learning in psychiatry research*. Bull World Health Organ, 2020. **98**(4): p. 270-276.
394. Corral-Pérez, J., et al., *Risk and Protective Factors for Frailty in Pre-Frail and Frail Older Adults*. International Journal of Environmental Research and Public Health, 2023. **20**(4): p. 3123.
395. Woo, J., *Challenges of population ageing: putting frailty as a cornerstone of health and social care systems*. European Geriatric Medicine, 2018. **9**(3): p. 273-276.
396. Manfredi, G., et al., *Prevalence of frailty status among the European elderly population: Findings from the Survey of Health, Aging and Retirement in Europe*. Geriatrics & Gerontology International, 2019. **19**(8): p. 723-729.
397. Midão, L., et al., *Frailty Status and Polypharmacy Predict All-Cause Mortality in Community Dwelling Older Adults in Europe*. Int J Environ Res Public Health, 2021. **18**(7).
398. Guo, Y., et al., *Frailty in Older Patients Undergoing Hemodialysis and Its Association with All-Cause Mortality: A Prospective Cohort Study*. Clin Interv Aging, 2022. **17**: p. 265-275.
399. Young, H.M.L., et al., *Living with frailty and haemodialysis: a qualitative study*. BMC Nephrol, 2022. **23**(1): p. 260.

400. Pereira, A., et al., *Pre-Frailty and Frailty in Dialysis and Pre-Dialysis Patients: A Systematic Review of Clinical and Biochemical Markers*. Int J Environ Res Public Health, 2021. **18**(18).
401. Fenn, J., C.-S. Tan, and S. George, *Development, validation and translation of psychological tests*. BJPsych Advances, 2020. **26**: p. 306-315.
402. Sousa, V.D. and W. Rojjanasirrat, *Translation, adaptation and validation of instruments or scales for use in cross-cultural health care research: a clear and user-friendly guideline*. J Eval Clin Pract, 2011. **17**(2): p. 268-74.
403. Chang, R., et al., *Web-based software applications for frailty assessment in older adults: a scoping review of current status with insights into future development*. BMC Geriatr, 2021. **21**(1): p. 723.

ANNEXES

Annex 1 - Detailed prevalence of the criteria used in frailty assessment.

		FRAILTY CRITERIA														
		EXHAUSTION			APPETITE			SLOWNESS			LOW ACTIVITY			WEAKNESS		
		OVERALL	MALE	FEMALE	OVERALL	MALE	FEMALE	OVERALL	MALE	FEMALE	OVERALL	MALE	FEMALE	OVERALL	MALE	FEMALE
AUSTRIA	Overall (n=2901)	29.5 (29.1-29.9)	25.0 (24.5-25.5)	32.7 (32.1-33.3)	8.4 (8.2-8.6)	6.0 (5.8-6.3)	10.0 (9.7-10.4)	5.5 (5.3-5.6)	4.8 (4.6-5.1)	5.9 (5.6-6.1)	12.6 (12.3-12.8)	13.6 (13.2-14.0)	11.9 (11.5-12.3)	13.0 (12.7-13.2)	11.6 (11.2-11.9)	14.0 (13.6-14.4)
	50-64 (n=1000)	20.8 (20.3-21.4)	19.6 (18.8-20.3)	21.6 (20.9-22.4)	6.7 (6.4-7.0)	6.0 (5.6-6.4)	7.2 (6.7-7.6)	1.5 (1.4-1.7)	1.5 (1.3-1.7)	1.5 (1.3-1.7)	7.7 (7.4-8.0)	11.5 (11.0-12.1)	5.2 (4.8-5.6)	3.7 (3.5-3.9)	2.8 (2.5-3.1)	4.3 (4.0-4.7)
	65-74 (n=1089)	26.4 (25.8-27.2)	22.7 (21.8-23.6)	29.4 (28.4-30.5)	7.3 (7.0-7.7)	5.6 (5.2-6.1)	8.7 (8.2-9.3)	3.4 (3.2-3.7)	3.8 (3.4-4.1)	3.1 (2.8-3.5)	9.8 (9.4-10.3)	11.5 (10.8-12.1)	8.5 (8.0-9.1)	8.7 (8.3-9.1)	6.7 (6.2-7.2)	10.3 (9.7-11.0)
	75-84 (n=632)	42.2 (41.1-43.4)	33.0 (31.6-34.4)	49.0 (47.4-50.8)	9.8 (9.3-10.4)	5.6 (5.1-6.2)	12.9 (12.0-13.8)	9.5 (9.0-10.0)	7.9 (7.2-8.6)	10.7 (9.9-11.5)	15.5 (14.8-16.2)	12.0 (11.2-12.9)	18.1 (17.1-19.2)	23.1 (22.3-23.9)	21.0 (19.9-22.1)	24.7 (23.5-25.9)
	≥85 (n=180)	56.1 (54.1-58.2)	43.3 (40.7-45.9)	63.7 (60.6-66.9)	18.3 (17.2-19.6)	9.0 (7.8-10.2)	23.9 (22.0-25.9)	25.0 (23.6-26.4)	19.4 (17.7-21.2)	28.3 (26.3-30.5)	42.8 (41.0-44.6)	37.3 (35.0-39.8)	46.0 (43.4-48.8)	54.4 (52.4-56.5)	55.2 (52.4-58.2)	54.0 (51.1-56.9)
GERMANY	Overall (n=4094)	32.6 (32.2-33.0)	29.4 (28.9-30.0)	35.6 (35.0-36.3)	6.2 (6.0-6.4)	5.2 (5.0-5.5)	7.1 (6.8-7.4)	4.1 (3.9-4.2)	3.6 (3.4-3.8)	4.6 (4.4-4.9)	12.0 (11.8-12.3)	11.2 (10.9-11.6)	13.0 (12.7-13.4)	10.6 (10.3-10.8)	8.3 (8.0-8.6)	13.0 (12.6-13.4)
	50-64 (n=1904)	31.0 (30.3-31.7)	28.0 (27.1-28.9)	33.3 (32.3-34.3)	5.1 (4.9-5.4)	4.0 (3.7-4.4)	6.0 (5.6-6.4)	1.2 (1.1-1.3)	0.9 (0.7-1.0)	1.5 (1.3-1.7)	8.1 (7.8-8.4)	8.9 (8.4-9.4)	7.5 (7.0-7.9)	3.5 (3.2-3.7)	2.9 (2.7-3.2)	3.9 (3.6-4.2)
	65-74 (n=1284)	28.8 (28.1-29.6)	26.5 (25.5-27.5)	31.3 (30.2-32.4)	4.8 (4.5-5.1)	5.8 (5.3-6.3)	3.8 (3.5-4.2)	2.8 (2.6-3.0)	3.4 (3.0-3.7)	2.2 (2.0-2.5)	9.3 (8.9-9.7)	9.3 (8.7-9.9)	9.3 (8.7-9.9)	6.8 (6.4-7.1)	4.6 (4.2-5.0)	9.1 (8.5-9.7)
	75-84 (n=753)	35.5 (34.4-36.5)	31.4 (30.0-32.8)	40.4 (38.8-41.9)	8.1 (7.6-8.6)	6.3 (5.7-7.0)	10.2 (9.5-11.0)	7.8 (7.4-8.3)	5.4 (4.8-6.0)	10.8 (10.0-11.7)	16.2 (15.5-16.9)	12.4 (11.6-13.3)	20.8 (19.7-21.9)	17.8 (17.1-18.5)	14.4 (13.5-15.3)	21.9 (20.8-23.1)
	≥85 (n=153)	49.7 (47.7-51.7)	44.7 (42.2-47.4)	54.6 (51.7-57.5)	12.4 (11.5-13.4)	6.6 (5.6-7.7)	18.2 (16.6-19.9)	15.0 (14.0-16.1)	14.5 (13.0-16.1)	15.6 (14.1-17.2)	34.0 (32.4-35.6)	29.0 (26.9-31.1)	39.0 (36.6-41.5)	46.4 (44.5-48.3)	36.8 (34.5-39.3)	55.8 (53.0-58.9)
	Overall (n=3682)	37.5 (37.0-38.0)	32.3 (31.7-33.0)	41.9 (41.2-42.6)	6.1 (5.9-6.3)	4.5 (4.2-4.7)	7.5 (7.2-7.8)	2.7 (2.6-2.8)	2.4 (2.2-2.5)	3.0 (2.8-3.2)	8.7 (8.5-8.9)	8.3 (8.0-8.6)	9.0 (8.7-9.4)	10.4 (10.1-10.6)	8.9 (8.6-9.2)	11.7 (11.3-12.1)
SWEDEN	50-64 (n=1029)	38.0 (37.3-38.7)	31.1 (30.2-32.1)	43.5 (42.4-44.6)	4.1 (3.8-4.3)	2.2 (2.0-2.5)	5.6 (5.2-6.0)	1.3 (1.1-1.4)	1.1 (0.9-1.3)	1.4 (1.2-1.6)	5.5 (5.3-5.8)	5.5 (5.1-5.9)	5.6 (5.2-6.0)	3.5 (3.3-3.7)	1.8 (1.5-2.0)	4.9 (4.5-5.3)
	65-74 (n=1508)	30.8 (30.0-31.5)	26.3 (25.3-27.3)	34.5 (33.4-35.7)	5.7 (5.4-6.0)	4.1 (3.7-4.5)	7.1 (6.6-7.6)	1.8 (1.6-2.0)	1.2 (1.0-1.4)	2.3 (2.0-2.6)	6.4 (6.1-6.8)	5.0 (4.6-5.4)	7.7 (7.1-8.2)	6.1 (5.8-6.4)	5.6 (5.1-6.0)	6.6 (6.1-7.1)
	75-84 (n=877)	42.4 (41.3-43.6)	40.0 (38.5-41.6)	44.9 (43.3-46.6)	7.9 (7.4-8.4)	7.0 (6.3-7.6)	8.8 (8.1-9.6)	4.3 (4.0-4.7)	3.6 (3.2-4.1)	5.1 (4.6-5.7)	12.1 (11.5-12.7)	12.6 (11.7-13.5)	11.6 (10.8-12.4)	18.1 (17.4-18.9)	16.0 (15.0-17.0)	20.4 (19.3-21.5)
	≥85 (n=268)	50.4 (48.4-52.4)	44.2 (41.6-46.9)	56.1 (53.2-59.1)	13.8 (12.8-14.9)	11.6 (10.3-13.1)	15.8 (14.3-17.5)	10.1 (9.2-11.0)	10.9 (9.6-12.2)	9.4 (8.2-10.6)	26.5 (25.1-28.0)	26.4 (24.4-28.5)	26.6 (24.6-28.7)	45.5 (43.7-47.4)	43.4 (40.9-46.1)	47.5 (44.8-50.3)
	Overall (n=4698)	34.3 (33.9-34.8)	28.8 (28.2-29.4)	39.0 (38.4-39.7)	8.9 (8.6-9.1)	7.0 (6.7-7.2)	10.5 (10.2-10.9)	6.3 (6.2-6.5)	4.4 (4.2-4.7)	8.0 (7.7-8.3)	18.0 (17.6-18.3)	16.1 (15.7-16.5)	19.7 (19.2-20.2)	29.7 (29.3-30.1)	27.5 (26.9-28.1)	31.6 (31.0-32.2)
	50-64 (n=1788)	26.5 (25.9-27.1)	21.3 (20.5-22.1)	30.6 (29.7-31.5)	4.7 (4.4-5.0)	3.3 (3.0-3.7)	5.8 (5.4-6.2)	2.2 (2.0-2.4)	2.2 (1.9-2.4)	2.2 (1.9-2.5)	11.4 (11.0-11.8)	12.6 (12.0-13.2)	10.5 (10.0-11.1)	12.2 (11.8-12.7)	10.6 (10.1-11.2)	13.5 (12.9-14.1)
SPAIN	65-74 (n=1492)	33.2 (32.5-34.0)	28.6 (27.6-29.7)	37.4 (36.3-38.6)	8.0 (7.6-8.4)	6.4 (5.9-6.9)	9.5 (8.9-10.1)	4.8 (4.5-5.1)	2.8 (2.5-3.2)	6.5 (6.0-7.0)	14.9 (14.4-15.4)	12.0 (11.3-12.7)	17.5 (16.7-18.3)	26.1 (25.4-26.8)	23.4 (22.5-24.4)	28.5 (27.5-29.5)
	75-84 (n=1072)	43.9 (42.8-45.1)	33.9 (32.5-35.4)	53.1 (51.4-54.9)	13.8 (13.2-14.5)	9.9 (9.2-10.7)	17.4 (16.4-18.4)	11.2 (10.6-11.8)	6.8 (6.2-7.5)	15.2 (14.3-16.2)	25.7 (24.9-26.6)	20.7 (19.6-21.8)	30.4 (29.1-31.8)	53.5 (52.2-54.7)	51.1 (49.4-52.8)	55.6 (53.8-57.5)
	≥85 (n=346)	55.8 (53.7-57.9)	57.0 (54.0-60.0)	54.9 (52.0-57.9)	22.3 (21.0-23.6)	21.2 (19.4-23.1)	23.1 (21.2-25.0)	22.8 (21.5-24.2)	17.2 (15.6-18.9)	27.2 (25.2-29.3)	46.0 (44.1-47.9)	40.4 (37.9-43.0)	50.3 (47.5-53.1)	77.2 (74.8-79.6)	74.2 (70.8-77.6)	79.5 (76.0-83.1)
	Overall (n=4508)	34.6 (34.2-35.1)	26.7 (26.1-27.2)	41.8 (41.1-42.5)	10.2 (10.0-10.5)	7.9 (7.6-8.2)	12.4 (12.0-12.7)	5.4 (5.2-5.5)	3.9 (3.7-4.1)	6.9 (6.6-7.1)	32.9 (32.4-33.3)	29.4 (28.9-30.0)	36.4 (35.8-37.1)	19.2 (18.9-19.5)	17.7 (17.2-18.1)	20.1 (20.1-21.1)
	50-64 (n=1933)	28.5 (27.9-29.1)	20.7 (19.9-21.5)	34.4 (33.4-35.4)	8.4 (8.0-8.7)	6.7 (6.3-7.2)	9.6 (9.1-10.2)	1.3 (1.2-1.4)	1.2 (1.0-1.4)	1.4 (1.2-1.6)	28.9 (28.2-29.5)	28.6 (27.7-29.6)	29.0 (28.1-30.0)	5.9 (5.7-6.2)	4.6 (4.2-5.0)	7.0 (6.6-7.5)
ITALY	Overall (n=4508)	34.6 (34.2-35.1)	26.7 (26.1-27.2)	41.8 (41.1-42.5)	10.2 (10.0-10.5)	7.9 (7.6-8.2)	12.4 (12.0-12.7)	5.4 (5.2-5.5)	3.9 (3.7-4.1)	6.9 (6.6-7.1)	32.9 (32.4-33.3)	29.4 (28.9-30.0)	36.4 (35.8-37.1)	19.2 (18.9-19.5)	17.7 (17.2-18.1)	20.1 (20.1-21.1)
	50-64 (n=1933)	28.5 (27.9-29.1)	20.7 (19.9-21.5)	34.4 (33.4-35.4)	8.4 (8.0-8.7)	6.7 (6.3-7.2)	9.6 (9.1-10.2)	1.3 (1.2-1.4)	1.2 (1.0-1.4)	1.4 (1.2-1.6)	28.9 (28.2-29.5)	28.6 (27.7-29.6)	29.0 (28.1-30.0)	5.9 (5.7-6.2)	4.6 (4.2-5.0)	7.0 (6.6-7.5)

FRANCE	65-74 (n=1540)	34.9 (34.1-35.7)	27.0 (26.1-28.1)	42.0 (40.8-43.3)	9.4 (8.9-9.8)	7.1 (6.6-7.6)	11.4 (10.8-12.1)	4.4 (4.1-4.6)	2.6 (2.3-2.9)	6.0 (5.5-6.5)	28.7 (28.0-29.4)	25.5 (24.6-26.5)	31.6 (30.5-32.7)	15.3 (14.7-15.8)	13.3 (12.6-14.0)	17.0 (16.3-17.9)
	75-84 (n=888)	41.7 (40.6-42.8)	33.1 (31.7-34.6)	51.3 (49.6-53.1)	12.5 (11.9-13.1)	9.6 (8.8-10.3)	15.8 (14.9-16.8)	9.7 (9.2-10.2)	8.3 (7.6-9.0)	11.3 (10.5-12.1)	38.4 (37.3-39.5)	31.0 (29.7-32.4)	46.8 (45.1-48.5)	37.7 (36.7-38.8)	36.9 (35.5-38.5)	38.6 (37.1-40.2)
	≥85 (n=147)	48.3 (46.4-50.3)	40.5 (38.1-43.1)	56.2 (53.3-59.2)	17.7 (16.5-18.9)	13.5 (12.1-15.0)	21.9 (20.1-23.8)	20.4 (19.2-21.7)	12.2 (10.8-13.6)	28.8 (26.7-31.0)	57.8 (55.7-60.0)	46.0 (43.3-48.7)	69.9 (66.6-73.2)	59.2 (57.1-61.4)	56.8 (53.8-59.8)	61.6 (58.6-64.8)
	Overall (n=3630)	40.1 (39.6-40.6)	33.3 (32.7-33.9)	45.3 (44.5-46.0)	9.2 (9.0-9.5)	7.0 (6.7-7.2)	10.8 (10.5-11.2)	6.2 (6.0-6.4)	5.1 (4.9-5.4)	6.8 (6.5-7.1)	18.8 (18.5-19.2)	14.9 (14.5-15.3)	21.7 (21.2-22.2)	16.6 (16.3-16.9)	14.5 (14.1-14.9)	18.3 (17.8-18.7)
	50-64 (n=1551)	35.1 (34.4-35.8)	29.3 (28.4-30.2)	39.8 (38.8-40.9)	6.6 (6.3-6.9)	5.6 (5.2-6.0)	7.4 (6.9-7.9)	2.5 (2.3-2.6)	2.0 (1.8-2.3)	2.8 (2.5-3.1)	14.4 (14.0-14.9)	12.6 (12.0-13.2)	15.9 (15.3-16.6)	5.0 (4.8-5.3)	3.6 (3.3-3.9)	6.2 (5.8-6.6)
	65-74 (n=1094)	36.0 (35.2-36.8)	28.1 (27.1-29.2)	42.6 (41.4-43.9)	7.2 (6.9-7.6)	5.0 (4.6-5.5)	9.1 (8.5-9.7)	3.7 (3.5-4.0)	4.4 (4.0-4.8)	3.2 (2.9-3.6)	14.7 (14.2-15.2)	12.3 (11.6-12.9)	16.8 (16.0-17.6)	10.8 (10.3-11.2)	8.0 (7.5-8.6)	13.1 (12.4-13.8)
	75-84 (n=707)	49.4 (48.2-50.6)	45.0 (43.4-46.6)	52.6 (50.8-54.4)	14.0 (13.4-14.7)	11.7 (10.9-12.6)	15.7 (14.7-16.6)	10.3 (9.8-10.9)	7.4 (6.7-8.1)	12.5 (11.6-13.4)	23.1 (22.2-23.9)	14.4 (13.5-15.4)	29.3 (28.0-30.7)	29.7 (28.8-30.7)	26.2 (25.0-27.5)	32.3 (30.9-33.7)
	≥85 (n=278)	60.1 (57.9-62.3)	46.2 (43.5-48.9)	66.8 (63.7-70.1)	19.4 (18.2-20.7)	9.9 (8.7-11.2)	24.1 (22.2-26.1)	25.5 (24.2-27.0)	18.7 (17.0-20.5)	28.9 (26.8-31.1)	48.9 (47.0-50.9)	39.6 (37.1-42.1)	53.5 (50.7-56.4)	69.1 (66.8-71.4)	70.3 (67.1-73.7)	68.5 (65.2-71.8)
	Overall (n=3543)	33.2 (32.7-33.6)	31.4 (30.8-32.0)	34.5 (33.9-35.1)	6.4 (6.3-6.6)	4.3 (4.1-4.5)	8.1 (7.8-8.4)	4.7 (4.6-4.9)	4.2 (3.9-4.4)	5.3 (5.0-5.5)	8.9 (8.7-9.1)	7.7 (7.4-8.0)	9.9 (9.6-10.2)	9.6 (9.4-9.8)	8.8 (8.5-9.2)	10.3 (10.0-10.7)
	50-64 (n=1757)	32.2 (31.5-32.9)	29.9 (29.0-30.8)	34.13 (33.2-35.1)	3.8 (3.5-4.0)	2.76 (2.5-3.1)	4.58 (4.2-5.0)	1.4 (1.2-1.5)	1.13 (0.96-1.33)	1.56 (1.36-1.79)	5.2 (4.9-5.5)	5.40 (5.02-5.81)	4.99 (4.62-5.39)	1.8 (1.6-1.9)	0.88 (0.7-1.1)	2.5 (2.2-2.8)
	65-74 (n=1108)	27.2 (26.5-27.9)	28.2 (27.2-29.2)	26.1 (25.2-27.1)	4.6 (4.3-4.9)	3.4 (3.1-3.8)	5.8 (5.3-6.2)	3.7 (3.4-4.0)	3.1 (2.8-3.4)	4.3 (3.9-4.7)	6.4 (6.1-6.8)	5.8 (5.3-6.3)	7.0 (6.5-7.6)	5.5 (5.2-5.8)	5.1 (4.6-5.5)	6.0 (5.5-6.4)
	75-84 (n=510)	38.2 (37.2-39.3)	35.0 (33.6-36.5)	41.0 (39.5-42.6)	10.4 (9.8-11.0)	8.0 (7.3-8.7)	12.5 (11.6-13.3)	9.0 (8.5-9.6)	7.6 (6.9-8.3)	10.3 (9.5-11.1)	12.9 (12.3-13.6)	9.3 (8.6-10.1)	16.1 (15.2-17.1)	17.8 (17.1-18.6)	15.6 (14.7-16.6)	19.8 (18.7-20.9)
	≥85 (n=168)	50.6 (48.6-52.6)	43.6 (41.0-46.2)	54.7 (51.9-57.7)	18.5 (17.3-19.7)	6.5 (5.5-7.5)	25.5 (23.5-27.5)	16.1 (15.0-17.2)	16.1 (14.6-17.8)	16.0 (14.5-17.7)	29.2 (27.7-30.7)	24.2 (22.3-26.2)	32.1 (29.9-34.4)	47.6 (45.7-49.6)	50.0 (47.3-52.9)	46.2 (43.6-49.0)
	Overall (n=4349)	33.2 (32.7-33.6)	28.6 (28.0-29.2)	37.0 (36.4-37.7)	11.4 (11.2-11.7)	8.3 (8.0-8.6)	14.1 (13.7-14.5)	6.6 (6.4-6.8)	4.7 (4.5-5.0)	8.3 (8.0-8.6)	20.9 (20.6-21.3)	20.6 (20.1-21.1)	21.4 (20.9-21.9)	22.2 (21.8-22.5)	20.5 (20.0-21.0)	23.8 (23.3-24.3)
	50-64 (n=2045)	28.4 (27.8-29.1)	23.6 (22.8-24.5)	31.7 (30.7-32.7)	10.0 (9.7-10.4)	7.1 (6.7-7.6)	12.0 (11.4-12.6)	2.1 (1.9-2.2)	2.1 (1.8-2.3)	2.1 (1.8-2.3)	16.6 (16.1-17.1)	18.2 (17.5-18.9)	15.6 (14.9-16.2)	8.6 (8.3-9.0)	9.0 (8.5-9.6)	8.3 (7.8-8.8)
	65-74 (n=1269)	30.4 (29.7-31.2)	26.4 (25.4-27.4)	34.4 (33.3-35.6)	9.3 (8.9-9.7)	7.1 (6.6-7.7)	11.4 (10.8-12.1)	5.4 (5.1-5.7)	3.8 (3.5-4.2)	6.9 (6.4-7.4)	18.4 (17.9-19.0)	18.4 (17.6-19.3)	18.5 (17.7-19.3)	18.2 (17.6-18.8)	14.8 (14.0-15.5)	21.6 (20.7-22.5)
	75-84 (n=855)	39.3 (38.2-40.4)	35.7 (34.3-37.2)	42.4 (40.8-44.0)	14.3 (13.6-14.9)	9.4 (8.6-10.1)	18.5 (17.5-19.6)	11.2 (10.7-11.8)	6.3 (5.7-7.0)	15.4 (14.5-16.4)	27.5 (26.6-28.4)	23.8 (22.6-25.0)	30.7 (29.3-32.0)	39.2 (38.1-40.3)	36.2 (34.8-37.7)	41.7 (40.2-43.3)
	≥85 (n=180)	54.4 (52.4-56.5)	46.2 (43.5-48.9)	62.9 (59.9-66.1)	20.6 (19.3-21.9)	16.5 (14.9-18.2)	24.7 (22.8-26.8)	23.9 (22.6-25.3)	18.7 (17.0-20.5)	29.2 (27.1-31.4)	37.8 (36.1-39.5)	34.1 (31.8-36.4)	41.6 (39.1-44.2)	67.8 (65.5-70.1)	65.9 (62.8-69.2)	69.7 (66.4-73.0)
GREECE	Overall (n=2705)	28.4 (28.0-28.9)	23.1 (22.5-23.6)	33.0 (32.3-33.6)	6.5 (6.3-6.7)	5.7 (5.5-6.0)	7.2 (6.9-7.5)	1.9 (1.8-2.1)	1.9 (1.7-2.0)	2.0 (1.9-2.2)	9.5 (9.2-9.7)	10.5 (10.2-10.9)	8.6 (8.2-8.9)	11.6 (11.4-11.9)	9.7 (9.4-10.1)	13.3 (12.9-13.7)
	50-64 (n=1033)	26.0 (25.4-26.7)	21.1 (20.3-21.9)	29.6 (28.7-30.6)	5.5 (5.2-5.8)	5.3 (4.9-5.7)	5.7 (5.3-6.1)	0.4 (0.3-0.5)	0.5 (0.4-0.6)	0.3 (0.2-0.5)	7.5 (7.1-7.8)	10.4 (9.9-11.0)	5.3 (4.9-5.7)	3.3 (3.1-3.5)	3.2 (2.9-3.6)	3.3 (3.0-3.7)
	65-74 (n=946)	24.8 (24.2-25.5)	20.1 (19.2-20.9)	29.6 (28.5-30.6)	5.6 (5.3-5.9)	4.5 (4.1-4.9)	6.7 (6.2-7.2)	1.7 (1.5-1.9)	1.9 (1.7-2.2)	1.5 (1.2-1.7)	8.0 (7.7-8.4)	9.8 (9.2-10.4)	6.3 (5.8-6.8)	6.4 (6.1-6.8)	4.7 (4.3-5.1)	8.2 (7.6-8.7)
	75-84 (n=546)	34.6 (33.6-35.6)	28.1 (26.8-29.4)	40.6 (39.0-42.1)	7.7 (7.2-8.2)	6.5 (5.9-7.2)	8.7 (8.0-9.5)	2.9 (2.6-3.2)	2.7 (2.3-3.1)	3.2 (2.7-3.6)	10.8 (10.2-11.4)	10.0 (9.3-10.8)	11.5 (10.7-12.4)	22.9 (22.1-23.7)	18.5 (17.4-19.5)	26.9 (25.7-28.2)
	≥85 (n=180)	40.6 (38.8-42.4)	33.3 (31.1-35.7)	45.4 (42.8-48.1)	12.2 (11.3-13.2)	11.1 (9.8-12.5)	13.0 (11.6-14.5)	8.9 (8.1-9.8)	6.9 (6.0-8.1)	10.2 (9.0-11.5)	22.8 (21.5-24.1)	15.3 (13.8-16.9)	27.8 (25.8-29.9)	48.9 (47.0-50.9)	43.1 (40.5-45.7)	52.8 (50.0-55.7)
SWITZERLAND	Overall (n=5333)	37.3 (36.8-37.7)	31.5 (30.9-32.2)	42.1 (41.4-42.8)	12.0 (11.8-12.3)	10.0 (9.7-10.4)	13.8 (13.4-14.2)	6.4 (6.2-6.6)	4.8 (4.6-5.1)	7.7 (7.4-8.0)	18.1 (17.7-18.4)	15.8 (15.3-16.2)	20.0 (19.5-20.4)	15.0 (14.7-15.3)	13.7 (13.3-14.1)	16.1 (15.7-16.5)
	50-64 (n=2576)	36.0 (35.3-36.7)	30.1 (29.2-31.0)	40.8 (39.7-41.9)	9.4 (9.0-9.7)	7.8 (7.3-8.3)	10.6 (10.1-11.2)	2.8 (2.6-3.0)	2.7 (2.4-3.0)	2.8 (2.5-3.1)	12.3 (11.9-12.7)	10.4 (9.9-11.0)	13.8 (13.2-14.5)	4.3 (4.0-4.5)	3.2 (2.9-3.5)	5.2 (4.8-5.6)
	65-74 (n=1528)	32.4 (31.6-33.2)	27.2 (26.2-28.2)	37.8 (36.0-38.4)	8.8 (8.4-9.2)	7.0 (6.5-7.5)	10.4 (9.8-11.0)	4.5 (4.2-4.7)	3.0 (2.7-3.4)	5.8 (5.3-6.2)	12.8 (12.3-13.3)	12.5 (11.8-13.2)	13.0 (12.3-13.7)	10.4 (10.0-10.9)	9.1 (8.5-9.7)	11.6 (11.0-12.3)
	75-84 (n=912)	42.4 (41.3-43.6)	35.6 (34.1-37.0)	47.9 (46.3-49.7)	18.0 (17.3-18.7)	15.6 (14.6-16.6)	19.9 (18.9-21.0)	9.8 (9.2-10.3)	7.9 (7.2-8.6)	11.2 (10.4-12.1)	26.9 (26.0-27.8)	23.2 (22.1-24.4)	29.8 (28.5-31.1)	28.2 (27.3-29.1)	27.4 (26.2-28.7)	28.8 (27.5-30.1)
	≥85 (n=317)	51.1 (49.1-53.1)	47.2 (44.6-50.0)	54.3 (51.5-57.3)	24.9 (23.6-26.3)	20.1 (18.4-22.0)	28.9 (26.8-31.1)	25.6 (24.2-27.0)	16.0 (14.4-17.6)	33.5 (31.3-35.9)	48.6 (46.7-50.6)	38.9 (36.5-41.4)	56.7 (53.7-59.7)	58.0 (56.0-60.2)	54.9 (52.0-57.8)	60.7 (57.7-63.8)
Overall		31.0	27.9	33.5	8.5	6.9	10.0	7.7	6.24	8.8	28.0	26.7	28.6	29.6	27.4	31.1

CZECH REPUBLIC	(n=1579)	(30.6-31.4)	(27.4-28.5)	(32.9-34.1)	(8.3-8.8)	(6.6-7.2)	(9.7-10.3)	(7.5-7.9)	(5.97-6.52)	(8.5-9.2)	(27.6-28.4)	(26.2-27.3)	(28.0-29.2)	(29.2-30.0)	(26.9-28.0)	(30.5-31.7)
	50-64 (n=546)	20.3 (19.8-20.9)	19.1 (18.3-19.8)	21.2 (20.4-21.9)	5.3 (5.0-5.6)	6.1 (5.6-6.5)	4.8 (4.5-5.2)	2.7 (2.6-3.0)	1.9 (1.6-2.1)	3.3 (3.0-3.7)	22.9 (22.3-23.5)	17.2 (16.5-17.9)	26.6 (25.7-27.5)	14.3 (13.8-14.7)	11.6 (11.1-12.2)	16.0 (15.3-16.7)
	65-74 (n=569)	29.2 (28.4-29.9)	25.6 (24.6-26.6)	32.1 (31.0-33.2)	6.3 (6.0-6.7)	2.8 (2.5-3.1)	9.2 (8.6-9.8)	5.1 (4.8-5.4)	3.9 (3.6-4.3)	6.0 (5.6-6.5)	26.5 (25.8-27.2)	28.4 (27.3-29.4)	25.1 (24.1-26.1)	25.3 (24.6-26.0)	20.9 (20.0-21.8)	28.9 (27.9-29.9)
	75-84 (n=368)	43.5 (42.4-44.6)	36.6 (35.1-38.1)	49.7 (48.0-51.5)	14.1 (13.5-14.8)	9.7 (9.0-10.5)	18.1 (17.1-19.2)	14.9 (14.3-15.6)	11.4 (10.6-12.3)	18.1 (17.1-19.2)	32.3 (31.4-33.3)	34.9 (33.4-36.3)	30.1 (28.7-31.4)	48.4 (47.2-49.6)	46.3 (44.7-48.0)	50.3 (48.6-52.0)
	≥85 (n=96)	63.5 (61.4-65.8)	63.0 (60.0-66.2)	64.0 (60.9-67.2)	20.8 (19.6-22.1)	21.7 (20.0-23.7)	20.0 (18.3-21.8)	26.0 (24.6-27.5)	26.1 (24.1-28.2)	26.0 (24.0-28.1)	50.0 (48.1-52.0)	50.0 (47.3-52.9)	50.0 (47.3-52.9)	81.3 (78.8-83.8)	91.3 (87.6-95.1)	72.0 (68.7-75.4)
	Overall (n=4427)	35.5 (35.0-35.9)	30.1 (29.5-30.7)	39.2 (38.5-39.9)	7.5 (7.3-7.8)	7.1 (6.8-7.4)	7.9 (7.6-8.2)	5.6 (5.4-5.7)	5.0 (4.8-5.3)	6.1 (5.8-6.4)	16.8 (16.5-17.1)	16.0 (15.6-16.5)	17.3 (16.9-17.8)	13.7 (13.4-14.0)	12.4 (12.0-12.8)	14.5 (14.1-14.9)
	50-64 (n=1607)	30.2 (29.5-30.8)	25.1 (24.2-25.9)	33.3 (32.4-34.3)	5.9 (5.6-6.2)	6.0 (5.6-6.5)	5.8 (5.4-6.3)	2.7 (2.5-2.9)	3.8 (3.4-4.1)	2.1 (1.9-2.4)	12.1 (11.7-12.6)	11.9 (11.3-12.5)	12.3 (11.7-12.9)	5.4 (5.1-5.6)	3.4 (3.1-3.8)	6.6 (6.1-7.0)
	65-74 (n=1803)	29.5 (28.7-30.2)	24.9 (24.0-25.9)	32.7 (31.6-33.8)	6.8 (6.4-7.1)	5.9 (5.4-6.3)	7.4 (6.9-8.0)	4.3 (4.0-4.6)	4.3 (3.9-4.7)	4.4 (4.0-4.8)	14.6 (14.1-15.2)	14.7 (13.9-15.4)	14.6 (13.9-15.4)	8.7 (8.3-9.1)	8.1 (7.6-8.7)	9.1 (8.6-9.7)
	75-84 (n=860)	47.0 (45.8-48.2)	39.4 (37.9-41.0)	52.6 (50.9-54.4)	10.5 (9.9-11.0)	7.9 (7.2-8.6)	12.4 (11.6-13.3)	9.0 (8.4-9.5)	5.7 (5.1-6.3)	11.4 (10.6-12.2)	20.3 (19.6-21.1)	17.4 (16.4-18.4)	22.6 (21.4-23.8)	25.6 (24.7-26.5)	22.8 (21.7-24.0)	27.6 (26.4-29.0)
	≥85 (n=157)	59.2 (57.1-61.4)	55.3 (52.4-58.3)	63.0 (59.9-66.2)	12.1 (11.2-13.1)	15.8 (14.3-17.4)	8.6 (7.5-9.9)	17.2 (16.1-18.4)	13.2 (11.8-14.7)	21.0 (19.2-22.9)	41.4 (39.6-43.2)	40.8 (38.3-43.4)	42.0 (39.5-44.6)	48.4 (46.5-50.4)	51.3 (48.6-54.2)	45.7 (43.1-48.4)
POLAND	Overall (n=1628)	45.3 (44.7-45.8)	37.8 (37.1-38.5)	51.1 (50.4-51.9)	10.3 (10.1-10.6)	7.8 (7.5-8.1)	12.3 (11.9-12.7)	8.4 (8.2-8.6)	7.2 (6.9-7.5)	8.9 (8.6-9.3)	25.2 (24.8-25.6)	23.5 (23.0-24.0)	26.3 (25.8-26.9)	17.8 (17.5-18.1)	16.5 (16.0-16.9)	19.0 (18.6-19.5)
	50-64 (n=799)	34.0 (33.4-34.7)	28.9 (28.0-29.8)	38.1 (37.1-39.2)	7.1 (6.8-7.5)	4.5 (4.2-4.9)	9.2 (8.7-9.7)	1.9 (1.7-2.0)	2.0 (1.8-2.2)	1.8 (1.6-2.0)	12.0 (11.6-12.4)	11.6 (11.1-12.2)	12.3 (11.8-12.9)	4.6 (4.4-4.9)	3.4 (3.1-3.7)	5.6 (5.21-6.02)
	65-74 (n=503)	45.1 (44.2-46.0)	38.8 (37.6-40.0)	50.6 (49.2-51.9)	9.1 (8.7-9.6)	7.8 (7.2-8.3)	10.3 (9.7-11.0)	7.2 (6.8-7.5)	7.8 (7.2-8.3)	6.6 (6.2-7.2)	20.7 (20.1-21.3)	21.1 (20.3-22.0)	20.3 (19.4-21.2)	11.3 (10.9-11.8)	9.9 (9.3-10.5)	12.6 (11.9-13.2)
	75-84 (n=258)	61.2 (59.9-62.6)	50.0 (48.3-51.8)	70.7 (68.7-72.8)	18.2 (17.5-19.0)	14.4 (13.5-15.4)	21.4 (20.3-22.6)	14.7 (14.1-15.4)	15.3 (14.3-16.2)	14.3 (13.4-15.2)	47.7 (46.5-48.9)	44.9 (43.3-46.6)	50.0 (48.3-51.8)	39.9 (38.8-41.0)	36.4 (35.0-37.9)	42.9 (41.3-44.5)
	≥85 (n=68)	64.7 (62.5-67.0)	50.0 (47.3-52.9)	72.7 (69.4-76.2)	11.8 (10.8-12.8)	8.3 (7.2-9.6)	13.6 (12.2-15.2)	32.4 (30.8-34.0)	12.5 (11.2-14.0)	43.2 (40.6-45.8)	57.4 (55.3-59.5)	41.7 (39.2-44.3)	65.9 (62.8-69.2)	58.8 (56.7-61.0)	62.5 (59.4-65.7)	56.8 (53.9-59.9)
	Overall (n=1427)	33.5 (33.1-34.0)	26.7 (26.1-27.3)	39.8 (39.1-40.5)	8.7 (8.5-8.9)	6.2 (5.9-6.5)	11.2 (10.8-11.5)	4.0 (3.9-4.2)	3.7 (3.5-3.9)	4.4 (4.2-4.6)	12.8 (12.6-13.1)	10.3 (9.9-10.6)	15.3 (14.9-15.7)	14.7 (14.4-15.0)	13.1 (12.7-13.5)	16.2 (15.7-16.6)
LUXEMBOURG	50-64 (n=771)	31.5 (30.9-32.2)	23.6 (22.8-24.5)	37.4 (36.4-38.5)	6.1 (5.8-6.4)	5.2 (4.8-5.6)	6.8 (6.4-7.3)	1.2 (1.0-1.3)	1.2 (1.0-1.4)	1.1 (1.0-1.3)	7.3 (6.9-7.6)	5.8 (5.4-6.2)	8.4 (7.9-8.9)	5.4 (5.2-5.7)	3.6 (3.3-4.0)	6.8 (6.4-7.3)
	65-74 (n=430)	31.4 (30.6-32.2)	20.8 (20.0-21.7)	42.6 (41.3-43.9)	9.1 (8.7-9.5)	6.3 (5.9-6.8)	12.0 (11.3-12.6)	4.0 (3.7-4.2)	2.3 (2.0-2.6)	5.7 (5.3-6.2)	13.0 (12.5-13.5)	11.8 (11.1-12.4)	14.4 (13.6-15.1)	10.0 (9.6-10.4)	6.8 (6.3-7.3)	13.4 (12.7-14.1)
	75-84 (n=175)	40.6 (39.5-41.7)	40.5 (38.9-42.0)	40.7 (39.2-42.3)	10.9 (10.3-11.4)	9.0 (8.3-9.8)	12.8 (11.9-13.7)	6.3 (5.9-6.7)	7.9 (7.2-8.6)	4.7 (4.1-5.2)	17.7 (17.0-18.5)	13.5 (12.6-14.4)	22.1 (21.0-23.3)	29.1 (28.2-30.1)	32.6 (31.2-34.0)	25.6 (24.4-26.8)
	≥85 (n=51)	35.3 (33.7-37.0)	32.0 (29.8-34.3)	38.5 (36.1-41.0)	15.7 (14.6-16.8)	4.0 (3.3-4.9)	26.9 (24.9-29.0)	13.7 (12.7-14.8)	12.0 (10.7-13.4)	15.4 (13.9-17.0)	29.4 (27.9-31.0)	20.0 (18.3-21.8)	38.5 (36.1-41.0)	47.1 (45.2-49.0)	40.0 (37.6-42.6)	53.9 (51.0-56.8)
	Overall (n=1412)	36.9 (36.4-37.3)	26.0 (25.4-26.5)	45.7 (45.0-46.4)	11.9 (11.7-12.2)	8.5 (8.2-8.9)	14.6 (14.2-15.0)	9.4 (9.2-9.7)	7.1 (6.8-7.4)	11.4 (11.0-11.8)	27.9 (27.5-28.3)	24.9 (24.4-25.4)	30.6 (30.0-31.2)	32.7 (32.3-33.2)	31.8 (31.2-32.4)	33.5 (32.8-34.1)
	50-64 (n=572)	30.1 (29.4-30.7)	16.4 (15.7-17.1)	39.4 (38.4-40.5)	9.8 (9.4-10.2)	6.0 (5.6-6.5)	12.4 (11.8-13.0)	3.0 (2.8-3.2)	1.7 (1.5-2.0)	3.8 (3.5-4.2)	20.1 (19.6-20.6)	16.4 (15.7-17.1)	22.7 (21.9-23.5)	14.3 (13.9-14.8)	10.8 (10.2-11.3)	16.8 (16.1-17.5)
PORTUGAL	65-74 (n=543)	35.2 (34.4-36.0)	25.9 (24.9-26.9)	43.2 (41.9-44.4)	10.5 (10.1-10.9)	7.2 (6.7-7.7)	13.4 (12.7-14.1)	10.1 (9.7-10.6)	6.8 (6.3-7.3)	13.0 (12.3-13.7)	25.2 (24.6-25.9)	22.7 (21.8-23.6)	27.4 (26.4-28.4)	31.1 (30.4-31.9)	32.3 (31.2-33.4)	30.1 (29.1-31.2)
	75-84 (n=245)	46.5 (45.4-47.7)	34.9 (33.5-36.4)	58.8 (57.0-60.7)	15.9 (15.2-16.6)	13.5 (12.6-14.4)	18.5 (17.5-19.6)	14.3 (13.6-15.0)	11.9 (11.1-12.8)	16.8 (15.8-17.8)	39.2 (38.1-40.3)	32.5 (31.2-34.0)	46.2 (44.6-47.9)	54.3 (53.0-55.6)	52.4 (50.6-54.2)	56.3 (54.5-58.2)
	≥85 (n=52)	55.8 (53.7-57.9)	55.0 (52.1-58.0)	56.3 (53.4-59.3)	19.2 (18.0-20.5)	15.0 (13.5-16.6)	21.9 (20.1-23.8)	28.8 (27.4-30.4)	25.0 (23.1-27.0)	31.3 (29.1-33.5)	51.9 (49.9-54.0)	60.0 (57.0-63.1)	46.9 (44.2-49.6)	82.7 (80.2-85.3)	90.0 (86.3-93.8)	78.1 (74.7-81.7)
	Overall (n=3834)	31.0 (30.6-31.4)	25.6 (25.1-26.2)	34.9 (34.3-35.6)	6.5 (6.3-6.7)	5.3 (5.1-5.6)	7.4 (7.1-7.7)	9.6 (9.3-9.8)	8.0 (7.7-8.4)	10.6 (10.2-10.9)	10.8 (10.6-11.1)	11.5 (11.1-11.9)	10.4 (10.0-10.7)	15.6 (15.3-15.9)	13.9 (13.5-14.3)	16.9 (16.4-17.3)
	50-64 (n=1678)	24.9 (24.3-25.5)	20.2 (19.5-21.0)	28.3 (27.4-29.2)	4.5 (4.2-4.7)	3.7 (3.4-4.0)	5.0 (4.7-5.4)	2.8 (2.6-3.0)	2.7 (2.4-3.0)	2.9 (2.6-3.2)	4.5 (4.3-4.8)	6.0 (5.6-6.4)	3.5 (3.2-3.8)	4.1 (3.9-4.4)	2.1 (1.9-2.4)	5.5 (5.1-5.9)
	65-74 (n=1244)	28.8 (28.1-29.5)	23.8 (22.9-24.8)	33.0 (31.9-34.1)	5.3 (5.0-5.6)	4.7 (4.3-5.2)	5.8 (5.3-6.3)	7.8 (7.4-8.2)	7.4 (6.9-7.9)	8.2 (7.6-8.7)	8.2 (7.8-8.6)	8.6 (8.0-9.2)	7.9 (7.4-8.4)	10.4 (9.9-10.8)	9.1 (8.5-9.7)	11.4 (10.8-12.1)
SLOVENIA	75-84 (n=722)	41.8 (40.7-43.0)	35.3 (33.8-36.8)	46.3 (44.6-48.0)	10.8 (10.2-11.4)	6.5 (5.9-7.2)	13.7 (12.8-14.7)	19.0 (18.2-19.7)	14.4 (13.5-15.3)	22.1 (21.0-23.3)	19.7 (18.9-20.4)	19.9 (18.8-21.0)	19.5 (18.5-20.6)	33.0 (32.0-34.0)	30.5 (29.2-31.9)	34.7 (33.2-36.1)

	≥85 (n=190)	44.7 (42.9-46.6)	37.0 (34.6-39.5)	49.6 (46.9-52.4)	11.6 (10.7-12.6)	13.7 (12.3-15.2)	10.3 (9.0-11.6)	28.9 (27.5-30.5)	23.3 (21.4-25.3)	32.5 (30.3-34.8)	33.2 (31.6-34.8)	31.5 (29.3-33.8)	34.2 (31.9-36.6)	54.7 (52.7-56.8)	54.8 (51.9-57.8)	54.7 (51.8-57.7)
ESTONIA	Overall (n=4856)	51.3 (50.8-51.9)	47.1 (46.4-47.9)	53.9 (53.1-54.7)	7.3 (7.1-7.5)	6.1 (5.8-6.3)	8.0 (7.7-8.3)	7.4 (7.2-7.6)	6.7 (6.5-7.0)	7.8 (7.5-8.1)	14.2 (13.9-14.4)	13.5 (13.1-13.9)	14.5 (14.0-14.9)	16.1 (15.8-16.4)	14.7 (14.3-15.1)	17.0 (16.5-17.4)
	50-64 (n=1941)	44.1 (43.3-44.9)	38.1 (37.1-39.2)	48.0 (46.8-49.2)	4.8 (4.6-5.1)	4.1 (3.7-4.4)	5.4 (5.0-5.8)	3.0 (2.8-3.2)	2.5 (2.2-2.8)	3.3 (3.0-3.6)	8.2 (7.9-8.6)	9.2 (8.7-9.7)	7.6 (7.2-8.1)	5.0 (4.8-5.3)	2.8 (2.5-3.1)	6.5 (6.1-7.0)
	65-74 (n=1425)	49.7 (48.7-50.6)	48.1 (46.8-49.4)	50.7 (49.3-52.1)	6.3 (6.0-6.7)	5.1 (4.7-5.6)	7.1 (6.6-7.6)	5.8 (5.4-6.1)	7.0 (6.5-7.5)	5.0 (4.6-5.5)	10.8 (10.4-11.3)	10.5 (9.9-11.1)	11.0 (10.4-11.7)	11.5 (11.1-12.0)	10.1 (9.5-10.7)	12.4 (11.7-13.1)
	75-84 (n=1200)	61.3 (60.0-62.7)	56.9 (55.0-58.7)	63.6 (61.7-65.6)	10.0 (9.5-10.6)	8.5 (7.8-9.2)	10.8 (10.0-11.6)	12.8 (12.1-13.4)	10.0 (9.2-10.8)	14.1 (13.2-15.1)	21.9 (21.1-22.7)	19.5 (18.4-20.6)	23.3 (22.0-24.4)	30.9 (30.0-31.9)	30.4 (29.1-31.8)	31.2 (29.8-32.6)
	≥85 (n=290)	71.4 (69.1-73.8)	66.4 (63.2-69.6)	74.2 (70.9-77.7)	17.6 (16.4-18.8)	14.4 (13.0-16.0)	19.4 (17.7-21.2)	24.5 (23.1-25.9)	20.2 (18.5-22.0)	26.9 (24.9-29.0)	40.0 (38.3-41.8)	34.6 (32.4-37.0)	43.0 (40.5-45.7)	56.2 (54.1-58.3)	57.7 (54.8-60.8)	55.4 (52.5-58.4)
CROATIA	Overall (n=2210)	43.0 (42.5-43.5)	36.5 (35.9-37.2)	48.6 (47.8-49.3)	9.4 (9.2-9.7)	7.2 (6.9-7.5)	11.1 (10.8-11.5)	8.7 (8.5-8.9)	5.8 (5.5-6.1)	10.6 (10.2-11.0)	16.7 (16.4-17.1)	16.0 (15.6-16.5)	17.1 (16.7-17.6)	20.0 (19.7-20.3)	17.0 (16.5-17.4)	22.3 (21.8-22.8)
	50-64 (n=1182)	35.6 (34.9-36.3)	27.8 (30.0-28.8)	41.5 (40.4-42.6)	6.6 (6.3-6.9)	5.5 (5.1-5.9)	7.4 (7.0-7.9)	3.9 (3.7-4.1)	3.1 (2.9-3.5)	4.5 (4.1-4.8)	8.7 (8.4-9.1)	10.8 (10.2-11.4)	7.1 (6.7-7.6)	5.4 (5.1-5.7)	4.5 (4.2-4.9)	6.1 (5.7-6.5)
	65-74 (n=666)	42.9 (42.1-43.8)	35.5 (34.3-36.6)	50.2 (48.8-51.5)	8.7 (8.3-9.1)	6.4 (6.0-6.9)	10.9 (10.3-11.6)	5.3 (4.9-5.6)	4.6 (4.2-5.0)	5.9 (5.4-6.4)	14.4 (13.9-14.9)	14.7 (14.0-15.4)	14.2 (13.5-14.9)	15.9 (15.4-16.5)	14.1 (13.4-14.8)	17.7 (16.9-18.5)
	75-84 (n=311)	50.2 (49.0-51.4)	42.5 (41.0-44.2)	55.9 (54.1-57.8)	12.5 (11.9-13.2)	10.5 (9.7-11.3)	14.1 (13.2-15.1)	15.4 (14.8-16.1)	11.2 (10.4-12.0)	18.6 (17.6-19.7)	27.0 (26.1-27.9)	22.4 (21.3-23.6)	30.5 (29.2-31.9)	38.9 (37.8-40.0)	30.6 (29.3-32.0)	45.2 (43.6-46.9)
	≥85 (n=51)	64.7 (62.5-67.0)	72.2 (68.9-75.6)	60.6 (57.6-63.7)	19.6 (18.4-20.9)	11.1 (9.8-12.5)	24.2 (22.4-26.3)	31.4 (29.8-33.0)	11.1 (9.8-12.5)	42.4 (39.9-45.1)	43.1 (41.3-45.0)	33.3 (31.1-35.7)	48.5 (45.8-51.3)	66.7 (64.4-69.0)	61.1 (58.1-64.3)	69.7 (66.5-73.1)
	Overall (n=60816)	35.7 (35.2-36.1)	30.1 (29.5-30.7)	40.1 (39.4-40.7)	8.3 (8.1-8.6)	6.6 (6.3-6.9)	9.7 (9.4-10.1)	5.5 (5.4-5.7)	4.5 (4.3-4.7)	6.4 (6.1-6.7)	16.2 (15.9-16.5)	15.1 (14.7-15.6)	17.0 (16.6-17.5)	15.8 (15.5-16.1)	14.3 (13.9-14.7)	17.0 (16.6-17.5)
TOTAL	50-64 (n=25712)	30.7 (30.1-31.4)	25.2 (24.4-26.1)	34.8 (33.8-35.8)	6.4 (6.1-6.7)	5.1 (4.7-5.5)	7.3 (6.8-7.8)	2.1 (1.9-2.3)	1.9 (1.7-2.1)	2.2 (2.0-2.5)	11.9 (11.5-12.3)	11.8 (11.3-12.4)	11.9 (11.3-12.5)	6.1 (5.8-6.4)	4.7 (4.4-5.1)	7.2 (6.7-7.6)
	65-74 (n=20041)	33.2 (32.4-33.9)	28.0 (27.0-29.1)	37.7 (36.6-38.9)	7.4 (7.0-7.8)	5.7 (5.2-6.2)	8.9 (8.3-9.5)	4.8 (4.5-5.1)	4.1 (3.7-4.5)	5.4 (4.9-5.8)	14.6 (14.1-15.1)	14.1 (13.4-14.9)	15.1 (14.3-15.8)	13.3 (12.8-13.8)	11.5 (10.8-12.1)	14.9 (14.1-15.6)
	75-84 (n=11891)	44.5 (43.4-45.7)	38.2 (36.7-39.7)	50.1 (48.4-51.8)	12.2 (11.6-12.8)	9.4 (8.7-10.2)	14.6 (13.7-15.5)	10.7 (10.1-11.3)	8.4 (7.7-9.2)	12.5 (11.7-13.4)	24.2 (23.3-25.0)	20.8 (19.7-21.9)	27.2 (25.9-28.5)	32.7 (31.7-33.7)	30.3 (29.0-31.7)	34.7 (33.3-36.2)
	≥85 (n=3172)	54.2 (52.2-56.3)	48.7 (46.0-51.5)	58.2 (55.3-61.3)	17.1 (16.0-18.3)	12.8 (11.4-14.3)	20.2 (18.5-22.1)	22.0 (20.7-23.4)	16.3 (14.8-18.0)	25.9 (23.9-27.9)	41.1 (39.4-43.0)	35.7 (33.4-38.1)	45.1 (42.5-47.8)	59.4 (57.3-61.6)	58.9 (55.9-61.9)	60.1 (57.1-63.3)

Annex 2 – PROSPERO register of the systematic review.

Pre-frailty and frailty in dialysis and pre-dialysis patients - a systematic review of clinical and biological markers

To enable PROSPERO to focus on COVID-19 submissions, this registration record has undergone basic automated checks for eligibility and is published exactly as submitted. PROSPERO has never provided peer review, and usual checking by the PROSPERO team does not endorse content. Therefore, automatically published records should be treated as any other PROSPERO registration. Further detail is provided [here](#).

Citation

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Review question [1 change]

The aim of this systematic review is to summarise studies regarding clinical and biological markers identified in pre-frail and frail in dialysis and pre-dialysis patients

Searches [1 change]

PubMed, Embase and Web of Science

Types of study to be included [1 change]

Observational studies

Condition or domain being studied [1 change]

Frailty is known to be an aged-related syndrome characterised by increasing vulnerability to adverse health outcomes due to decreased functional and biological reserves and resistance to external stressors. Aging related clinical and biochemical markers identified in dialysis and pre-dialysis patients will be the domain to be study.

Participants/population [1 change]

Studies including pre-frail and frail in pre-dialysis and dialysis individuals

Intervention(s), exposure(s) [1 change]

Inclusion criteria: studies reporting on clinical and biological markers associated to dialysis and pre-dialysis in pre-frail and frail individuals

Comparator(s)/control [1 change]

Control: Non frail individuals

Context

Main outcome(s) [1 change]

Reporting on levels/presence of clinical and biological markers related to pre-frailty and frailty in pre-dialysis and dialysis individuals

Additional outcome(s)

None

Data extraction (selection and coding) [1 change]

The literature search will be done using the databases PubMed, Embase and Web of Science. Language restrictions will be applied to include studies published in English. No restrictions will be applied to published date. The search will include the following query 'frail* OR geriatric assessment' AND 'dialys* OR hemodialys* OR haemodialys* OR 'end stage kidney disease' OR 'chronic kidney disease' AND 'marker* OR biomarker*'.

Two reviewers will independently search and extract data from databases mentioned above and the duplicates will be removed using excel tools. The same reviewers will then independently review the titles and abstracts of all articles of potential interest. The full-text of all selected articles will be reviewed for final eligibility evaluating against inclusion and exclusion criteria. Divergences will be resolved by a third reviewer through discussion.

Risk of bias (quality) assessment [1 change]

The quality of included studies will be assessed following standard methodological procedures.

Strategy for data synthesis [1 change]

The data from the included studies will be organised in tables with the following structure:

- 1) Studies characteristics (first author, publication year, country, data collection years and study type)
- 2) Sample characteristics (sampling method, size, age, gender, ethnicity, comorbidities)
- 3) Method used for frailty assessment
- 4) Clinical and biological markers
- 5) Group comparison
- 6) Outcome

Analysis of subgroups or subsets

Subgroup analysis will be applied to recognise the potential source of heterogeneity among studies

Contact details for further information

Ana Pereira

anasrbp@gmail.com

Organisational affiliation of the review

FMUP, FFUP, ICBAS, Porto4Ageing, UCIBIO REQUIMTE, Universidade do Porto

Review team members and their organisational affiliations

Ms Ana Pereira. Faculdade de Medicina da Universidade do Porto

Mr Luis Midao. ICBAS, Porto4Ageing, UCIBIO REQUIMTE, Universidade do Porto

Mr Elisio Costa. FFUP, Porto4Ageing, UCIBIO REQUIMTE, Universidade do Porto

Type and method of review

Systematic review

Anticipated or actual start date

02 November 2020

Anticipated completion date

02 November 2021

Funding sources/sponsors

Not funded or sponsored

Grant number(s)

State the funder, grant or award number and the date of award

Conflicts of interest

Language

English

Country

Portugal

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Biomarkers; Dialysis; Frailty; Humans; Kidney Failure, Chronic; Renal Dialysis

Date of registration in PROSPERO

20 November 2020

Date of first submission

20 October 2020

Stage of review at time of this submission [1 change]

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	No

Revision note

No major changes to the study, however instead of studying dialysis population only we are also including pre-dialysis population. Minor changes and updated made to the original protocol.

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

20 November 2020

02 December 2021

Annex 3 - Final version of the European Portuguese Version of
the Groningen Frailty Indicator.

Indicador de Fragilidade de Groningen – Versão Português Europeu

É capaz de levar a cabo estas tarefas de forma independente? (A utilização de recursos como uma bengala, um andarilho, uma cadeira de rodas, é considerado independente)
1. Compras
2. Andar no exterior (à volta da casa ou nas redondezas)
3. Vestir-se e despir-se
4. Ir à casa de banho
5. Que pontuação é que dá à sua própria capacidade física (0 a 10)?
6. Tem dificuldades na vida diária devido à falta de visão?
7. Tem dificuldades na vida diária devido a dificuldades auditivas?
8. Durante os últimos 6 meses perdeu involuntariamente muito peso? (3kg num mês ou 6kg em 2 meses)?
9. Toma 4 ou mais tipos diferentes de medicamentos?
10. Tem alguma queixa relacionada com a sua memória?
11. Sente, por vezes, um vazio à sua volta?
12. Sente, por vezes falta de pessoas à sua volta?
13. Sente-se abandonado?
14. Sentiu-se, recentemente, abatido ou triste?
15. Sentiu-se, recentemente, nervoso ou ansioso?
Scoring: Questões 1-4: Sim = 0; Não = 1 Questão 5: 0-6 = 1; 7-10 = 0 Questões 6-15: Não = 0; Sim = 1

