



**Muscle quality in aging: analysis of non-invasive diagnostic methods, from morphological to functional approach, for routine community implementation and identification of key factors for an exercise protocol to enhance muscle quality.**

Ph.D. dissertation developed by

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and supervised by

Dr. Maria Begoña Garcia-Zapirain Soto

Dr. Amaia Méndez Zorrilla

within the doctoral programme of Health, Well-being and Bioethics.

Bilbao, May 2025





Universidad de Deusto  
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## Abstract

Current ageing paradigm reflects the extraordinary adaptive capacity of human beings and constitutes an unprecedented societal success. However, reforming health and social systems to meet the demands of this demographic shift remains a major public health challenge. In this context, musculoskeletal disorders, especially those exacerbating aging-related conditions like sarcopenia and frailty, are a public health priority due to their impact on adverse outcomes (Alkhodary et al., 2020; Cruz-Jentoft et al., 2019; Sayer & Cruz-Jentoft, 2022). Despite the knowledge about the negative consequences of these musculoskeletal pathologies, there are still barriers and knowledge gaps. Sarcopenia, in particular, has emerged as a major concern due to its association with loss of function, frailty and dependency. Over the last decade there have been significant advances incorporating the importance of muscle function and introducing the concept of muscle quality (MQ) (Cruz-Jentoft et al., 2019). MQ encompasses muscle composition factors, including microscopic and macroscopic alterations in muscle architecture, as well as functional performance per unit of muscle mass (de Lucena Alves et al., 2023; M. S. Fragala et al., 2015). However, its assessment remains an emerging area with diagnostic tools still under development, which hampers its clinical and community implementation (Cruz-Jentoft et al., 2019).

This dissertation aligns with international and national sarcopenia guidelines, ensuring consistency with public health priorities and promoting comprehensive assessment of muscle quality and function (Basque Government, 2019, 2021; Cruz-Jentoft et al., 2019; Spain ministry of health, 2022; WHO, 2021). A key objective is to enhance the understanding and treatment of sarcopenia through a comprehensive evaluation of muscle quality and function, advocating for a shift from focusing solely on muscle mass to emphasizing strength, quality, and function. The guidelines highlight the need to advance non-invasive tools for assessing these parameters, establish optimal indicators, and determine which tools are accessible in different settings. However, their use is currently limited to research environments due to technical challenges. Therefore, a central objective is to identify the most effective and accessible tools for assessing MQ and to facilitate their implementation in clinical and community practice.

Within the non-invasive tools for the assessment of MQ, two areas can be distinguished: morphological tools, which assess muscle composition and architecture, and functional ones, which assess strength in relation to muscle mass (de Lucena Alves et al., 2023; M. S. Fragala et al., 2015). Among direct non-invasive morphological assessment tools, computed tomography (CT) and magnetic resonance imaging (MRI) provide detailed information on muscle composition; however, their high cost and radiation exposure restrict their use to research settings. In contrast, ultrasound (US) has emerged as an accessible, non-invasive alternative with a significant correlation to these imaging modalities, though it faces challenges due to the lack of standardized protocols and operator-dependent variability. Other tools, such as bioimpedance analysis, electromyography, and tensiomyography, are being explored for MQ assessment, but their application requires more standardization (Virto, Río, Méndez-Zorrilla, et al., 2024). In this context, US is a promising technique for quantifying morphological MQ due to its accessibility, speed, and strong correlation with more precise imaging, making it valuable for both clinical practice and research (Virto, Río, Angulo-Garay, et al., 2024).

However, in resource-limited settings, the assessment of muscle quality using ultrasound (US) presents accessibility challenges despite its advantages in accuracy and correlation with other imaging modalities. Therefore, although US is a precise tool with a high correlation to other techniques, this study aims to explore the integration and correlation of US with more accessible methods, such as functional muscle quantification tools. The pilot study establishes a correlation between ultrasound geometric variables and functional variables, suggesting a more accessible technique for community-based muscle quality assessment (Virto, Río, Angulo-Garay, et al., 2024). The analysis of functional MQ offers significant potential for daily use, as it involves fewer

technical challenges, making it a practical tool in clinical and community settings with limited resources.

As for functional methods, they allow a more accessible assessment of muscle quality, usually quantified through the relationship between strength and muscle mass (de Lucena Alves et al., 2023). A variety of non-invasive tools are available for assessing MQ, with handheld dynamometers and IRM tests being practical for community use, while isokinetic dynamometers and power assessments are more specialized (Abe et al., 2016; American College of Sports Medicine et al., 2009; Baechle et al., 2000; Cruz-Jentoft et al., 2019; Grgic et al., 2020; Jenner et al., 2024). For muscle mass, MRI, CT and Dual-energy X-ray Absorptiometry (DXA) are highly accurate but costly, whereas Bioelectric Impedance Analysis (BIA) and US offer more accessible and cost-effective alternatives for community settings. In the following studies of this thesis work, accessible tools were selected, given their feasibility for use in resource-limited settings and their potential for widespread application in daily practice (Albano et al., 2020; Blake & Fogelman, 2007; Correa-de-Araujo et al., 2017; Cruz-Jentoft et al., 2019; Faron et al., 2020; Jain & Vokes, 2017; Niklasson et al., 2022; Oba et al., 2021; Sconfienza et al., 2018). The measurement of strength was performed by manual handgrip dynamometer and segmental bioimpedance analysis for body composition. Despite some variations from reference methods like MRI, DXA, or CT, these tools correlate well with them, making them suitable for community settings.

The final studies of this dissertation explore in depth the multifactorial nature of sarcopenia, muscle quality, and functionality in older adults, highlighting the complex interactions among the factors involved. The results indicate that the primary determinants of sarcopenia include reduced muscle power, age, strength, body mass index (BMI), and sex, while balance, muscle and fat mass, and socioeconomic status also have a significant impact on its development and severity (Virto, Dequin, et al., 2024). Muscle quality, particularly in women, is influenced by age, BMI, muscle mass, fat mass, gait speed, squat test time (reflecting lower limb strength and power), balance, and socioeconomic level. Regarding functionality, which is closely related to gait speed and the neuromuscular and cognitive decline associated with aging, lower limb power and balance emerge as crucial factors (Virto, Río, Muñoz-Pérez, et al., 2024).

In conclusion, this dissertation outlines guidelines for developing an exercise protocol to improve muscle quality and sarcopenia, based on previous studies. It also presents a protocol for selecting non-invasive muscle quality assessment tools, focusing on key parameters. This approach aims to deepen understanding of how different factors influence sarcopenia and muscle quality, with a focus on their assessment and targeted intervention in a more precise and accessible manner, thus contributing to improvements in the health and functionality of older adults in various contexts.

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# Acronyms

<b>Notation</b>	<b>Description</b>
<b>5STS</b>	Five-repetition Chair Stand Test
<b>ANOVA</b>	Analysis of Variance
<b>BB</b>	Biceps Brachii
<b>BF</b>	Biceps Femoris
<b>BIA</b>	Bioimpedance
<b>BMI</b>	Body Mass Index
<b>BR</b>	Brachialis
<b>CG</b>	Control Group
<b>CON</b>	Low-intensity + normal speed
<b>CP</b>	Chest Press
<b>CSA</b>	Cross-Sectional Area
<b>CT</b>	Computed Tomography
<b>Dm</b>	Maximal Radial Displacement
<b>DXA</b>	Dual Energy X-ray Absorptiometry
<b>EG</b>	Exercise Group
<b>EWGSOP</b>	European Working Group on Sarcopenia in Older People
<b>GL</b>	Gastrocnemius Lateralis
<b>GLM</b>	Generalized Linear Model
<b>GM</b>	Gastrocnemius Medialis
<b>HHD</b>	Hand-held Dynamometers
<b>HITT</b>	High-Intensity Interval Training
<b>IMAT</b>	Intramuscular Adipose Tissue
<b>KE</b>	Knee Extension
<b>LE</b>	Leg Extension
<b>LF</b>	Leg Flexion
<b>LP</b>	Leg Press
<b>LPD</b>	Latissimus Pull-down
<b>LST</b>	Low-intensity + slow movement
<b>MGS</b>	Manual Grip Strength
<b>MQ</b>	Muscle Quality
<b>MQI</b>	Muscle Quality Index
<b>MRI</b>	Magnetic Resonance Imaging
<b>MSK-US</b>	Musculoskeletal Ultrasound

<b>MVIC</b>	Maximum Voluntary Isometric Contraction
<b>OLS</b>	Ordinary Least Squares
<b>PA</b>	Pennation Angle
<b>PC</b>	Preacher Curl
<b>PhA</b>	Phase Angle
<b>QF</b>	Quadriceps Femoris
<b>RF</b>	Rectus Femoris
<b>RM</b>	Repetition Max
<b>RMSE</b>	Root Mean Square Error
<b>RT</b>	Resistance Training
<b>S/W</b>	Session/Week
<b>SPPB</b>	Short Physical Performance Battery
<b>SRE</b>	Studentized Residual
<b>TA</b>	Tibialis Anterior
<b>Tc</b>	Time Contraction
<b>TMG</b>	Tensiomyography
<b>US</b>	Ultrasound Sonography
<b>VI</b>	Vastus Intermedius
<b>VL</b>	Vastus Lateralis
<b>VM</b>	Vastus Medialis



# 1 Introduction

*It always seems impossible until it's done. - Nelson Mandela*

Ageing is an international phenomenon, an expression of the adaptive capacity of human beings, both at the individual and population level. The demographic changes that our society has faced over the last century have conditioned a demographic and epidemiological transition that has generated a structural modification of populations, significantly increasing life expectancy (Preston & Biddell, 2021). While this achievement reflects the development and success of modern society, it also presents a significant challenge: the need to reform social and healthcare systems to meet the demands of this new population paradigm.

If this population trend persists, it is estimated that by 2050, the proportion of the world's population over 60 years of age will almost double from 12% in 2015 to 22% in 2050 (WHO, 2024). These projections require an adaptation of the current system, as the increase in life expectancy has not led to a similar increase in healthy life years (Crimmins, 2021). Longer life offers new opportunities; however, the focus should not only be on delaying death but on increasing quality of life over the years, avoiding disability (Pola-Ferrández et al., 2021).

In this endeavour to improve quality of life, sarcopenia emerges as a critical challenge that directly impacts the functionality and general health of older adults, being associated with increased risks of adverse outcomes such as falls, functional decline, frailty, and mortality (Cruz-Jentoft et al., 2019). Moreover, the incidence of sarcopenia increases with age, underscoring the importance of addressing this geriatric pathology (Dodds et al., 2017; R. Yu et al., 2014).

Over the past decade, there have been significant advancements in the field of sarcopenia. One pivotal advancement was the recognition of sarcopenia as an independent condition, leading to its inclusion in the International Classification of Diseases-10 in 2016 (Anker et al., 2016). Another crucial development was the incorporation of muscle function into the definition of sarcopenia. This emphasis on muscle function stemmed from its consistent demonstration as a more robust predictor of clinically relevant outcomes compared to muscle mass alone (Clark & Manini, 2008; Cruz-Jentoft & Sayer, 2019; Goodpaster et al., 2006). The updated definition proposed by European Working Group on Sarcopenia in Older People (EWGSOP) in 2019 reflects this emphasis on muscle function, the only definition that has garnered endorsement from various international scientific societies (Cruz-Jentoft & Sayer, 2019).

The updated definition proposed by the EWGSOP in 2019 reflects this emphasis on muscle function, reshaping our comprehension of sarcopenia. This definition characterizes sarcopenia as a muscle disease where diminished muscle strength takes precedence over reduced muscle mass as the primary determinant (Cruz-Jentoft et al., 2019). Since it has been observed that force and power losses occur earlier than mass losses (Goodpaster et al., 2006). In addition to incorporating measures of physical functionality, it introduces the concept of muscle quality in the diagnosis of sarcopenia (Cruz-Jentoft et al., 2019).

The definition now stands as follows: the first criterion indicating the probable presence of sarcopenia is the characteristic decrease in muscle strength, while the reduction in muscle mass and quality confirms the diagnosis. In cases where inferior physical performance is identified, sarcopenia is categorized as severe (Cruz-Jentoft et al., 2019).

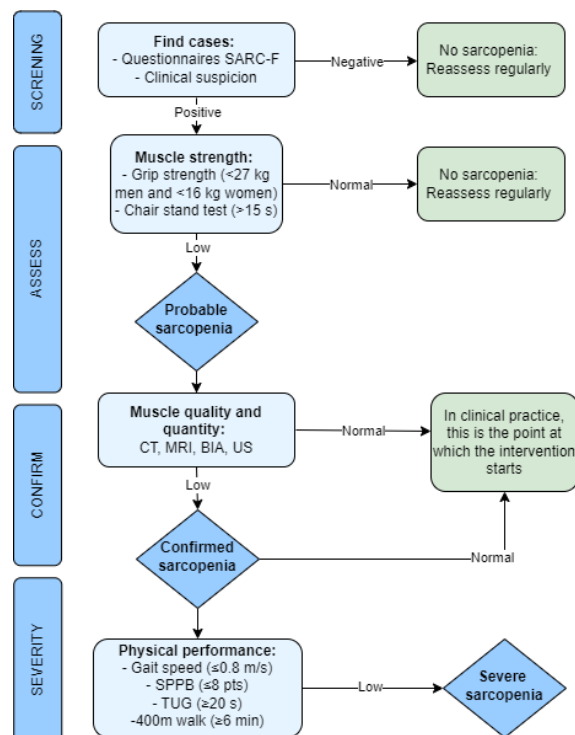


Figure 1. Classification of sarcopenia.

As mentioned previously, the update from the EWGSOP-2 underscores the significance of assessing not just the quantity of muscle but also its quality (Cruz-Jentoft et al., 2019). Muscle quality (MQ) encompasses factors of muscle composition; including both microscopic and macroscopic alterations in muscle architecture, as well as the functional output per unit of muscle mass (Cruz-Jentoft et al., 2019; de Lucena Alves et al., 2023). Specifically, MQ is typically defined by the two aforementioned domains: the morphological and the functional. The morphological domain involves direct evaluations of muscle architecture, including both microscopic and macroscopic aspects of muscle structure and composition. The functional domain pertains to indirect measurements of muscle function relative to its mass (de Lucena Alves et al., 2023). Additionally, though less frequently addressed, metabolism, thermoregulation, and signaling/myokine production are also proposed domains of muscle quality, which require further exploration for broader acceptance (Correa-de-Araujo et al., 2017; Correa-de-Araujo & Hadley, 2014; de Lucena Alves et al., 2023).

Muscle quality is a relatively new term, and consequently, the diagnostic tools for assessing it are not yet well-defined (Cruz-Jentoft et al., 2019). On one hand, there are direct quantification tools that examine the morphological domain with high sensitivity. Techniques such as Magnetic Resonance Imaging (MRI) and X-ray Computed Tomography (CT) are currently considered state-of-the-art in research on direct muscle quality assessment (Cruz-Jentoft et al., 2019; Huber et al., 2020; Sabatino et al., 2024). Additionally, methods like ultrasound, tensiomyography, and Phase Angle derived from Bioelectrical Impedance Analysis (BIA) contribute to this field (Cruz-Jentoft et al., 2019; de Lucena Alves et al., 2023). However, due to their high cost and lower accessibility, these imaging methods are primarily limited to research applications (Sergi et al., 2016).

On the other hand, MQ has also been assessed using ratios of muscle strength to appendicular skeletal muscle mass or muscle volume. These indirect methods use various formulas to assess muscle quality (functional) and have greater accessibility, making them more feasible for daily clinical practice and potential implementation in health programs. However,

there is no universal consensus on the assessment methods, which represents a significant gap highlighted by the EWGSOP (Cruz-Jentoft et al., 2019).

The EWGSOP states that there are still many unknowns regarding sarcopenia, and it suggests addressing this gap by exploring MQ, determining optimal MQ indicators and developing accurate, affordable tools and measurements (Cruz-Jentoft et al., 2019).

Another challenge in sarcopenia is the high prevalence of undiagnosed cases. The existing screening tools often lack accuracy (Cruz-Jentoft et al., 2019; Cruz-Jentoft & Sayer, 2019; Ida et al., 2018; Locquet et al., 2018; Miller et al., 2018), and their impact on early detection remains uncertain (Cruz-Jentoft et al., 2019; Cruz-Jentoft & Sayer, 2019). Thus, a critical imperative is to enhance tools for sarcopenia detection while promoting the maintenance of functional capacity to mitigate disability and dependency. Globally, advocating for healthy aging is a paramount objective, as evidenced by the World Health Organization's initiative for the Decade of Healthy Ageing (WHO, 2021). Also, the EWGSOP acknowledges significant strides made but underscores the ongoing necessity for a clear definition of sarcopenia and definitive diagnostic criteria to inform clinical practice and research (Cruz-Jentoft et al., 2019). Moreover, on a national scale, initiatives like the Roadmap for Addressing Frailty, endorsed by the Public Health Commission in 2019 and updated in 2022, play a crucial role (Spain ministry of health, 2022). This initiative strategically aligns with priorities outlined in the Basque Country's Science, Technology, and Education Plan (PCTI) 2030, particularly in fostering personalized health and promoting healthy aging (Basque Government, 2021).

These gaps in understanding and these strategic initiatives prompt us to formulate the research questions that will guide this thesis, aiming to contribute to the advancement of knowledge and practice in the field of sarcopenia assessment and management:

- How can muscle quality be best assessed non-invasively in older adults? What are the most effective indicators of muscle quality predicting outcomes and analyzing the effects of exercise interventions? What factors, such as cost, accessibility, required training, and the distinctions between direct (morphological) and indirect (functional) non-invasive tools, influence the adoption and implementation of muscle quality assessments?.

- Can novel methods using advanced non-invasive tools improve our understanding and application of key muscle quality determinants in older adults in clinical and community practice?.

- What specific factors significantly influence sarcopenia, muscle quality, and functionality?

- How can an evidence-based exercise protocol be developed and implemented to effectively assess and improve muscle quality in older adults, integrating non-invasive measurement tools and tailored physical activity interventions in both clinical and community settings?

## 1.1 Hypothesis, general objective and specific objectives:

**Hypothesis:** It is hypothesized that non-invasive diagnostic methods, encompassing both morphological and functional approaches, are effective for assessing muscle quality in older adults, enabling their routine application in community settings and the identification of essential factors for the design of exercise protocols to enhance muscle quality and functionality.

**General Objective:** To demonstrate the potential of non-invasive methods for quantifying muscle quality in older adults for application in clinical and community practice, contributing to the identification and understanding of the determinants of muscle quality and its relationship with functionality and overall health.

**Specific objective I:** To identify and review direct non-invasive tools for the quantification of the morphological domain of muscle quality in older adults, with a focus on their applicability and sensitivity to detect changes following exercise interventions.

**Specific objective II:** To investigate effective indirect non-invasive tools for quantifying functional muscle quality in older adults, exploring trends, limitations, and factors such as accessibility, cost, and training, with the aim of identifying simple and accessible methods for community use.

**Specific objective III:** To establish a correlation between ultrasound-derived geometric variables of the rectus femoris and clinical and functional variables, exploring the sensitivity of direct muscle quantification tools and laying the groundwork for the potential use of these functional measures as indirect indicators of muscle quality.

**Specific objective IV:** To investigate the determinant factors of muscle quality and sarcopenia in older adults, as well as their relationship with physical functionality and overall health, using non-invasive tools for muscle quality assessment and advanced methods such as machine learning to identify key determinants and their applicability in clinical practice.

**Specific objective V:** To analyze, using regression models, the direction and magnitude of key characteristics related to functional muscle quality in older adults, with the aim of improving the application of these findings in clinical practice.

**Specific objective VI:** To determine the specific factors that influence walking speed in older adults, including muscle quality as a variable of interest, in order to improve the assessment and management of functionality in this population.

## 1.2 Research Contributions and Impact:

After presenting the framework of this dissertation, this section aims to highlight the social, scientific, economic, technological, and health system contributions and impacts of the research.

### **Social impact:**

Sarcopenia and frailty have become a public health priority due to their association with multiple adverse health outcomes, particularly in relation to musculoskeletal disorders (Alkhodary et al., 2020; Cruz-Jentoft et al., 2019; Cruz-Jentoft & Sayer, 2019). Currently, an increasing number of individuals are surpassing the age of 65, and this trend is expected to continue (INE, 2025). This aging population represents a significant challenge for health systems and public policies, as the probability of suffering from sarcopenia and frailty increases with age, leading to an increased burden on health services (Alkhodary et al., 2020; Cruz-Jentoft & Sayer, 2019). Spain, like its neighboring countries, faces a substantial social and public health challenge linked to the progressive aging of its population and the accompanying changes in the epidemiological pattern (WHO, 2024, 2021). This context underscores the importance of research that can help mitigate the epidemiological burden, enhance the quality of life for the elderly population, develop new early diagnostic tools, and alleviate the strain on healthcare systems.

This thesis project aims to align with global and national strategies that aim to contribute significantly to public health by addressing sarcopenia and frailty in older adults. The World Health Organization recently declared "aging well" as a global health priority, working in accordance with the UN Decade of Healthy Aging (2021-2030) (WHO, 2021). On the national level, the Roadmap for Addressing Frailty, approved by the Public Health Commission in 2019, and its update in 2022, are highlighted (Spain ministry of health, 2022). Focusing on strategic priorities at the regional level, this project aligns with several priorities outlined in the Basque Country's Science, Technology, and Education Plan (PCTI) 2030. These include personalized health (5.1.1.3), as the project seeks to offer individualized diagnosis and treatment. It also addresses the goal of territorial opportunities (5.1.2) by promoting a healthy lifestyle based on nutrition and physical exercise to preserve health. Regarding transversal driving initiatives (5.2), the project aligns with the goal of healthy aging (5.2.1) by aiming to foster and maintain functional capacity in older adults, thus promoting well-being in old age. Additionally, it complies with the basic technology maps (5.3) by applying artificial intelligence to select the most important characteristics of geriatric pathologies and their management (Basque Government, 2021). Finally, the project aligns with the RIS3 priorities of the Basque Government in Biosciences, as its main activity focuses on human health, including aging from both a healthcare and technological perspective (Basque Government, 2019).

### **Scientific impact:**

The expected scientific and research contributions of this thesis are manifold, addressing key challenges and advancing knowledge in the fields of sarcopenia and frailty in older adults. These challenges have been based on the documents and guidelines established by reference agencies and bodies. The main contributions are described below:

- Integration of machine learning algorithms in clinical settings for improved geriatric care and contribution to personalized medicine through advanced feature selection methods.
- Exploration of direct and indirect diagnostic tools for muscle quality assessment in aging populations.
- Comprehensive analysis of feature importance in elderly muscle quality, sarcopenia, and gait speed.

**Economic and health system contributions:**

Frailty and sarcopenia imposes substantial costs and places a significant burden on the healthcare system during the final stages of life (Álvarez-Bustos et al., 2022; Cruz-Jentoft et al., 2019; Cruz-Jentoft & Sayer, 2019). Understanding sarcopenia, muscle quality, and gait speed features is crucial for improving early diagnosis and effective stratification. By accurately identifying individuals at risk of developing sarcopenia and frailty and highlighting the most crucial factors influencing their progression and prevention within the Basque population, health interventions can be optimized. This approach aims to enhance both healthcare quality and the overall health status of the population. Moreover, emphasizing physical functionality and the role of exercise is essential. Cost-effectiveness analyses have demonstrated that multicomponent physical exercise interventions not only reduce costs but also outperform standard care scenarios for older adults at risk of falls and frailty (Alhambra-Borrás et al., 2019).

**Technologic contribution:**

While current scales and tools are used for assessing frailty and sarcopenia, there are significant gaps in our understanding, including their initiation, progression, diagnostic tools, cutoff points, and outcomes (Cruz-Jentoft et al., 2019). This project aims to address these gaps by focusing on which tools can quantify muscle quality (based on different domains) and which have early assessment capabilities. Leveraging machine learning techniques, the study aims to uncover crucial information about muscle quality, physical function and sarcopenia. This knowledge is essential to advance personalised medicine approaches tailored to the assessment of muscle quality and sarcopenia.

### 1.3 Research methodology

This section outlines the methodology employed in this dissertation's research. Given the study's nature, an experimental methodology was chosen because it enables rigorous testing of hypotheses through controlled experimentation. This dissertation has been submitted as a doctoral dissertation by publication compendium, emphasizing the dissemination of scientific publications throughout the research process, as depicted in **¡Error! No se encuentra el origen de la referencia.**. The steps shown in **¡Error! No se encuentra el origen de la referencia.** are synthesized in the following paragraphs.

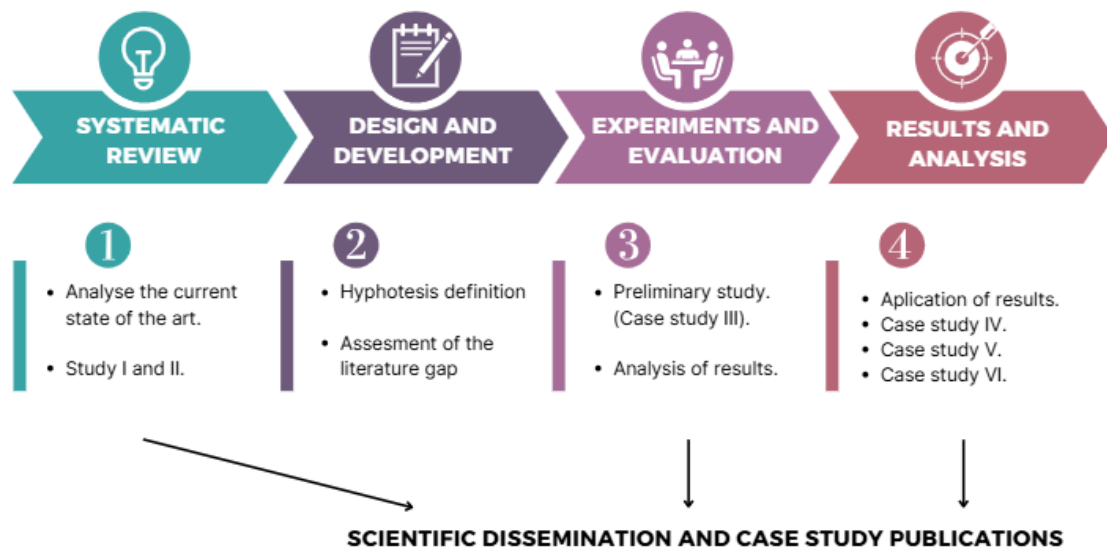


Figure 2. Research methodology.

- 1. State of the art review:** At this initial stage of the research methodology, the goal is to analyze, understand, and evaluate the current state of the art in the non-invasive direct and indirect quantification of muscle quality, focusing on functional and morphological measures, identifying the most effective tools, trends, limitations, and factors influencing their selection for clinical and community settings. To conduct the literature reviews, scientific publications and relevant documents in the field will be examined. This will allow for the identification of gaps, challenges, and emerging trends in the research area. Through this process, a theoretical foundation will be established, providing insight into the strengths and limitations of the current state of the art. This foundation will facilitate the formulation of research questions and objectives for the thesis. This stage is crucial for subsequent phases as it provides a comprehensive understanding of both the theoretical framework and practical aspects of the field. The insights gained during this stage were essential in shaping the research proposal during the PhD program and for the generation of the systematic review article.
- 2. Design and development:** Following the literature review and the establishment of the current theoretical basis, the identified literature gaps will guide the development of different research proposals and questions to be explored in subsequent stages. This approach ensures staying at the forefront of advancements in muscle quality assessment technologies and techniques, thereby strengthening the proposals by addressing the specific gaps identified in the literature.

**3. Experiments and evaluation:** This phase addresses some of the issues generated during the design and development phase. A preliminary study is carried out to correlate the direct techniques with the functional variables, with results that will serve as the basis for subsequent studies. The results obtained are carefully analyzed to measure their impact, ensuring that these results can be effectively incorporated into the development of subsequent studies.

**4. Results and final analysis:** In this final phase of the research methodology, the results obtained in the studies are analyzed and compared. This analysis not only evaluates the outcomes within the thesis framework but also contrasts them with different approaches documented in the literature. The main objective is to measure the effectiveness and strength of the proposed solutions.

By examining these methodologies comparatively, their strengths and limitations are identified, allowing for the discovery of patterns and the assessment of the implications of the research findings, particularly regarding their clinical applicability. From this comprehensive analysis, insights are gained to guide recommendations for future research directions and practical applications. Finally, the dissemination of the knowledge generated through academic publications and presentations is crucial to ensure broad impact and visibility within the academic community.

## 1.4 Structure of the thesis

This section presents an overview of the organization and content of the chapters that comprise this dissertation. The dissertation adopts a PhD by article compendium format, in which several chapters are included as articles published in peer-reviewed journals with an impact factor.

- **Chapter 1 - Introduction:** This first chapter situates the specific context of the work, explaining the overall design, methodology, concepts to be addressed, hypotheses, objectives, and the rationale and contributions of the thesis. Its primary objective is to familiarize the reader with the general concepts and research scenario to be explored.
- **Chapter 2 - Background and Related work:** This chapter will provide an overview of the background and related studies concerning the main case studies addressed throughout the thesis. It will define and clarify key terms and concepts used throughout the work, laying the groundwork for the proposed methodologies and solutions. It will begin by discussing non-invasive tools for direct quantification of muscle quality and their sensitivity to exercise interventions, offering essential technical context to underpin subsequent studies. This will be followed by a further review of indirect non-invasive tools, which aim to analyse functional muscle quality. In this way, all areas of knowledge necessary for the following case studies will be addressed.
- **Chapter 3 - Methods:** This chapter sets out the research methodology of the thesis, with a comprehensive breakdown of the approaches adopted for each case study. It details the procedures used to ensure robust data collection, analysis and interpretation in line with the research objectives.
- **Chapter 4 - Results:** This chapter presents the results of the thesis work, guiding the reader through the various phases of studies on muscle quality quantification tools, key features of muscle quality and sarcopenia, and their implications in clinical and community practice. The chapter also discusses the importance of parameters influencing gait speed in older adults. The scientific impact of the research work proposed will be thoroughly examined in this section.
- **Chapter 5 - Research mobility:** In this chapter, the focus is on exploring the research conducted during the international mobility period, focusing on how the acquired knowledge has profoundly influenced the development of the thesis. Particularly significant is its application in enhancing the psychological perspective, crucial for a comprehensive understanding of aging among older adults.
- **Chapter 6 - Conclusions:** This chapter summarizes the primary and specific objectives of this doctoral thesis, emphasizes the significant contributions of this research, and proposes promising lines for future investigation.

## 2 Background:

*Exercise is a journey, not a destination. It must be continued for the rest of your life. We do not stop exercising because we grow old - we grow old because we stop exercising. - Kenneth H. Cooper.*

This chapter provides a comprehensive overview of the key concepts underlying the contributions of this thesis. It examines the most relevant literature related to the pillars of this work, specifically the issues of frailty and sarcopenia resulting from aging. A particular focus is placed on the latest definition by the EWGSOP, which emphasizes muscle quality as a crucial parameter. The analysis of these concepts aims to offer the reader a clear understanding of the current landscape regarding aging process, musculoskeletal disorders and muscle quality and its role in major geriatric pathologies.

### 2.1 Aging process:

The aging process has been a subject of scientific inquiry since early human history. However, its intricate nature has made it difficult to understand precisely and therefore to establish a definition (Tartiere et al., 2024). Nowadays the majority of definitions of aging describe it as a gradual and heterogeneous biological process that leads to the progressive deterioration of organ systems. This process is driven by the accumulation of molecular and cellular damage in response to stressors. The outcome of aging is a gradual loss of physical and physiological integrity and a decline in tissue and organ function, which increases vulnerability to disease (Guo et al., 2022; Moqri et al., 2023; Tartiere et al., 2024). This decline is the main risk factor for major human pathologies (López-Otín et al., 2013; López-Otín, Pietrocola, et al., 2023).

Various theories on aging exist, which are mostly grouped into two main approaches: programmed (non-stochastic) theories, which postulate that aging fulfills an evolutionary function, and non-programmed (stochastic) theories, which consider it to be a consequence of accumulated damage over time (Kirkwood & Melov, 2011; Tartiere et al., 2024). The inherent complexity of this process represents one of the greatest challenges to its understanding. Therefore, in an attempt to integrate knowledge about aging, an approach was proposed in 2013 that sought to identify and categorize the main cellular and molecular hallmarks of aging (López-Otín et al., 2013; Tartiere et al., 2024). A decade later, the same authors have updated this conceptual model, incorporating the knowledge gained since then (López-Otín et al., 2013; Tartiere et al., 2024).

These major molecular hallmarks must fulfil three criteria. The first criteria refer to alterations that manifest themselves progressively over time and are dependent on the aging process. The second highlights the possibility of accelerating the aging process by intensifying the manifestation of the characteristic. Finally, one of the most relevant to our research is that there is the possibility of slowing down, halting or even reversing aging through specific therapeutic interventions targeted at each hallmark of aging (López-Otín, Blasco, et al., 2023; López-Otín, Pietrocola, et al., 2023). In the current state of the art, 12 hallmarks of aging have been proposed, representing an increase of three over those suggested in the first formulation in 2013 (López-Otín, Blasco, et al., 2023; López-Otín et al., 2013). The 12 proposed hallmarks of aging are as follows; genomic instability, epigenetic alterations, telomere attrition, loss of proteostasis, impaired macroautophagy, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis (López-Otín, Blasco, et al., 2023; López-Otín, Pietrocola, et al., 2023).

These hallmarks coexist throughout the aging process and are interrelated, so the intensification or attenuation of one of the hallmarks can influence all the other hallmarks. As a result, in practice it is common to observe the interaction between many of these hallmarks together with extrinsic factors, resulting in a dynamic and heterogeneous aging process, which is responsible over time for the varying clinical manifestations of the disease (López-Otín, Blasco, et al., 2023; Preston & Biddell, 2021). Consequently, different aging phenotypes can be found, determined by genetics, environment and behaviour.

With the aging of the population and the associated demographic changes, this phenomenon has become one of the major challenges for today's society (Preston & Biddell, 2021). The modern lifestyle, a result of the great social and technological development that humanity has experienced in recent decades, has influenced both longevity and quality of life, generating new demands and challenges for health systems and public policies.

All countries are now experiencing an increase in both the size and the proportion of older people in their populations. This shift in demographic distribution, which initially started in higher income countries, has started to spread to low-income countries as well. According to the World Health Organization (WHO), 1 in 6 people are expected to be over 60 by 2030. Moreover, it is projected that the number of people 60 and older would rise from 1 billion in 2020 to 1.4 billion in 2030. Furthermore, this population is predicted to double (to 2.1 billion) by 2050 (WHO, 2024).

In the Spanish context, if current demographic trends continue, the proportion of the population aged 65 and over, currently at 20.1%, is projected to rise to approximately 30.4% by 2050 (INE, 2022, 2024). Specifically, in the Basque Country, one of the most aged communities in Spain, individuals aged 65 and over already account for more than 25% of the population, with Eustat projections indicating that this percentage will rise to 29% by 2029 (INE, 2019).

Although we see that life expectancy continues to increase, adding years to life can be an ambiguous blessing if a good quality of life during those years is not assured (WHO, 2021). In this regard, in recent years there has been a growing interest in advocating healthy aging in which well-being and quality of life in old age are a priority, due to the increasing prevalence of age-related diseases in this population. These pathologies include metabolic, neurodegenerative, cardiovascular, skin and eye diseases, joint damage and cancer, all of which share aging as a major risk factor (Ikezoe, 2020; Tartiere et al., 2024). However, it also promotes the development of several intricate health issues that are referred to as geriatric syndromes.

During aging, complex conditions referred to as geriatric syndromes commonly emerge. Among these, frailty stands out as particularly prevalent, characterized as "a progressive decline in physiological systems that leads to decreased reserves of intrinsic capacity. This confers extreme vulnerability to stressors and increases the risk of various adverse health outcomes" (Rodríguez-Laso et al., 2018). Frailty is associated with dependency, hospitalization, institutionalization, falls, reduced quality of life, and increased mortality (Hoogendijk et al., 2019; Kojima, 2015, 2016, 2018; Kojima et al., 2016), as well as higher health care costs (Kojima, 2019). While sarcopenia, characterized by the progressive loss of skeletal muscle mass and strength, also becomes more common with age, it should not be classified as a geriatric syndrome. This is because sarcopenia can also occur in younger individuals due to factors such as physical inactivity, malnutrition, or chronic illness (Cruz-Jentoft et al., 2019). It is estimated that between 6% and 19% of individuals aged 60 and older are affected by sarcopenia, though prevalence rates vary depending on the definition used (Cruz-Jentoft et al., 2014, 2019).

Although each individual holds responsibility for their own healthy aging, which can be shaped by their habits, aging is a multifactorial phenomenon also influenced by social and structural factors. Therefore, a comprehensive public health response is essential, one that considers the different ways people age and addresses the specific needs of older adults. In this

context, the growing interest of social organizations in tackling these challenges is noteworthy, as it brings an innovative approach and reinforces the relevance of this research. This creates a synergy between individual actions, such as conducting this thesis, and collective and organizational efforts, fostering a deeper understanding of aging and promoting well-being in later life.

Focusing on the role of organizations, the United Nations (UN) declared the decade 2021-2030 as the decade of Healthy Ageing and WHO is taking the lead in this initiative. It is a collaboration between all global actors that calls for concerted, catalytic and collaborative action to promote longer and healthier living. This action plan aims to bring together the synergy of governments, civil society, international agencies, professionals, academia, the media and the private sector to promote Healthy Ageing (WHO, 2021, 2025). Healthy aging is the “process of developing and maintaining the functional ability that enables well-being in older age” (WHO, 2021). A person's physical and mental abilities, the circumstances they live in, and the manner in which they interact with their surroundings are all reflected in their functional ability (WHO, 2021).

Targeting on the national level, the Roadmap for Addressing Frailty, approved by the Public Health Commission in 2019 and updated in 2022, is a key reference (Spain ministry of health, 2022). At the regional level, the strategic priorities of the Basque Country's Science, Technology and Innovation Plan (STIP) 2030 are also aligned with the global objectives. These priorities include personalized health (5.1.1.3), healthy lifestyle through nutrition and physical activity to safeguard health (5.1.2). It also focuses on the objective of healthy aging (5.2.1), focusing on the maintenance of functional capacity in older adults, thus improving well-being in old age (Basque Government, 2021). Finally, there are priorities at regional level such as the Basque Government's RIS3 in the field of biosciences, which focus on human health, particularly aging, from both medical and technological perspectives (Basque Government, 2019).

We must bear in mind that it is not possible to approach aging and our well-being in isolation, as our habits, genetics, social environment, lifestyle and access to health services significantly influence different aspects of our lives (López-Otín, Blasco, et al., 2023). In order to know how to act, it is essential to understand the ageing process and, in this case, the effect on the muscular system of the pathologies related to this process on which this dissertation will focus. The purpose is to analyse how ageing affects the muscular system in the elderly, since, to prevent and mitigate its effects, the most effective way is to understand in depth both ageing and the related pathologies.

## 2.2 Musculoskeletal disorders:

As previously discussed, the aging process can contribute to the onset of geriatric syndromes. In this context, musculoskeletal pathologies are particularly prevalent among the elderly, primarily driven by the natural degeneration of muscle, bone, and joint tissues (Cai et al., 2024; Ikezoe, 2020). These conditions of the musculoskeletal system not only affect the physical functionality of older people, but also have an impact on the quality of life of the population, increasing the risk of falls, disability and related loss of independence, which leads to an increase in mortality (Cai et al., 2024; McGregor et al., 2014; McLeod et al., 2016). As the body ages, musculoskeletal tissues experience a decline in function, characterized by increased bone frailty, diminished cartilage resilience, decreased ligament flexibility, reduced muscle strength, and a redistribution of fat (Freemont & Hoyland, 2007; Goodpaster et al., 2006). These changes impair the tissues' ability to perform their normal roles effectively, leading to the development of prevalent musculoskeletal disorders such as osteoarthritis, osteoporosis, tendinopathies, and sarcopenia (Cai et al., 2024; Minetto et al., 2020).

Focusing solely on the muscular system, aging leads to progressive muscle atrophy, driven by alterations in both the neuromuscular system and the morphological structure of the muscle, contributing to the reduction of muscular parameters (Clark & Manini, 2008; Minetto et al., 2020; Morley et al., 2001). These reductions in muscular parameters imply both quantitative and qualitative changes in the structure and function of skeletal muscle, leading to the phenomenon of sarcopenia (Cruz-Jentoft et al., 2019; Larsson et al., 2019).

Sarcopenia has been defined by EWGSOP as a progressive and generalized disorder of skeletal muscle that is associated with an increased likelihood of developing adverse health outcomes such as falls, fractures, physical disability, frailty and mortality (Cruz-Jentoft et al., 2019). The first criterion indicating the probable presence of sarcopenia is the characteristic decrease in muscle strength, while the reduction in muscle mass and quality confirms the diagnosis. In cases where inferior physical performance is identified, sarcopenia is categorized as severe (Cruz-Jentoft et al., 2019). Sarcopenia plays a pivotal role as a key geriatric condition, closely intertwined with frailty, although it is not always associated with aging (Cattaneo et al., 2022; Cruz-Jentoft et al., 2019; Cruz-Jentoft & Sayer, 2019). In this context, frailty is described as “a progressive decline in physiological systems that leads to decreased reserves of intrinsic capacity. This confers extreme vulnerability to stressors and increases the risk of various adverse health outcomes” (Rodríguez-Laso et al., 2018). While standardized diagnostic criteria for frailty are not universally established, one of the most widely accepted frameworks is the Fried phenotype model (Faller et al., 2019). According to this model, frailty is diagnosed when three or more of the following criteria are met: unintentional weight loss, self-reported exhaustion, reduced grip strength, slow gait speed, and low levels of physical activity (Fried et al., 2001).

Frailty and sarcopenia are distinct yet overlapping syndromes that often coexist in older adults. While frailty is a more complex and multifactorial disorder, sarcopenia predominantly focuses on the musculoskeletal system (Cruz-Jentoft et al., 2019; Davies et al., 2018; Landi et al., 2015; Reijnierse et al., 2016). According to the definition of frailty phenotype by Fried et al (Fried et al., 2001), muscle dysfunction is at the core of frailty, considering that weakness, slowness, and impairment of the muscular system are characteristic features of frailty, sarcopenia is also likely a crucial physiopathological contributor and is often described as the biological foundation of physical frailty (X. Chen et al., 2014; Landi et al., 2015). Consequently, this relationship is bidirectional; musculoskeletal disorders contribute to the development of frailty syndrome, while frailty can exacerbate existing musculoskeletal diseases and increase the risk of developing new ones (Cattaneo et al., 2022; Cruz-Jentoft et al., 2019). This observation is evident in practice, where a substantial proportion of individuals with sarcopenia also experience frailty or pre-frailty. However, the prevalence of sarcopenia among frail individuals is significantly lower (Cattaneo et al., 2022; Davies et al., 2018; Mijnders et al., 2015).

### 2.3 Sarcopenia:

The concept of sarcopenia was first described in the 1890s, initially defined as an age-related decline in lean body mass that adversely affected independence, nutritional status and mobility (Cruz-Jentoft & Sayer, 2019; Rosenberg, 1997). Since that first characterisation, the concept has undergone significant refinement, driven by scientific advances in the field. A pivotal event for the definition of sarcopenia occurred in 2010, when the European Working Group on Sarcopenia in Older People (EWGSOP) incorporated muscle function, along with low muscle mass, as a defining criterion (Cruz-Jentoft et al., 2019; Fielding et al., 2011). This revised approach, in which muscle function comes to the forefront, encompasses strength, power and physical performance and has demonstrated greater clinical relevance compared to muscle mass alone. The second important landmark was the recognition of sarcopenia as a separate muscle disease, which led to its inclusion with its own diagnostic code in ICD-10-CM (Anker et al., 2016; Cao & Morley, 2016). However, despite these advances, it remains a disease for which healthcare professionals lack the standardized diagnostic tools required for clinical diagnosis and accurate identification of affected patients (Cruz-Jentoft & Sayer, 2019).

The latest significant advance in the understanding of sarcopenia has been the revision of the European consensus on its definition. This update has been enriched over the last decade by the exploration of complementary definitions by different expert groups around the world, as well as research on various aspects of sarcopenia by clinicians and researchers (L.-K. Chen et al., 2014; Morley et al., 2001; Studenski et al., 2011). Sarcopenia is now recognized as a skeletal muscle disease, or muscle failure, that can affect individuals of all ages and is not exclusively linked to aging. Also, this updated consensus reflects the evolving understanding of the multifaceted nature of sarcopenia, incorporating new research findings that emphasize not only the loss of muscle mass and functionality included in the 2010 definition but also the critical role of muscle strength (Cruz-Jentoft et al., 2010, 2019; Cruz-Jentoft & Sayer, 2019). Additionally, it highlights the importance of muscle quality and functional performance as key factors in this new consensus. Moreover, cut-off points are established for each diagnostic test, enabling a more precise approach to the evaluation and management of sarcopenia (Cruz-Jentoft et al., 2019; Cruz-Jentoft & Sayer, 2019).

Following the advancements and updates discussed regarding the definition of sarcopenia, the most widely cited definition today, supported by various scientific societies and working groups focused on sarcopenia, is the updated definition from the EWGSOP 2019 (L.-K. Chen et al., 2014; Cruz-Jentoft & Sayer, 2019). This definition characterizes sarcopenia as a progressive and generalized disorder of skeletal muscle that is associated with an increased likelihood of developing adverse health outcomes such as falls, fractures, physical disability, frailty and mortality (Cruz-Jentoft et al., 2019). The first criterion indicating the probable presence of sarcopenia is the characteristic decrease in muscle strength, while the reduction in muscle mass and quality confirms the diagnosis. In cases where inferior physical performance is identified, sarcopenia is categorized as severe (Cruz-Jentoft et al., 2019).

In these updated guidelines, the significance of muscle strength is emphasized, as it is recognized as a more effective predictor of adverse outcomes than muscle mass (Cruz-Jentoft et al., 2019; Ibrahim et al., 2016; Schaap et al., 2018). Additionally, the importance of muscle quality in the context of sarcopenia is introduced and highlighted. However, technological limitations have hindered the use of muscle quality as primary parameter in clinical practice, relegating them mainly to research settings.

Once the definition and diagnostic criteria have been established, people will be screened for sarcopenia. However, as the available tools are not sufficiently accurate, sarcopenia is often identified only after symptoms have started to manifest themselves. For this reason, case detection is carried out by means of specific questionnaires, such as the SARC-F (Cruz-Jentoft et al., 2019; Dent et al., 2018). The SARC-F is a self-reported 5-question questionnaire to screen for sarcopenia risk, with research supporting its use (Dent et al., 2018; Malmstrom et al., 2016). The questionnaire questions are based on the patient's perception of their limitations in terms of strength, ability to walk, climb stairs, get up from a chair and previous experiences with falls (Malmstrom et al., 2016). Once the questionnaires report symptoms or signs of the presence of sarcopenia among individuals, a more detailed diagnosis is carried out to determine the particular situation of each person.

For the diagnosis of sarcopenia, the EWGSOP advocates a systematic, multi-step approach, emphasizing the evaluation of three key parameters. Initially, muscle strength is assessed as a primary indicator. This is followed by the measurement of muscle mass and quality and finally, physical performance is evaluated (Cruz-Jentoft et al., 2019).

As mentioned above, the first step in assessing the presence of sarcopenia is the evaluation of muscle strength. The most commonly used tool to measure strength in the Superior extremities is the hand grip dynamometry (HG), while in the Inferior extremities the 5 sit to stand test (5-STs) is used. Grip strength is a widely accepted indicator of overall muscle strength (Bohannon & Williams Andrews, 2011; Cruz-Jentoft et al., 2010; Cruz-Jentoft & Sayer, 2019; Delinocente et al., 2021). It is measured using simple, cost-effective tests and serves as a reliable predictor of health outcomes in individuals (Leong et al., 2015). Once the HG test is performed, if grip strength is below reference values (<27kg for men and <16kg for women), the presence of sarcopenia should be suspected (Cruz-Jentoft et al., 2019). However, in older adults, other potential causes of low muscle strength, such as hand osteoarthritis or neurological disorders, must also be considered (Cruz-Jentoft et al., 2019; Cruz-Jentoft & Sayer, 2019). Leg muscular strength can be estimated using the chair stand test. The test consists of timing the time it takes a person to perform five repetitions of getting up and sitting on a chair, without the help of the arms and as quickly as possible. There are different variants of this test such as the timed standing test which counts the number of times a patient can stand up and sit down in a chair for 30 seconds (Cesari et al., 2009; Cruz-Jentoft et al., 2019). This test is a reliable measurement instrument because it has shown good intra and inter-rater reliability as well as consistency over multiple repetitions (Bohannon & Williams Andrews, 2011; Teo et al., 2013). Once the 5-STs test has been performed, if the person has not been able to perform the test in less than 15 seconds, the presence of sarcopenia should be suspected (Cruz-Jentoft et al., 2019).

Once sarcopenia is suspected, confirmation is sought through the measurement of muscle quantity and quality. For measuring muscle quantity, several methods are available. Magnetic resonance imaging (MRI) and X-ray computed tomography (CT) stand as the gold standard; however, their use in primary care is limited due to costs, portability, and the need for specialized personnel for their operation (Beaudart et al., 2020; Chianca et al., 2022; Cruz-Jentoft et al., 2019). On the other hand, the most effective procedure used to date would be Dual-energy X-ray absorptiometry (DXA). DXA provides a body composition model that includes fat, bone mineral density, and lean mass (Blake & Fogelman, 2007; Jain & Vokes, 2017). However, while it is considered a reference method for assessing total skeletal muscle mass, its lack of portability limits its use in community settings (Cruz-Jentoft et al., 2019; Scafoglieri & Clarys, 2018). In contrast to the preceding methods bioelectrical impedance analysis (BIA) is an affordable, simple, and portable technique that uses whole-body electrical conductivity to estimate body composition and can be used in individuals with and without limitations (Cruz-Jentoft et al., 2019; Sergi et al., 2016). The BIA does not measure muscle mass directly but calculates it through a conversion method based on whole body electrical conductivity, although its accuracy is limited due to a lack of standardization (Cruz-Jentoft et al., 2019; Cruz-Jentoft & Sayer, 2019).

On the other hand, the assessment of muscle quality is emphasized in the new EWGSOP guidelines, highlighting the importance of evaluating not only muscle quantity but also its quality (Cruz-Jentoft et al., 2019). Muscle quality is defined by two domains, which are the functional and the morphological ones; the former corresponds to indirect measures of muscle function in relation to mass, and the second entails direct evaluations of muscle architecture that pertain to both the microscopic and macroscopic features of muscle architecture and composition (Cruz-Jentoft et al., 2019; de Lucena Alves et al., 2023). There are a number of non-invasive methods available at the moment for direct assessment of muscle quality (morphological domain). Once again, MRI and CT are the leading technologies in the current state of the art; however, they remain limited by their complexity and cost (Beaudart et al., 2020; Chianca et al., 2022; Cruz-Jentoft et al., 2019). Furthermore, ultrasonic sonography (US) presents as a quick, inexpensive, non-invasive imaging technique and is gaining traction in clinical practice (Perkisas et al., 2018; Tagliafico et al., 2022; Virto, Río, Angulo-Garay, et al., 2024). Other methods include tensiomyography (TMG), a tool to assess neuromuscular function (Pus et al., 2023) and myotonometry, another device used for the assessment of viscoelastic properties of muscle (Garcia-Bernal et al., 2021). In addition, BIA-derived phase angle (PhA), a measure of cellular integrity and body water distribution, has recently become an important parameter for the assessment of muscle quality (Di Vincenzo et al., 2021). In contrast, the functional domain of muscle quality is often assessed using the relationship between muscle strength and appendicular skeletal muscle mass, muscle volume, or through other indirect measures (Barbat-Artigas et al., 2012; C.-J. Chang et al., 2021; Lynch et al., 1999). Although not yet sufficiently defined for clinical practice, the concept of muscle quality may prove to be a more relevant term in relation to health.

If low values of muscle quantity and quality are detected, a diagnosis of sarcopenia is confirmed. Finally, physical performance tests are conducted to assess the severity of sarcopenia (Cruz-Jentoft et al., 2019).

Physical performance is a multidimensional concept that involves the functioning of various body systems, not just the muscular one. It encompasses the musculoskeletal system, the nervous system, and other physiological systems. It is defined as the ability to perform physical tasks that enable independent living. It can be measured by various tests and the most commonly used are the gait speed, the Short Physical Performance Battery (SPPB), the Timed-Up and Go test (TUG) and the 400m test (Cruz-Jentoft et al., 2019; Cruz-Jentoft & Sayer, 2019). Gait speed is considered a vital sign and acts as a non-invasive predictor of health and functional status in older adults (Middleton et al., 2015). Assessments of gait speed are sensitive, valid and reliable (Middleton et al., 2015), among the various gait speed tests with different distance measurements, the 4 meter gait speed test is often among the most widely used (Hirabayashi et al., 2020). Research has shown that gait speed is a crucial aspect of physical function related to sarcopenia and functional independence, making it a significant predictor of frailty in older adults, the cut-off point of this test is set at 0.8m/s (Middleton et al., 2015; Navarrete-Villanueva et al., 2021). The SPPB is a commonly used clinical test for functional assessment, recognized for its strong reliability and validity (Santamaría-Peláez et al., 2023). This test consists of three components: evaluating balance (in standing, semi-tandem, and tandem positions), assessing gait speed over a distance of 4 meters (measuring the time taken to walk at a normal pace), and conducting the five-repetition sit-to-stand test (5STS) as quickly as possible (Guralnik et al., 1994). The highest possible score is 12, with a score of less than 8 points denoting poor physical performance. The TUG test evaluates agility and dynamic balance by having the participant rise from a chair, walk three meters, turn around a cone, and sit back down, all at their maximum walking speed, with a cutoff point established at 20 seconds. The 400-meter walk evaluates endurance and walking skills. Participants in this test have to finish 20 laps of 20 meters at their fastest pace, with a maximum of two rest breaks permitted, the cut-off point in this test would be 6 minutes.

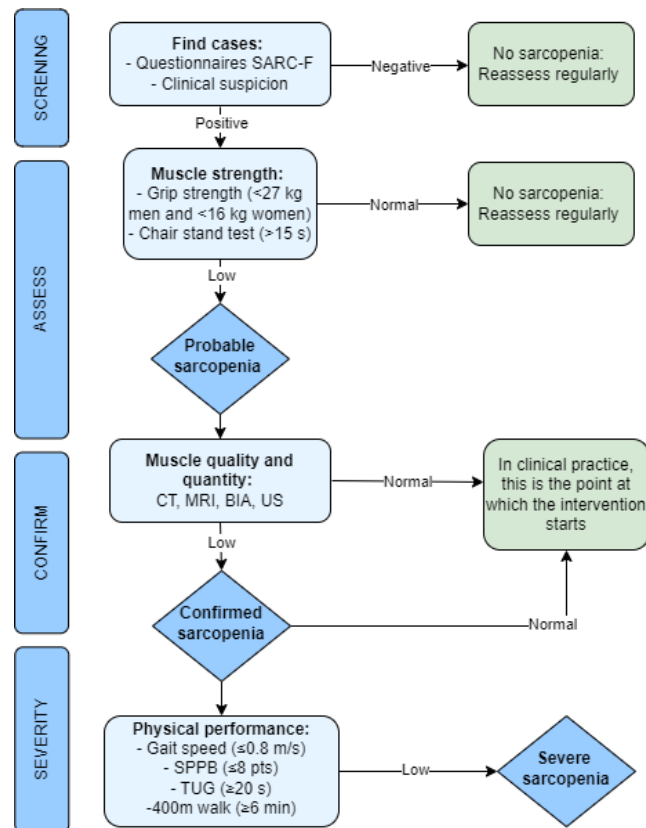


Figure 3. Sarcopenia case-finding algorithm for diagnosis and severity quantification in practice.

Adapted from: Cruz-Jentoft, A. J., Bahat, G., Bauer, J., Boirie, Y., Bruyère, O., Cederholm, T., ... & Zamboni, M. (2019). Sarcopenia: revised European consensus on definition and diagnosis. *Age and ageing*, 48(1), 16-31.

Based on these criteria established in the diagnosis of sarcopenia, a classification can be made according to the degree of severity of sarcopenia. When the examined person only meets the first criterion, low muscle strength, it is called mild sarcopenia or pre-sarcopenia. In case, in addition to the first criterion, the second one is met, low muscle mass or low muscle quality, then it is referred to as moderate sarcopenia. Finally, if, apart from meeting the above criteria, there is a reduction in physical performance, it is categorized as severe sarcopenia (Cruz-Jentoft et al., 2019; Cruz-Jentoft & Sayer, 2019; Sanchez-Tocino et al., 2024).

Although diagnostic criteria and cutoff points have been recently defined and consolidated, sarcopenia remains an underdiagnosed and, consequently, undertreated condition (Cruz-Jentoft & Sayer, 2019; Sanchez-Tocino et al., 2024). This is particularly concerning given its already high prevalence, affecting between 6% and 19% of the population over 60, depending on the definition used (Cruz-Jentoft et al., 2014). Although research in recent years has significantly advanced the understanding of sarcopenia, one of the main gaps identified by EWGSOP is the need to identify key variables that allow accurate detection and prediction of clinical outcomes. This is essential to implement more effective interventions. They also highlight that determining the optimal tools to measure each variable will contribute to improving both early diagnosis and comprehensive management of sarcopenia (Cruz-Jentoft et al., 2019).

### 2.3.1 Sarcopenia like conditions

In the context of sarcopenia, we identify a range of sarcopenia-like conditions, including sarcopenic obesity, malnutrition, cachexia, kratopenia, myopenia, dynapenia, and frailty, which collectively represent a spectrum of interrelated disorders characterized by muscle wasting. Each of these conditions shares a common underlying pathology involving the progressive deterioration of muscle tissue, albeit with distinct clinical presentations and contributory factors. The conditions or concepts most closely associated with sarcopenia include kratopenia, defined as a deficit in muscle power, which can be assessed through dynamometry or isometric contraction tests (Cruz-Jentoft et al., 2019). Myopenia, referring to the loss of muscle mass, is measured using tools such as BIA, DEXA, MRI, or CT, as mentioned in the previous section (Cruz-Jentoft et al., 2019). Additionally, dynapenia, known as the loss of muscle strength, is commonly assessed through functional tests like gait speed, the 5STS, or the TUG, among others (Sanchez-Tocino et al., 2024). These three terms; kratopenia, myopenia, and dynapenia, are the most directly related to sarcopenia, as they encompass the core components of the condition: severe sarcopenia = kratopenia + myopenia + dynapenia (Cruz-Jentoft et al., 2019).

Among the conditions similar to sarcopenia is sarcopenic obesity, this pathology involves the combination of the low muscle mass of sarcopenia combined with excess fat. This pathology favours fatty infiltration of muscle, increasing the physical limitations observed in isolated sarcopenia and enhances the risk of mortality (Barbat-Artigas et al., 2014; Johnson Stoklossa et al., 2017; Kalinkovich & Livshits, 2017). The sarcopenia phenotype is also related to malnutrition, which contributes to muscle wasting by impairing the body's ability to repair and maintain muscle tissue. Similarly, cachexia, often associated with chronic diseases, accelerates muscle loss due to inflammatory and metabolic disturbances (Cederholm et al., 2017; Cruz-Jentoft et al., 2019). As highlighted above, sarcopenia and frailty are distinct but overlapping syndromes that often coexist in older adults. While frailty is a more complex and multifactorial disorder, sarcopenia focuses predominantly on the musculoskeletal system (Cruz-Jentoft & Sayer, 2019; Davies et al., 2018; Landi et al., 2015; Reijnierse et al., 2016).

### 2.3.2 Pathophysiology and determinant factors

The pathophysiology of sarcopenia is complex; in age related sarcopenia, which will be the focus of this dissertation, the aging process disrupts the homeostasis of various systems, and multiple interrelated factors contribute to its development. Recent research suggests that, among these multiple factors, there are both environmental and behavioral aspects, such as physical inactivity, immobility, and malnutrition, as well as other more physiological factors, including cellular and molecular changes, neuromuscular aging, low-grade systemic inflammation, and hormonal and metabolic alterations (Cho et al., 2022; Cruz-Jentoft & Sayer, 2019; Ogawa et al., 2016).

Cellular and molecular changes in sarcopenic muscle include reductions in both the total number and size of muscle fibers, particularly affecting type II fibers (fast-twitch fibers). This occurs due to the transition of type II fibers to type I fibers as a consequence of the aging process. Additionally, there is a reduction in mitochondrial density and a decrease in the activation of satellite cells, which are responsible for muscle regeneration and repair (Correa-de-Araujo et al., 2017; Cruz-Jentoft & Sayer, 2019; Ferri et al., 2020; Verdijk et al., 2014). However, type I fibers are much less affected by these processes (Dhillon & Hasni, 2017). In terms of neurological signalling and control mechanisms, anatomical and electrophysiological studies indicate that ageing leads to a loss of motor neurons, which in turn leads to a reduction in satellite cell activation and thus muscle mass (Correa-de-Araujo et al., 2017; Dhillon & Hasni, 2017; Doherty & Brown, 1997).

It can be posited that many of the molecular and neuromuscular changes observed are either driven or exacerbated by hormonal alterations and systemic inflammation. However, the precise mechanisms that initiate these changes remain unclear, and further research is needed to fully understand the underlying processes.

It can be postulated that many of the observed molecular and neuromuscular changes are driven or exacerbated by hormonal alterations and systemic inflammation. However, the precise mechanisms that initiate these changes remain unclear, and more research is needed to fully understand the underlying processes (Dhillon & Hasni, 2017). As for the hormonal role, the decrease in anabolic hormonal signals, resulting from reduced concentrations of growth hormone, testosterone, thyroid hormone and insulin-like growth factor, leads to loss of muscle mass and strength. This is compounded by increased catabolic signals, mediated through pro-inflammatory cytokines, which further aggravate this process (Dhillon & Hasni, 2017). Additionally, there is an imbalance in protein turnover, where a disproportionate reduction in skeletal muscle protein synthesis and/or an increase in protein degradation occurs. This leads to the accumulation of oxidized proteins (non-contractile dysfunctional proteins) in skeletal muscle, which is a key factor contributing to the significant decline in muscle strength seen in sarcopenia (Cruz-Jentoft & Sayer, 2019; Fielding et al., 2011; Marcell, 2003). This process is compounded by chronic low-grade inflammation associated with aging, an inflammatory phenomenon unrelated to infections, which is characterized by an increase in serum levels of inflammatory markers, generating responses that lead to tissue degeneration. This inflammation is associated with a decrease in T and B cells, along with an increase in natural killer cells and elevated levels of proinflammatory cytokines. These cytokines play a crucial role in sarcopenia by altering cell signaling pathways and negatively affecting muscle synthesis and maintenance in older adults (Cho et al., 2022; Ogawa et al., 2016).

### **2.3.3 Prevention and treatment.**

To date, no effective treatment for sarcopenia has been universally established. However, in practice, different strategies, both non-pharmacological and pharmacological, are used to manage sarcopenia. The choice between these treatment options depends on the individual characteristics of each person and on the basis of these a personalized action plan should be generated.

In terms of non-pharmacological therapeutic options, physical exercise and nutritional approaches play a crucial role in the management of sarcopenia, as they can mitigate, delay or even reverse the associated adverse effects (Bernabei et al., 2022; Casas-Herrero et al., 2022; Cruz-Jentoft & Sayer, 2019; Najm et al., 2024; Sayer & Cruz-Jentoft, 2022). Specifically, current clinical practice guidelines advocate strength training as one of the main strategies for the treatment of sarcopenia (Dent et al., 2018; Sayer & Cruz-Jentoft, 2022). Research and systematic reviews have shown the benefits of strength training, including improvements in strength, muscle mass, muscle quality, balance, physical functioning and metabolic health in older adults with sarcopenia (Lozano-Montoya et al., 2017; M. Seo et al., 2021; Vlietstra et al., 2018).

Despite the clear potential of strength training as a therapeutic intervention, standardized reference programs for its clinical implementation have only recently begun to emerge and are not routinely offered to patients (Offord et al., 2019). Furthermore, there is significant variability in the programs that are currently delivered in clinical practice (Witham et al., 2020). This creates a substantial gap between research findings and widespread clinical application. Addressing this gap presents an opportunity to further develop and standardize these programs, ensuring their integration into routine medical practice (Hurst et al., 2022; Sayer & Cruz-Jentoft, 2022). By doing so, healthcare professionals and exercise specialists will be better equipped to apply evidence-based strategies, ultimately improving outcomes for older adults affected by sarcopenia.

The evidence for nutritional interventions is less consistent than that for physical exercise; however, an increasing amount of research indicates that diet plays a significant role in the prevention and treatment of sarcopenia. Therefore, it is essential to adhere to high-quality dietary patterns that ensure adequate intake of proteins, antioxidant nutrients, vitamin D, and long-chain polyunsaturated fatty acids to support muscle health and overall well-being.

Several studies have examined the combined effects of lifestyle factors, specifically exercise and nutrition, in the treatment of sarcopenia. The effectiveness of these protocols has been supported by large-scale trials, such as the European SPRINTT trial, which confirms that the incorporation of nutritional interventions into exercise therapies produces a significant positive effect on several related variables (Bernabei et al., 2022; Cruz-Jentoft & Sayer, 2019; Sayer & Cruz-Jentoft, 2022; Shen et al., 2023). In conclusion, the multicomponent intervention proved to be feasible, safe and effective in a highly vulnerable population such as individuals affected by sarcopenia (Bernabei et al., 2022; Shen et al., 2023).

Even while dietary assistance and exercise regimens have been shown to be effective, these therapy modalities are not always practical for patients with sarcopenia, particularly in senior populations who are fragile and polymorbid (Rolland et al., 2023). As an alternative, a number of pharmaceutical compounds have been suggested as treatment approaches. However, progress in drug treatment developments is slow and there are no drugs approved by the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA) for sarcopenia (Cho et al., 2022; Sayer & Cruz-Jentoft, 2022; Zazzara et al., 2021).

#### **2.3.4 Health benefits of physical activity and exercise**

Over the past decades, the relationship between physical activity and health has been extensively documented, with a growing body of evidence reinforcing its positive impact. Two pioneering studies in this area, the ‘London Bus Drivers’ Study’ and the ‘Nurses’ Study’, laid the groundwork for demonstrating that increased physical activity is associated with better overall health. These seminal works underline the value of physical activity in the prevention of non-communicable diseases, providing an early understanding of its crucial role in health promotion (Belanger et al., 1978; Morris et al., 1953).

Physical activity, defined as “any bodily movement produced by skeletal muscles that results in energy expenditure” (Bull et al., 2020; Caspersen et al., 1985), has shown well-established benefits in adults and older people, such as reducing the risk of all-cause mortality, attenuating functional decline of systems (respiratory, musculoskeletal, cardiovascular and immune), preventing and treating chronic diseases (some cancers, cardiovascular diseases, hypertension and type 2 diabetes, etc.), obesity and falls. It has also been observed to improve physical functioning and independence, musculoskeletal system, mental health, cognitive function, sleep quality, body composition and metabolic system. This has led to a reduction in the burden of non-communicable diseases and an increase in quality of life (American College of Sports Medicine et al., 2009; Fiuza-Luces et al., 2013; McArdle, 2010; Pedersen & Saltin, 2015; Ruegsegger & Booth, 2018; Zhao et al., 2020).

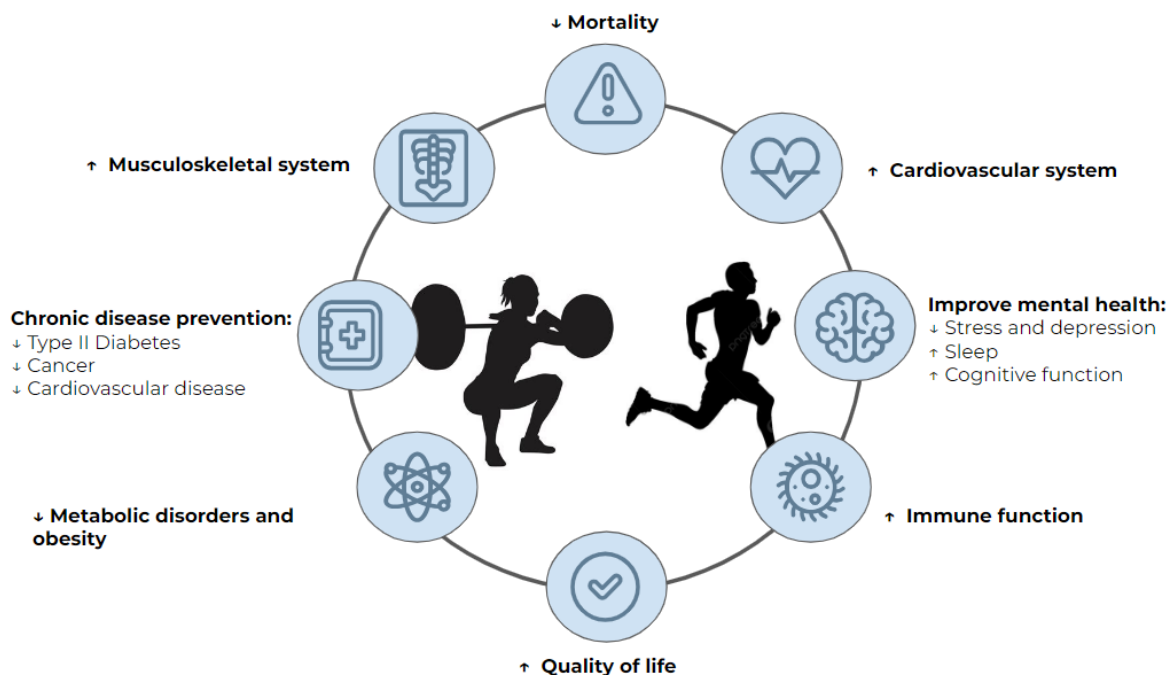


Figure 4. Health benefits of physical activity and exercise

Although there is clear evidence that physical activity is beneficial to health, the central question is how much activity is needed to maximize these benefits. To this end, recommendations have been developed that specify the appropriate volume and intensity to optimize health outcomes (American College of Sports Medicine et al., 2009; Bull et al., 2020).

The World Health Organisation (WHO) and the ACSM recommend that adults and older people should engage in at least 150-300 minutes of moderate-intensity aerobic physical activity per week, or 75-150 minutes of vigorous aerobic activity. In addition, it is advisable to incorporate muscle-strengthening activities on two or more days per week, as well as exercises that improve balance and coordination to prevent falls, particularly in older populations (Bull et al., 2020; Medicine, 2013; Medicine et al., 2018). However, it should be noted that these guidelines represent minimum recommended levels of physical activity.

Although the recommendations are well-founded, few people manage to comply with them, especially among older adults (Fried, 2016). This lack of adherence to physical activity guidelines has serious consequences, and is estimated to contribute to approximately 1.3 million deaths worldwide each year (GBD, 2016). The scientific evidence is clear and consistent on the benefits of physical activity; not only does it play a crucial role in disease prevention, but it also helps to alleviate the effects of aging and reduce the impact of age-related diseases (Bull et al., 2020; Fiuza-Luces et al., 2013; McArdle, 2010; Medicine, 2013; Medicine et al., 2018; Pedersen & Saltin, 2015; Rueggsegger & Booth, 2018). This is where the promotion of physical activity and exercise comes into play as a priority objective and therapeutic agent.

Although these two terms are often confused and confusing, it is important to highlight their differences as they refer to different concepts. Physical exercise is a specific type of planned, structured and repetitive physical activity that aims to improve or maintain one or more components of physical fitness (Caspersen et al., 1985).

Table 1. Differences between physical activity and exercise

Aspect	Physical activity	Exercise
<b>Purpose</b>	Planned and structured to improve physical fitness, with a specific goal.	Any body movement that burns energy, without a specific goal.
<b>Structure</b>	Planned and structured, intentionally performed with specific routines.	Spontaneous and include daily tasks (walking, cleaning, gardening).
<b>Intensity</b>	It generally involves intensity, measured at specific levels (light, moderate, vigorous) and adapted to specific objectives.	Generally less intense than exercise
<b>Measurement</b>	Evaluated through logs of time, frequency, repetitions, and progression of loads.	Can be measured more informally and lacks systematic tracking.

Adapted from: Caspersen, C. J., Powell, K. E., & Christenson, G. M. (1985). Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public health reports*, 100(2), 126.

In the context of aging and age-related diseases, due to the aforementioned benefits, physical exercise is used as a therapeutic agent to mitigate age-related losses (Fiuza-Luces et al., 2013; Izquierdo et al., 2021; Medicine et al., 2018). To this end, it is essential to understand the different classifications of physical exercise and the health benefits each provides, including strength training, aerobic exercise, and flexibility. To maximize the benefits of exercise and ensure individual safety, it is important to prescribe the appropriate type of exercise, taking into account factors such as age, fitness level, and health conditions (Izquierdo et al., 2021; Medicine et al., 2018). The following sections will detail each type of exercise, the adaptations they promote, and their importance in fostering an active and healthy lifestyle.

Aerobic exercise, which involves repetitive, structured activities that engage large muscle groups and can be sustained over extended periods, is the most recognised training modality for improving cardiorespiratory markers such as VO<sub>2</sub>max. It also promotes metabolic, cardiovascular and neuromuscular adaptations, among others (N. Chen et al., 2021; Khalafi et al., 2022). On the other hand, resistance training involves activities that cause muscles to contract against an external resistance and is considered the main method for generating adaptations that cause muscle hypertrophy leading to an increase in muscle mass, strength and quality, among others (N. Chen et al., 2021; Khalafi et al., 2022). However, a notable degree of convergence exists between the early physiological responses to exercise and the long-term adaptations elicited by these two distinct exercise modalities (Fyfe et al., 2014; Fyfe & Loenneke, 2018). In addition, you can find flexibility training which focuses on improving joint range of motion and muscle elasticity. It includes static and dynamic stretching exercises. However, by identifying the most significant variables and aligning with recent studies, multicomponent exercise, which includes strength, aerobic and balance training, is the best strategy to improve health aspects as it generates a holistic approach to overall health and functionality, especially for older adults (Izquierdo et al., 2021; Izquierdo & Cadore, 2024).

### 3 Related work:

As previously noted, the recent EWGSOP update highlights the relevance of assessing muscle quality as a key indicator of the physiological properties of skeletal muscle tissue that affect both muscle strength and function (Cruz-Jentoft et al., 2019). Muscle quality (MQ) Muscle quality refers to the functional performance and physiological capacity of muscle tissue. MQ encompasses various factors related to muscle composition, including microscopic and macroscopic changes in muscle structure, as well as functional performance per unit of muscle mass (Cruz-Jentoft et al., 2019; de Lucena Alves et al., 2023). Generally, MQ is defined by two key domains: morphological and functional. The morphological domain focuses on direct assessments of muscle architecture (taking into account the microscopic and macroscopic characteristics of muscle structure) and composition (Coronado-Zarco & de León, 2023; de Lucena Alves et al., 2023; M. S. Fragala et al., 2015). This domain focuses on the physical properties and architecture of the muscle rather than its functional performance. Regarding the composition dimension of muscle, factors such as muscle density, fat, lipid infiltration, and water content are evaluated. Essential tools for analyzing this muscle composition include CT and MRI, which provide accurate assessments of muscle quality by measuring intramuscular fat infiltration, muscle density, and cross-sectional area. In addition, echo intensity measures the reflectivity of the sound waves emitted to the tissue, in this case muscle tissue. This technique makes it possible to evaluate the composition of the muscle, as connective tissue and lipids are more reflective than muscle tissue, which is denser (Cruz-Jentoft et al., 2019; Faron et al., 2020; M. S. Fragala et al., 2015; Oba et al., 2021). Furthermore, the architectural features of muscles are linked to their contractile action. Key architectural characteristics that influence the force-generating ability of muscles include the length of the muscle fibers (fascicle length) and their arrangement relative to the direction of the force produced by the entire muscle (pennation angle). Modern B-mode ultrasound methods allow for a thorough analysis of muscle architecture, such as, fascicle length, pennation angle, cross sectional area and echo intensity (a proxy of muscle composition) (Correa-de-Araujo et al., 2017). Finally, within the assessment of muscle quality from the morphological domain, we find muscle ultrastructure. The changes in muscle ultrastructure associated with the aging process include an increase in the stiffness of muscle fibers related to age, as well as a reduction in contractility and specific tension (M. S. Fragala et al., 2015; Ochala et al., 2007; Šimunič et al., 2018). Tensiomyography and myotonometry are non-invasive diagnostic tools that measure muscles mechanical properties (M. S. Fragala et al., 2015; Ochala et al., 2007; Šimunič et al., 2018).

In contrast, the functional domain refers to indirect assessments of muscle performance in relation to its mass (Barbat-Artigas et al., 2012; de Lucena Alves et al., 2023; M. S. Fragala et al., 2015; Naimo et al., 2021). In this domain, the goal is to quantify how efficiently a muscle can generate force relative to its size, which is represented as a muscle quality index. From this functional perspective, evaluating muscle quality requires assessing key aspects of muscle performance, such as strength, power, or function, in relation to quantitative parameters of muscle size, including muscle mass, lean mass, muscle thickness, and cross-sectional area. These indicators can be measured both in specific body regions and across the whole body, providing a comprehensive view of the muscle's functional capacity (Barbat-Artigas et al., 2012; de Lucena Alves et al., 2023; M. S. Fragala et al., 2015; Naimo et al., 2021). It is important to highlight in this domain the interrelation between muscle quality, muscle strength and mass, as the definition of this functional domain is; muscle strength or power per unit of muscle mass (McGregor et al., 2014). Muscle quality indices are often defined as muscle strength relative to muscle quantity; however, it is important to consider the type of movement (isometric, isotonic, or isokinetic) and the anatomical location (upper or lower extremities) (M. S. Fragala et al., 2015). Another recognized approach is the Muscle Quality Index (MQI), proposed by Barbat-Artigas et al. This index is calculated by dividing handgrip strength by relative skeletal muscle mass. The

MQI has been utilized in numerous studies, demonstrating its reliability in assessing muscle quality (Barbat-Artigas et al., 2012; M. S. Fragala et al., 2015).

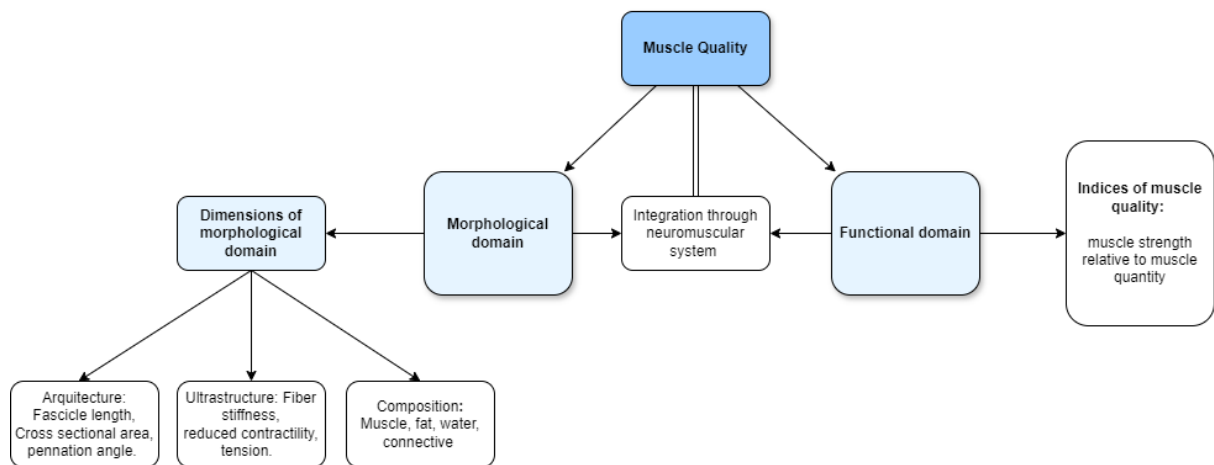


Figure 5. Muscle quality domains

In addition, although less frequently discussed, other aspects such as metabolism, thermoregulation and the production of signaling molecules or myokines have been suggested as additional domains of muscle quality (Correa-de-Araujo et al., 2017; Correa-de-Araujo & Hadley, 2014; de Lucena Alves et al., 2023).

Age-related changes in muscle quality appear earlier than muscle mass loss, suggesting that muscle quality may be a more sensitive marker of muscle function than mass alone (de Lucena Alves et al., 2023). This observation is relevant, as changes in muscle quality may help to explain, more precisely, the losses in muscle strength and function associated with aging (Kuschel et al., 2022). In this context, maintaining and monitoring muscle quality is crucial in older adults to help prevent the deterioration of muscle mass and strength and slow down alterations in muscle metabolism (Distefano & Goodpaster, 2018). Furthermore, it is important to note that muscle quality is a relatively novel concept, and the diagnostic tools for its assessment are not yet fully established (Cruz-Jentoft et al., 2019), highlighting the necessity for further research in this area. Finally, a number of assessment tools can provide valuable information on muscle quality and are detailed below.

Techniques for assessing muscle quality can be categorized into three main groups. First, there are direct invasive techniques. Second, direct non-invasive techniques are available. Finally, there are indirect non-invasive techniques.

Direct and invasive muscle quantification techniques include mainly muscle biopsy and invasive electromyography. In the field of muscle biopsy, the most commonly used techniques include the Bergstrom needle biopsy and the Well-Blakesley conchotome, which provide accurate data on muscle fibre distribution, capillarisation, intramuscular fat content and muscle metabolism (Ekblom, 2017; Naimo et al., 2021). Although needle biopsy techniques have made significant advances, they are still invasive procedures that require the removal of muscle tissue (Townsend et al., 2015). Invasive electromyography is another invasive diagnostic option, involving the insertion of needle electrodes directly into the muscle to record and analyse its electrical activity, providing detailed information on muscle and nerve function at the level of individual motor units (Rubin, 2019).

On the other hand, there are direct non-invasive muscle quality quantification tools that examine the morphological domain with high sensitivity. Techniques such as Magnetic Resonance Imaging (MRI) and X-ray Computed Tomography (CT) are currently considered state-of-the-art in research on direct muscle quality assessment (Beudart et al., 2020; Chianca et al., 2022; Cruz-Jentoft et al., 2019). Additionally, methods like ultrasound, tensiomyography, myotonometry and Phase Angle derived from Bioelectrical Impedance Analysis (BIA) contribute to this field (Cruz-Jentoft et al., 2019; Perkisas et al., 2018; Pus et al., 2023; Sergi et al., 2016; Tagliafico et al., 2022). However, due to their high cost and lower accessibility, these imaging methods are primarily limited to research applications (Sergi et al., 2016).

Finally, muscle quality has also been assessed using non invasive indirect measurement, which uses ratios of muscle strength to muscle mass or muscle volume, among others. These indirect methods rely on various formulas to evaluate muscle quality and offer greater accessibility, making them more practical for routine clinical use and potential integration into health programs. However, the lack of a universal consensus on the assessment techniques remains a significant limitation, as highlighted by the EWGSOP (Cruz-Jentoft et al., 2019).

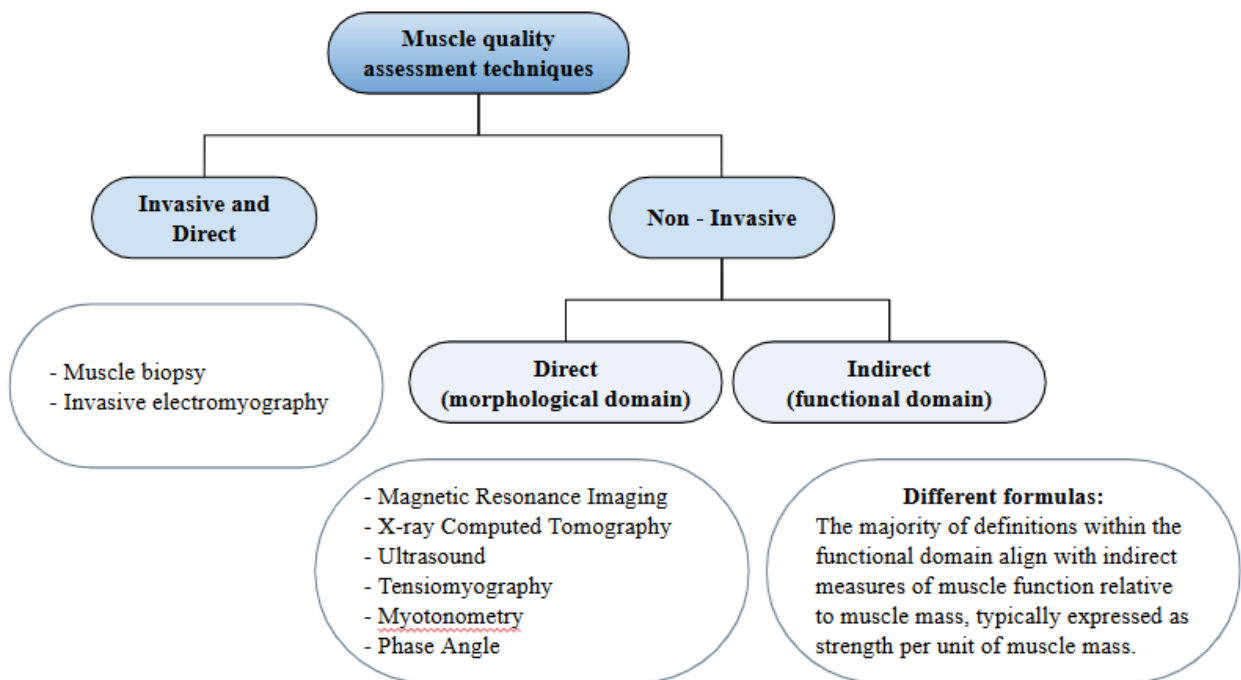


Figure 6. Muscle quality assessment techniques.

The EWGSOP, along with other recognized working groups, has indicated that one of the current challenges in the diagnosis and recognition of sarcopenia could be addressed through the exploration of muscle quality, identifying the most effective indicators and developing measurement tools that are accurate and affordable (Cruz-Jentoft et al., 2019). To achieve this, the assessment of muscle quality faces some key questions;

- What is the best way to assess muscle quality? What are the most effective indicators of muscle quality in predicting outcomes? Which tools and methods provide accurate and affordable measurements?

Moreover, although direct non-invasive imaging techniques can capture key factors related to muscle quality, there is a need to develop more practical methods to implement these evaluations in community and clinical settings (xx). In this context, the question arises;

- What strategies or tools can be used to adapt and optimize non-invasive imaging techniques for assessing muscle quality, ensuring they are accessible, viable, and effective in clinical and community settings?

### **3.1 Article I: Non invasive techniques for direct muscle quality assessment after exercise intervention in older adults: a systematic review.**

This section introduces the first of the two systematics reviews and four case studies that comprise this dissertation. It provides an overview of the non-invasive techniques utilized to directly assess muscle quality in older adults following physical exercise interventions, one of the gaps presented and the objectives of this dissertation. Since the EWGSOP highlighted the importance of muscle quality in the diagnosis of sarcopenia in 2019, there has been a growing recognition of its significance, along with the analysis and measurement of the morphological and functional characteristics of skeletal muscle, which serve as crucial indicators of muscle quality. However, gaps remain in the understanding of the most effective non-invasive tools for assessing muscle quality in older adults (Cruz-Jentoft et al., 2019).

Accordingly, the aim is to present a comprehensive understanding of the various non invasive techniques and methods available for measuring muscle architecture and composition, thereby elucidating the best approaches to evaluate muscle quality. Additionally, it analyzes the predominant parameters or indicators currently recognized, along with the techniques employed and the priority assigned to them. Recent advancements in the development of new non-invasive tools for quantifying muscle quality are also examined. By addressing these questions, the article aims to fill another gap in the existing literature regarding the most effective indicators of muscle quality morphological domain and the tools and methods that yield precise and affordable measurements. Furthermore, it evaluates the effectiveness of various exercise programs (e.g., resistance, aerobic, and concurrent training) in improving or preserving muscle quality. These objectives align with the overarching aims of the dissertation.

A comprehensive review was conducted to assess non-invasive techniques to directly measure muscle quality in older adults, analyzing 34 studies that met the inclusion criteria. This framework was used to draw conclusions about the efficacy of various exercise interventions and the tools used to measure muscle quality to answer the research questions. It is clear that recent advances in these techniques have provided significant information, allowing researchers to assess muscle quality more accurately and to tailor exercise programmes aimed at optimizing health outcomes for older adults.

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RESEARCH

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# Non invasive techniques for direct muscle quality assessment after exercise intervention in older adults: a systematic review

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## Abstract

**Background** The aging process induces neural and morphological changes in the human musculoskeletal system, leading to a decline in muscle mass, strength and quality. These alterations, coupled with shifts in muscle metabolism, underscore the essential role of physical exercise in maintaining and improving muscle quality in older adults. Muscle quality's morphological domain encompasses direct assessments of muscle microscopic and macroscopic aspects of muscle architecture and composition. Various tools exist to estimate muscle quality, each with specific technical requirements. However, due to the heterogeneity in both the studied population and study methodologies, there is a gap in the establishment of reference standards to determine which are the non-invasive and direct tools to assess muscle quality after exercise interventions. Therefore, the purpose of this review is to obtain an overview of the non-invasive tools used to measure muscle quality directly after exercise interventions in healthy older adults, as well as to assess the effects of exercise on muscle quality.

**Main text** To address the imperative of understanding and optimizing muscle quality in aging individuals, this review provides an overview of non-invasive tools employed to measure muscle quality directly after exercise interventions in healthy older adults, along with an assessment of the effects of exercise on muscle quality.

**Results** Thirty four studies were included. Several methods of direct muscle quality assessment were identified. Notably, 2 studies harnessed CT, 20 utilized US, 9 employed MRI, 2 opted for TMG, 2 adopted myotonometry, and 1 incorporated BIA, with several studies employing multiple tests. Exploring interventions, 26 studies focus on resistance exercise, 4 on aerobic training, and 5 on concurrent training.

**Conclusions** There is significant diversity in the methods of direct assessment of muscle quality, mainly using ultrasound and magnetic resonance imaging; and a consistent positive trend in exercise interventions, indicating their efficacy in improving or preserving muscle quality. However, the lack of standardized assessment criteria poses a challenge given the diversity within the studied population and variations in methodologies. These data emphasize the need to standardize assessment criteria and underscore the potential benefits of exercise interventions aimed at optimizing muscle quality.

**Keywords** Older adults, Physical exercise intervention, Muscle quality, Non-invasive techniques

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## Introduction

The aging process generates neural [1] and morphological [2] changes in the human musculoskeletal system triggering a reduction in muscular parameters [3]. Given the increase in life expectancy [4], it is imperative to promote active and healthy aging that improves the quality of life of older adults [5, 6]. Muscle quality is an important indicator of the overall health status of older adults [3, 7]. The decline in muscle quantity and quality with age is a normal process that affects everyone [8, 9], which can lead to frailty, dependence, decreased quality of life and increased mortality [10, 11, 12].

Maintaining and controlling muscle quality is of vital importance in the older adult, as it can help prevent the decline in muscle mass, strength and regenerative capacity, as well as slowing or preventing alterations in muscle metabolism [13]. Physical exercise interventions have been shown to be an effective means of prolonging average life expectancy [14, 15], as well as preventing and delaying the deterioration and loss of muscle quality inherent to aging [13, 14]. Research has shown that physical exercise not only enhances muscle quality [16, 17, 18] and function [18] but also improves functional fitness and metabolic health [12, 19]. Additionally, it contributes to the stability and integrity of the cell membrane [20, 21, 22], which are key markers currently indicative of muscle quality. This scenario indicates that physical exercise plays a crucial role in mitigating the decline of muscle regeneration, boosting the number and activation of satellite cells, increasing myogenic potential, and reducing fibrosis formation. Furthermore, exercise effectively reduces the accumulation of age-related intermuscular fat and influences the composition of intramyocellular lipids [13]. Among exercise strategies, strength training, in its various forms, has proven to be a powerful tool to combat age-associated muscle decline [17, 23]. Firstly, moderate- to high-repetition strength training followed by high- and moderate-intensity aerobic exercise is a potential strategy to reverse the molecular features of skeletal muscle aging [24], with power training being a preferred exercise modality in clinical populations [25]. Additionally, various strategies are explored, ranging from traditional strength training [23] to low-volume HIIT [26], as well as resistance methods such as plyometrics [27]. Equally important is recognizing the vital role of dietary interventions in promoting muscle health [28].

However, it is important to monitor, through systematic assessment, changes in muscle tissue after a physical exercise intervention in order to evaluate its effectiveness [29]. The European Working Group on Sarcopenia in Older People (EWGSOP) emphasizes the importance of assessing not only the quantity of muscle, but also its quality [30]. Muscle quality is characterized

by functional and morphological domains; the first one aligns with indirect measurements of muscle function relative to mass, while the second involves direct assessments of muscle architecture referring to the microscopic and macroscopic aspects of muscle architecture and composition [31]. Despite the lack of a precise definition of muscle quality, it's crucial to analyze its construct and its relation to physical performance and muscle function [32]. Our focus will be on analysing muscle quality through direct techniques that measure muscle architecture and composition.

Currently, there are several non-invasive techniques for monitoring muscle quality, but our focus will be on direct techniques measuring muscle architecture and composition [33–35]. These techniques are relatively easy to perform, do not require the insertion of invasive devices, and are an important tool for evaluating the effectiveness of physical exercise interventions in older adults [36].

Radiological imaging techniques allow the investigation of degenerative processes in individual muscle groups. These techniques can identify and quantify abnormalities, monitor patient progress and evaluate therapeutic interventions. Magnetic resonance imaging (MRI) and X-ray computed tomography (CT) stand as the current state-of-the-art in muscle quality assessment research [37–39]. CT, considered the gold standard for body composition analysis, excels in assessing muscle mass and quality, and diagnosing abnormal body composition phenotypes [40]. Notably, it offers exceptional visualization of intermuscular and intramuscular fat in tomographic sections [41]. Whereas, the development of new MRI sequences and tools has further increased the accuracy allowing for simultaneous assessment of body composition and identification of muscle quality issues such as disruption, edema, myosteosis, and myofibrosis with the latter two tending to increase within muscles during aging [37, 42, 43]. In contrast, Dual-energy X-ray absorptiometry (DXA) is recommended as a reference in most EWGSOP guidelines to diagnose sarcopenia in clinical practice [30, 44]. DXA provides a body composition model that includes fat, bone mineral density, and lean mass [45, 46], but even though it is a reference method for measuring total skeletal muscle mass, it cannot evaluate an individual muscle or assess muscle quality [7, 47].

In addition, ultrasound sonography (US) is a fast, non-invasive, and affordable imaging modality. The use of musculoskeletal ultrasound (MSK-US) for muscle quality assessment is rapidly gaining traction in clinical practice [40, 48]. A major advantage over other methods is that different muscle groups can be examined separately [49]. Common tissue characterization parameters measured include morphological measures of muscle thickness, pennation angle, cross-sectional area, echo intensity, and

fascicle length [50•], which have shown correlations with muscle mass and strength [51]. Perkisas et al. [50•] standardized the use of ultrasound to assess muscle quality. In recent years, several qualitative tools aimed at identifying muscle quality loss have been developed in various care settings [52, 53]. Recent meta-analyses [54] underline the comparable and superior performance of MRI and CT in quantifying age-related morphological changes, highlighting their robustness in assessing muscle quality. In contrast, ultrasound, does not show a comparable level of accuracy in capturing age-related morphological changes [54, 55].

Another current non-invasive method is tensiomyography (TMG), a valuable tool for assessing neuromuscular function in older adults. The method is sensitive to muscle composition, architecture, and pre-atrophic changes in skeletal muscles, and may be sensitive to changes in muscle quality in aging and diseased populations [56, 57]. On the other hand, myotonometry is another tool that has been studied for the assessment of muscle viscoelastic properties [58]. Additionally, Bioelectrical Impedance Analysis (BIA) is a non-invasive, quick, and accessible technique that uses whole-body electrical conductivity to estimate body composition [59]. Notably, the Phase Angle (PhA) derived from BIA, a measure of cellular integrity and body water distribution, has become an important parameter for muscle quality assessment [60]. In fact, the European Working Group on Sarcopenia in Older People (EWGSOP) incorporates BIA-derived PhA in their criteria for muscle quality assessment, highlighting its potential for identifying sarcopenia [30••].

Thus, there is a need for a comprehensive review to compile and analyze the existing scientific evidence on the techniques mentioned in the evaluation of muscle architecture and composition in the field of promotion, intervention and design of physical exercise in the clinic of the older adult. Therefore, the aim of this systematic review is to obtain an overview of the non-invasive tools used to measure muscle quality directly after exercise interventions in healthy older adults. We aim to identify the different tools, measurement methods and their applicability in the direct assessment of muscle quality, providing a solid guide in the field of assessment and application of physical exercise interventions in older adults for future research in this area.

To achieve this goal, our research questions are as follows: (1) Which are the direct non-invasive tools used to measure muscle quality in older adults after exercise interventions?; (2) What are the effects of physical exercise programs on muscle quality in older adults measured by non-invasive tools?; (3) Which multisource objective parameters are predominantly utilized in the state of the art, and what priority have they shown in papers

to measure muscle quality in older adults after exercise intervention?; and (4) What recent trends or advancements have been observed in the development of new non-invasive tools for quantifying muscle quality in older adults after exercise interventions?.

## Methods

### Registration

The systematic review was registered on the Open Science Framework (OSF) platform ([https://osf.io/anjr4/?view\\_only=05969c336a0847028766e96f574eb63e](https://osf.io/anjr4/?view_only=05969c336a0847028766e96f574eb63e)), in October 24, 2023 (registration DOI: <https://doi.org/https://doi.org/10.17605/OSF.IO/3GD6Y>).

### Procedures

The review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [61].

### Eligibility criteria

Original, peer-reviewed, full-text studies were included/excluded using the PICOS method (participants, interventions, comparators, outcomes, and study design) [62]. The selection criteria are summarized in Table 1.

### Literature search and screening process

Search strategy was developed by one reviewer (NV) specifically for PubMed (added below), and it was applied to the title, abstract, and keywords. This search strategy was later modified to align with the syntax and relevant subject headings of other databases. The literature search was performed in the electronic databases PubMed, Web of Science and Scopus, using the Boolean operators AND/OR, in combinations with the keywords (resistance OR strength\* OR exercise\* OR aerobic\* OR multicomponent) AND (aged OR old OR elder\* OR aging OR frail\* OR older OR senior OR geriatric) AND ("contraction time" OR "reaction time" OR "contraction sustain time" OR "relaxation time" OR "muscle tone" OR stiffness OR "echo intensity" OR "pennation angle" OR "fat infiltration" OR "muscle lipid" OR "muscle hydration" OR "muscle microscopic fat" OR "macroscopic fatty infiltration" OR radiodensity OR "skeletal muscle radiodensity" OR "muscle density" OR "intermuscular adipose tissue" OR "extracellular water" OR "intracellular water" OR "phase angle" OR "muscle quality" OR "muscle composition") AND (muscle). The search was performed without date restriction and was updated until October 2023.

One author (NV) conducted the initial search, during which all the entries gathered from the databases were uploaded to the Rayyan QCRI website for the purpose of removing duplicates. Two reviewers (NV and XR) screened identified potentially eligible titles and

**Table 1** Eligibility criteria

Category	Inclusion criteria	Exclusion criteria
Participants	Healthy older adults (+60 years)	Studies that included participants under 60 years of age and health problems (e.g., injuries or chronic pathologies)
Interventions	Exercise interventions	No exercise intervention
Comparators	- Different exercise interventions and control groups - Testing procedures used for direct quantification of muscle quality	Not applicable
Outcomes	Studies that reported muscle quality outcomes before and after exercise intervention. Testing procedures used for direct quantification of muscle quality	Muscle quality asses indirectly or invasively
Study design	Randomized controlled and non-randomized controlled trials and one group studies	Studies including case, observational studies, and systematic reviews

abstracts, resolving disagreements together to mitigate interpretation bias. The full text of potentially eligible records was analyzed following the eligibility criteria for final inclusion. Reasons for exclusions were identified. When articles were not available we solicited authors by e-mail.

We decided not to include noninvasive imaging techniques in the search, given that our research question about the best noninvasive methods for assessing muscle quality could introduce bias by prejudging the results. Therefore, we chose to focus the search on relevant results related to muscle quality without explicitly incorporating the noninvasive techniques used. This decision was made to maintain impartiality in identifying the available evidence.

#### Data collection

Data from the included studies were collected and coded in Microsoft Excel (Microsoft Corp). The following information was extracted from each included study: (1) reference, author and year of publication, (2) participants characteristics (sample size; sex; age and health status), (3) intervention characteristics (frequency, type, duration), (4) muscle quality assessment procedures and outcomes, (5) group of muscles on which the measurement has been performed, and (6) results of the exercise intervention on muscle quality.

#### Risk of bias

To ensure the transparency and reliability of the results and findings, a Bias Risk Assessment has been performed for each study included in this review, using the Physiotherapy Evidence Database (PEDro) scale. The reliability of the PEDro scale in rating the quality of randomised controlled trials has been documented in a paper by Maher et al. [63].

To ascertain the overall risk of bias across the studies, the following convention was employed. The highest

attainable score is ten, as the initial item is not included in the PEDro score computation. The methodological quality of the studies was classified as excellent when scores ranges from eight to ten, high with scores between six and seven, moderate with scores from four to five, and low with scores of three or below.

## Results

### Study selection

From scientific databases, potential studies were directly exported into Rayyan (<https://www.rayyan.ai/>) for removing duplicates and performing the screening applying inclusion and exclusion criteria previously determined. After the above procedure was completed, the following 6465 records were identified. A flow chart illustrating the study selection process is shown in Fig. 1. Duplicate records were removed (n=3297). After titles and abstracts were screened, 2985 records were removed and 183 full texts were evaluated. An additional 143 studies were excluded after full text assessments for eligibility. Thereafter, 40 studies were considered eligible for the systematic review. After eliminating the original non-primary studies [64], a total of 34 studies were included.

### Risk of bias of the included studies

The median score of the PEDro checklist (Table 2) was five (some risk of bias-moderate quality). 28 studies achieved four to fivepoints (some risk of bias-moderate quality) and six studies achieved six to seven points (low risk of bias-good quality).

### Study characteristics

The characteristics of the included studies are detailed in Table 3. A total of 1,040 participants, with an age older than 60 years, were analyzed in this systematic review. Regarding participants sex, 21 studies reported a sample consisting of both male and females (n: 632, 61% of total participants). Five studies were composed of only men (n:

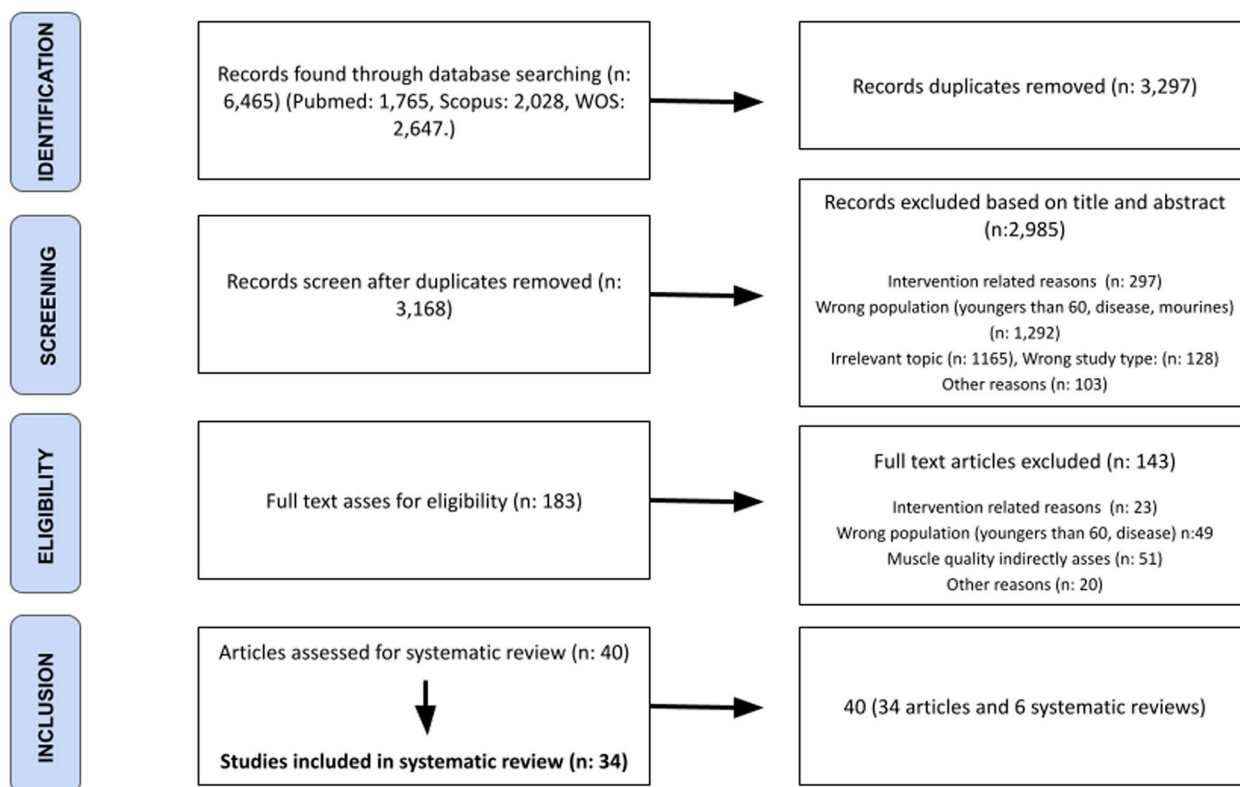


Fig. 1 Flow diagram of the systematic search process

116, 11% of total participants) and nine groups involved only females (n: 292, 28% of total participants).

From the analyzed articles, two articles use CT, 18 use US, nine use MRI, two use TMG, two use myotonometry and one use BIA (there are articles with more than one test). Among the articles that analyze more than one test, one MRI+US and one tensiomyography+myotonometry.

As for the interventions performed in the studies analyzed, 25 studies conducted only resistance exercise, four studies only aerobic activity, five studies performed concurrent training. The frequency of the weekly sessions ranged from two to five sessions per week, with the majority of studies conducting two sessions per week (n: 14, 39%) and three sessions per week (n: 18, 50%). A total of 891 participants were enrolled in the intervention groups. This number exceeds that of the control groups, a discrepancy attributable to the inclusion of multiple studies evaluating diverse training regimens.

In our results, CT was predominantly used to evaluate cross-sectional areas, IMAT, thigh muscle density, total adipose tissue in the thigh, and muscle attenuation, focusing on the quadriceps and hamstrings muscles [71, 87]. MRI provided a wide range of muscle assessments, cross-sectional area analysis constituted 66.67% of the

assessments, while IMAT and fat infiltration accounted for 22.22%, single assessments of muscle fat/water ratio, muscle mechanical quality, and intramuscular non-contractile tissue (IMNCT) comprised the remainder of the evaluations. The majority of MRI measurements (88.89%) targeted the quadriceps, except for one evaluation (11.11%) which assessed the BB [66, 68, 72, 74, 75, 88, 90–92].

US imaging revealed echo intensity as the most common measurement at 66.7%, predominantly analyzed in the RF (ten studies) and VL (seven studies). Pennation angle and fascicle length were assessed in 50% and 38.9% of studies, respectively, with the VL as the primary muscle of interest. CSA was examined in 22.2% of cases, focusing mainly on the RF and VL [43, 65–67, 69, 70, 73, 76, 77, 80–86, 89, 93–95]. Another muscle quality assessment tool highlighted in this review is the BIA, conducted in one study, to measure the PhA.

Building on this, the systematic review also reveals that TMG primarily assessed contraction time and displacement in the VL, along with the RF, BF, TA, GM, and GL [32, 96•]. Similarly, myotonometry [32, 78•] measured muscle tone and stiffness, focusing on the RF and TA, with additional tests on the BF, gluteus major, gastrocnemius, and VL. To conclude, a comprehensive

**Table 2** The median score of the PEDro checklist

Pedro scale	1	2	3	4	5	6	7	8	9	10	11	Score	Study Quality
Baptista et al., 2016 [65]	0	1	0	1	0	0	1	1	0	1	1	6	Good
Bruseghini et al., 2019 [66]	1	0	0	1	0	0	0	1	1	1	1	5	Moderate
Cepeda et al., 2015 [67]	0	1	0	1	0	0	0	0	0	1	1	4	Moderate
Da boilt et al., 2016 [68]	1	0	0	1	0	0	0	1	1	1	1	5	Moderate
Franchi et al., 2019 [69]	1	0	0	1	0	0	0	1	0	1	1	4	Moderate
Gallo et al., 2019 [70]	1	0	0	1	0	0	0	1	0	1	1	4	Moderate
Goodpaster et al., 2008 [71]	0	1	0	1	0	0	1	0	0	1	1	5	Moderate
Greig et al., 2011 [72]	1	0	0	0	0	0	0	1	1	1	1	4	Moderate
Hill et al., 2022 [73]	1	0	1	0	0	0	0	1	0	1	1	5	Moderate
Jacobs et al., 2014 [74]	1	1	0	1	0	0	0	1	0	1	1	6	Good
Konopka et al., 2018 [75]	1	0	0	0	0	0	0	1	1	1	1	5	Moderate
Labata-Lezaun N, 2023 [32]	1	0	0	1	0	0	0	1	1	1	1	5	Moderate
Lopez et al., 2020 [76]	1	1	1	1	0	0	1	1	0	1	1	7	Good
Lopez-Lopez et al., 2021 [77]	1	1	0	1	0	0	1	1	0	1	1	6	Good
Mollà-Casanova et al., 2023 [78]	1	1	1	1	1	0	0	1	0	1	1	7	Good
Nunes et al., 2019 [79]	1	0	0	1	0	0	0	1	1	1	1	5	Moderate
Radaelli et al., 2013 [80]	0	1	0	1	0	0	0	1	0	1	1	5	Moderate
Radaelli, Wilhelm, et al., 2014 [81]	1	1	0	1	0	0	0	1	0	1	1	5	Moderate
Radaelli, et al., 2019 [82]	1	1	0	1	0	0	0	1	0	1	1	5	Moderate
Raj et al., 2012 [83]	1	1	0	1	0	0	0	1	0	1	1	5	Moderate
Rodriguez-Lopez et al., 2022 [84]	1	1	0	1	0	0	0	1	0	1	1	5	Moderate
Scanlon et al., 2014 [85]	1	1	0	1	0	0	0	1	0	1	1	5	Moderate
Suetta et al., 2008 [86]	1	1	0	1	0	0	1	0	0	1	1	5	Moderate
Taaffe DR, 2009 [87]	1	1	0	1	0	0	0	1	0	1	1	5	Moderate
Tanton et al., 2009 [88]	1	0	0	0	0	0	0	1	1	1	1	4	Moderate
Teodoro et al., 2020 [89]	1	1	0	1	0	0	1	1	0	1	1	6	Good
Tracy et al., 1999 [90]	1	0	0	0	0	0	0	1	1	1	1	4	Moderate
Vojciechowski et al., 2021 [91]	1	0	0	1	0	0	0	1	0	1	1	4	Moderate
Watanabe et al., 2014 [92]	0	1	0	1	0	0	0	0	0	1	1	4	Moderate
Wilhelm et al., 2014 [43]	1	0	0	1	0	0	0	1	0	1	1	4	Moderate
Yoshiko, Kaji, et al., 2018 [93]	1	0	0	1	0	0	0	1	1	1	1	5	Moderate
Yoshiko, Tomita, et al., 2018 [94]	1	0	0	1	0	0	0	1	0	1	1	4	Moderate
Yoshiko et al., 2021 [95]	1	0	0	1	0	0	0	1	0	1	1	4	Moderate
Zubac et al., 2019 [96]	1	1	0	1	0	0	0	0	0	1	1	4	Moderate

summary outlining the specific outcomes measured to assess muscle quality using non-invasive tools is provided in Table 4.

For exercise effects on muscle quality in our systematic review, echo intensity decreased in eight studies [43, 73, 77, 80–82, 94, 95], while it remained unchanged in four [76, 85, 89, 93]. Within the review, seven articles reported improvements in pennation angle [65–67, 69, 70, 84, 86], while three articles observed no change [77, 83, 85]. In the systematic review we conducted, we observed that resistance exercise interventions improve CSA [66, 68, 75, 84, 85, 88, 90, 92] or maintain it [74,

77, 91, 95]. Also, our findings indicate improvements in fascicle length in two studies [65, 67], while five others reported no change [65, 70, 83–85].

## Discussion

One of the key objectives of this systematic review was to collect and analyze studies focused on the use of non-invasive tools for direct assessment of muscle quality in older adults after exercise interventions. In addition, we aimed to understand the impact of these interventions on muscle quality.

**Table 3** Descriptive characteristics of participants, intervention, testing procedures and outcomes, muscle group and results of the exercise intervention

Reference	Participants	Intervention	Testing procedures and Outcomes	Muscle group	Results of the exercise intervention
Baptista et al., 2016 [65]	23 healthy elderly males (62.74 ± 2.20 yrs.)	2 session weeks. Knee extensors of one limb subjected to an eccentric training program (n:23) and the contralateral side to a concentric training program (n:23)	<b>Ultrasound B-mode:</b> - PA - fascicle length	VL	PA ↑
Bruseghini et al., 2019 [66]	12 moderately active men (65–75 years)	Subject received both interventions 8-week (3 s/w) High-Intensity Interval Training (n:12) 8-week (3 s/w) Isoinertial Resistance Training (n:12)	<b>MRI:</b> - CSA - IMAT <b>Ultrasound B-mode:</b> - PA	<b>CSA:</b> OF, RF, VL, VI, VM <b>IMAT:</b> Quadriceps <b>PA:</b> VL	CSA of all areas ↑ IMAT: ↓ PA: ↑
Cepeda et al., 2015 [67]	34 healthy elderly females (mean 70 yrs.)	- <b>EG:</b> Dancing Group (DG) n: 19 8 weeks (3 s/w) - <b>CG:</b> n:15	<b>Ultrasound:</b> - PA - fascicle length	VL, TA, BF, GM	DG PA ↑ in all CG: ↔ from pre to post
Da bolit et al., 2016 [68]	23 healthy older adults (71.3 ± 4.1 yrs.)	All underwent RT of the lower limbs for 18 weeks (2 s/w)	<b>MRI:</b> - Fatty infiltration - CSA - Muscle fat/water ratio	Lower limb	- CSA ↑ - Fatty infiltration and muscle fat/water ratio ↔
Franchi et al., 2019 [69]	9 healthy elderly males (69.7 ± 3.4 yrs.)	All underwent 6 week (3 s/w) Plyometric training	<b>Ultrasound B mode:</b> - PA	VL	↑ in all parameters
Gallo et al., 2019 [70]	42 moderately active older women	12 weeks (3 s/w) Aerobic training (dance) CG: n: 20 EG: n: 22	<b>Ultrasound B mode:</b> - PA - fascicle length	GM	Penation angle ↑ Fascicle length ↔
Goodpaster et al., 2008 [71]	42 older adults (70–89 yrs.)	12 months. Concurrent training EG: n: 22 CG: n: 20	<b>CT:</b> - Cross-sectional areas - IMAT - Thigh muscle density - Thigh total adipose tissue	Thigh muscle	- IMAT and Thigh total adipose tissue: ↔, gain prevented - Cross-sectional areas ↓
Greig et al., 2011 [72]	9 older women (76–82 yrs.)	12 weeks (3 s/w) Resistance Unilateral Exercise training EG: Left leg (n:9) CG: Right leg (n:9)	<b>MRI:</b> - Fatty infiltration	Quadriceps	- Fatty infiltration ↔ in EG and increase in CG
Hill et al., 2022 [73]	19 healthy older adults (± 65 yrs.)	Resistance training 6 weeks (2 s/w) EG: n: 11 CG: n: 8	<b>Ultrasound B-mode:</b> - Echo intensity	VL and GM	- Echogenicity ↓ - Indicate Muscle quality: ↑
Jacobs et al., 2014 [74]	77 older adults who experienced a fall (age 75.5 ± 6.8)	2 groups resistance training 12 weeks (3 s/w) - Traditional RT (n: 38) - Eccentric RT (n: 39)	<b>MRI:</b> - IMAT - CSA	Thigh muscles	- IMAT ↔ - CSA ↔

**Table 3** (continued)

Reference	Participants	Intervention	Testing procedures and Outcomes	Muscle group	Results of the exercise intervention
Konopka et al., 2018 [75]	6 older men (74 ± 3 years) and 9 older women (69 ± 2 years)	All underwent aerobic 12-week training progressively increased from 3 to 4 s/w (n:15)	<b>MRI:</b> - IMAT - CSA	Thigh muscles	- IMAT ↓ - CSA ↑
Labata-Lezaun N, 2023 [32]	16 healthy older adults (76.5 ± 7.7)	All underwent 2 months (2 s/w) resistance training (n:16)	<b>Tensiomyography:</b> - Contraction Time (Tc) - maximal radial displacement (Dm)	RF and VL	All measures ↔ VL stiffness improves
Lopez et al., 2020 [76]	24 healthy older women (66.3 ± 5.8 yrs.)	RT 8 weeks (2 s/w) RT: n:12 CG: n:12	<b>Myotonometry:</b> - Stiffness	GM and soleus	All measures ↔
Lopez-Lopez et al., 2021 [77]	32 pre-frail older adults (+75 yrs)	12 weeks (3 s/w) Multicomponent training EG: n: 16 CG: n: 14	<b>Ultrasound B-mode:</b> - Echo intensity <b>Specific tension</b> <b>Ultrasound:</b> - CSA - Echo intensity - Echo variation - VL pennation angle	RF all measures except pennation angle VL	- Echo intensity and ↓ both legs - Echo variation ↓ both legs - CSA and VL PA ↔
Mollá-Casanova et al., 2023 [78]	38 pre-frail older adults	Virtual running training 8 weeks (3 s/w) n:19 Control group: n:19	<b>Myotonometry:</b> - Muscle tone - Stiffness - Frequency	dominant lower-limb (TA, RF, BF, gluteus major, gastrocnemius)	↔
Nunes et al., 2019 [79]	66 older women (mean 69 yrs.)	All underwent 12 weeks (3 s/w) resistance training	<b>Spectral Bioimpedance:</b> - Phase Angle (PhA)		- Phase Angle (PhA) ↑
Radaelli et al., 2013 [80]	30 healthy older women (60–74 yrs.)	2 groups RT 6 weeks (2 s/w) - Single set n:15 - Multiple set n:15	<b>Ultrasound B-mode:</b> - Echo intensity	VL, VM, RF, VI	Echo intensity: ↓ ↑ MQEI
Radaelli, Wilhelm, et al., 2014 [81]	20 healthy older women (60–74 yrs.)	2 groups resistance training 13 weeks (2 s/w) - Low-Volume Group n: 11 - High-Volume Group n:9	<b>Ultrasound B-mode:</b> - Echo intensity	RF	Echo intensity: ↓ ↑ MQEI
Radaelli, et al., 2019 [82]	24 healthy older women (60–74 yrs.)	2 groups RT 20 weeks (2 s/w) - Low-Volume Group n: 12 - High-Volume Group n:12	<b>Ultrasound:</b> - Echo intensity	Echo intensity: RF	Echo intensity: ↓ ↑ MQEI
Raj et al., 2012 [83]	28 healthy older adults (68 ± 5 years)	2 groups RT 16 weeks (2 s/w) - conventional RT: 7 men, 5 women - Eccentrically biased RT: 8 men, 5 women -CG: 7 men, 6 women	<b>Ultrasound:</b> - PA - Fascicle length	VL and GM	↔

**Table 3** (continued)

Reference	Participants	Intervention	Testing procedures and Outcomes	Muscle group	Results of the exercise intervention
Rodriguez-Lopez et al., 2022 [84]	42 older adults (>65 years)	All 8-week control period after 12 weeks of -One leg Light Loads (LL) vs non-exercise (n:15) -One leg Heavy Loads (HL) vs non-exercise (n:14) -LL vs HL (n:13)	<b>Ultrasound:</b> - CSA (RF, VL) - PA - Fascicle length	- CSA: RF, VL - PA: VL - Fascicle length VL	- CSA: ↑ in LL and HL - PA ↑ in HL ↔ in LL - Fascicle length ↔
Scanlon et al., 2014 [85]	26 healthy older men and women (60–69)	6 weeks (2 s/w) resistance training n:13 -CG n:13	<b>Ultrasound:</b> - CSA - PA - Fascicle length - Echo intensity	RF and VL	- CSA: ↑ in EG - echo intensity, PA and fascicle length ↔
Suetta et al., 2008 [86]	36 healthy older men and women (60–86)	-RT: 12-week program (3 s/w) (n:13). -Electrical Stimulation (ES): 1 h per day for 12 weeks (n:11) -Standard Rehabilitation (SR): 1 h per day for 12 weeks (n:12)	<b>Ultrasound:</b> - PA	VL	- PA ↑ in RT
Taaffe DR, 2009 [87]	13 healthy older men and women (65–83)	All underwent 60-week resistance training, detraining, and retraining	<b>CT:</b> - Muscle attenuation - IMAT	Quadriceps and Hamstrings	- Muscle attenuation ↑ - IMAT ↔
Tanton et al., 2009 [88]	9 older females (71 ± 5.9), and 9 older males (73 ± 3.7)	All underwent 12-week training of the non-dominant arm	<b>MRI:</b> - CSA	BB	↑
Teodoro et al., 2020 [89]	36 older men (67 ± 5.1 yrs.)	3 groups RT 20 weeks (2 s/w) -Repetitions to Failure n:13 - Repetitions Not to Failure n:12 -Equalized Volume Group n:11	<b>Ultrasound:</b> - Echo intensity	VL, VL, RF	↔
Tracy et al., 1999 [90]	23 healthy older men and women (65–75)	9 weeks (3 s/w) unilateral leg strength training (n:23) -CG: untrained leg (n:23)	<b>MRI:</b> - CSA	Quadriceps	↑
Vojciechowski et al., 2021 [91]	46 healthy older women (+65yrs)	12 weeks (3 s/w) dancing training -EG: n:21 -CG: n: 25	<b>MRI:</b> - CSA - Intramuscular noncontractile tissue	Quadriceps	↔
Watanabe et al., 2014 [92]	46 healthy older participants (+65yrs)	All 12 weeks (2 s/w) RT - Low-intensity + slow movement (LST) - Low-intensity + normal speed (CON)	<b>MRI:</b> - CSA	Quadriceps	- CSA ↑ LST ↔ CON

**Table 3** (continued)

Reference	Participants	Intervention	Testing procedures and Outcomes	Muscle group	Results of the exercise intervention
Wilhelm et al., 2014 [88]	36 healthy older men	12 weeks - CG: n: 13 - Strength-endurance group n:12 - Endurance-strength group n:11	<b>Ultrasound B mode:</b> - Echo intensity	VL, VM, RF	- echo intensity ↓ in both EG
Yoshiko, Kaji, et al., 2018 [92]	20 older participants (+70 yrs.)	12 months (2 s/w) concurrent training - EG (participants requiring long terms care): n: 10 - CG: healthy older adults n:10	<b>Ultrasound B mode:</b> - Echo intensity	RF and BF	- echo intensity ↔
Yoshiko, Tomita, et al., 2018 [94]	27 older participants (75.6 ± 6.4)	All 6 months once or 2 a week concurrent training (one-group before-and-after trial)	<b>Ultrasound B mode:</b> - CSA - Echo intensity	RF, VL, VI (anterior and lateral), BF, thigh muscles	- CSA ↔ in all - Echo intensity ↓ in all
Yoshiko et al., 2021 [95]	64 healthy older participants (+65 yrs.)	Both groups walk 2–3 s/w during 10 weeks - Walking group (WG): n:31 - Walking +RT (WR): n: 33	<b>Ultrasound B mode:</b> - Echo intensity	RF and VL	- Echo intensity ↓ in both but specially in W + R
Zubac et al., 2019 [96]	31 healthy older adults (66.8 ± 5.1 yrs.)	- CG: n: 12 - 8-week (3 s/w) Plyometric training: n:11	<b>Tensiomyography:</b> - Time contraction (Tc) - Dm	VL, BF, TA, GM and GL	- Tc ↑ of BF and GM ↔ VL, TA, GL - Dm ↑ of BF, ↔ VL, TA, GL, GM

*MRI* Magnetic Resonance Imaging, *CSA* cross-sectional area, *QF* of quadriceps femoris, *RF* rectus femoris, *VL* vastus lateralis, *VI* vastus intermedius, *VM* vastus medialis, *BF* Biceps Femoris, *TA* Tibialis anterior, *GM* Gastrocnemius medialis, *GL* Gastrocnemius lateralis, *IMAT* Intramuscular adipose tissue, *CT* Computed Tomography, *BB* biceps brachii, and *BR* brachialis, *S7M* session/week, *IMAT* intermuscular adipose tissue, *Tc* Time contraction, *Dm* Maximal radial displacement, *PA* Pennation angle, *RT* Resistance Training, *EG* Exercise group, *CG* Control group, *DG* Dancing group, *ES* Electrical Stimulation, *SR* Standard Rehabilitation, *LST* Low-intensity + slow movement, *CON* Low-intensity + normal speed, *WG* Walking group

**Table 4** Specific outcomes measured to assess muscle quality using non-invasive tools

Tool Outcomes Measured	
Magnetic Resonance Imaging	Intramuscular fat infiltration, cross-sectional area, intermuscular adipose tissue
Computed Tomography	Intramuscular fat infiltration, cross-sectional area, muscle density
Ultrasonography	Cross-sectional area, echo intensity, echo variation, fascicle length, pennation angle
Bioelectrical Impedance Analysis	Phase Angle (PhA)
Tensiomyography	Muscle contractile properties (contraction time and maximal radial displacement), muscle tone
Myotonometry	Muscle stiffness, compliance, elasticity

### Direct non-invasive muscle quality measurement tools

Non-invasive techniques provide a comprehensive assessment of muscle quality by evaluating factors such as muscle architecture, composition, fat infiltration, fibrosis, and neural activation [12•]. The following discussion will delineate the array of tools employed to directly measure muscle quality after physical exercise interventions. Direct methods for assessing muscle quality, involve the direct measurement of muscle architecture, addressing both microscopic and macroscopic aspects of muscle composition and structure [30••].

Among the non-invasive tools employed to directly assess muscular quality, the review of the literature revealed that US was utilized in 18 articles, MRI in nine, while CT, TMG, and myotonometry were each applied in two articles, and BIA was used in one, with some articles incorporating more than one diagnostic modality.

CT and MRI are essential for analyzing muscle composition, providing precise assessments of muscle quality through measures of intramuscular fat infiltration and cross-sectional area, both approved methodologies by EWGSOP2 for determining skeletal muscle quantity and quality [30, 39, 97–99••], these results are consistent with those obtained in this review. While CT offers rapid and cost-effective muscle quality analysis, it does generate radiation exposure. In contrast MRI ensures a radiation-free alternative at a higher cost. Notably both showed concordance in clinical muscle quality assessment [39, 98].

Ultrasonography is emerging as a fast, non-invasive, and accessible imaging modality for musculoskeletal assessment [100•]. Current B-mode ultrasound techniques enable detailed examination of muscle architecture, including cross-sectional area, echo intensity, fascicle length, and pennation angle, which are critical markers of muscle quality [97]. Our results highlight that the quadriceps is the most studied muscle due to its size and accessibility, corroborating what the scientific literature mentions [101]. Recent systematic reviews assessing the validity and reliability of ultrasonography for skeletal muscle evaluation have revealed strong interclass correlation coefficients and confirmed its comparative

validity against other imaging modalities [35, 101, 102]. Although efforts to standardize these measurements are ongoing, these measurements are still highly dependent on operator expertise and do not provide definitive results for the early detection of muscle quality loss [50, 77•]. These findings are in line with the observations of the EWGSOP, which identifies ultrasound as a promising method for assessing skeletal muscle although it emphasizes the need for further research for its clinical application [30••].

BIA, through PhA analysis, emerges as an effective non-imaging method to characterize muscle quality components. BIA-derived PhA can be used to detect muscle quality and identify sarcopenia [60, 97]. Recent studies have started to recognize it as a significant predictor of muscle quality in older adults, associated with adverse clinical outcomes, including mortality [103, 104]. Also, the EWGSOP incorporates BIA-derived PhA in their criteria for muscle quality assessment [30••].

Expanding on these techniques TMG and myotonometry are non-invasive diagnostic tools that measure muscles mechanical properties. TMG utilizes electrodes to assess muscle contractile properties and tone in superficial muscles by quantifying radial deformation resulting from electrically induced contractions [105, 106•]. TMG has proven to be a valuable tool for assessing neuromuscular function in older adults, as it is sensitive to changes in muscle composition, architecture, and pre-atrophy of skeletal muscles [57]. A promising tool for the non-invasive assessment of muscle quality in aging and diseased populations [57]. Myotonometry measures muscle stiffness by monitoring radial tissue deformation in response to a perpendicular force applied through a hand-held device. It evaluates key muscle biomechanical and viscoelastic properties, including stiffness, compliance and elasticity [107]. Compared to elastography and TMG, myotonometry is fast, portable and cost-effective, displaying higher reliability and validity for differentiating muscle stiffness levels [107]. While existing studies affirm its reliability and validity within musculoskeletal diagnostics [108–111], further extensive validation is necessary for its routine clinical application. The research suggests

that changes in muscle architecture, such as an increase in pennation angle, can impact tetanic tension and ultimately influence contractile properties [112]. This interplay between morphology, architecture, and contractile capacity in human pennate muscle is reflected in specific adaptation responses to intensive resistance training [112]. Additional studies emphasize the substantial influence of architectural parameters on muscular contractile dynamics, underscoring the relevance of architectural properties in the analysis of contractile behavior [113, 114].

### Exercise effects on muscle quality

The heterogeneity in defining and assessing muscle architecture and composition contributes to the variance in results across different studies. This variation is further influenced by different training protocols and measurement techniques, which could explain the outcomes observed.

The mechanisms underlying the association between echo intensity and MQ are not fully elucidated, but it is hypothesized that intramuscular content alterations reflect performance outcomes [115]. Higher echo intensity usually denotes lower muscle quality and performance due to increased fibrous and adipose infiltration, conversely, reduced echo intensity tends to indicate enhanced performance [9, 115, 116]. The results of our systematic review, in which echo intensity decreased, aligns with findings from systematic reviews in which echo intensity is improved after exercise training [115]. Although ultrasound-based echo intensity is a common method for assessing the quadriceps femoris, its use raises questions in both research and clinical settings, particularly regarding the physiological interpretation of echo intensity changes and potential technical inconsistencies.

Also, exercise can influence the pennation angle of muscles, which is a potential indicator of muscle hypertrophy, the plasticity of muscle architecture, and the efficiency of force transmission [117]. Other reviews corroborate our findings, with seven studies noting improvements in pennation angle in older adults and others showing no change [118••]. These discrepancies may stem from the eccentric nature of resistance training or the short duration of certain studies [83, 85•].

During the aging process, there is a reduction in the size and number of muscle fibers, leading to atrophy and a reduction in cross-sectional area (CSA) [118, 119••]. In the systematic review we conducted, we observed that resistance exercise interventions improve CSA [66, 68, 75, 84, 85, 88, 90, 92] or maintain it [74, 77, 91, 95]. These improvements are attributed to muscle hypertrophy and myofibrillar protein turnover [85]. The results of our

review are consistent with the results of other studies and reviews [118–121••], [119, 120].

Fascicle length is related to maximal shortening velocity and the force–length relationship. Such lengthening can result from an increase in serial sarcomere number or hypertrophy along the muscle fibers [115••]. As seen in some studies resistance training increased it in older men [122, 123]. Yet, our results align with research showing some or no muscle architecture changes after certain training periods [124, 125].

When exploring the assessment of muscle quality, it allows us to unravel the implications that aging generates on it. Aging-associated fatty infiltration of skeletal muscle has been linked to negative health effects and functional deficits [74, 126]. There is a connection between fat infiltration in skeletal muscle and physical inactivity in elderly persons. Less is known about the idea that an exercise program can alter an older adult's IMAT level measured by MRI [126]. This justifies the improvement of fat infiltration and IMAT [66, 75] with some exercise interventions analyzed in the systematic review, while being maintained in others [68, 72, 74]. Prior research has looked at how resistance and multimodal exercise training affect older adults' muscle composition and has demonstrated the ability to reduce IMAT [74, 127, 128]. Whereas others cite no change in fat infiltration with exercise interventions [129, 130]. It has also been observed that physical exercise is capable of generating significant changes in CSA [130, 131]. In our systematic review CSA improves in three [88, 90, 92] studies and remains unchanged in one [91]. Other studies have shown positive changes in CSA with moderate intensity resistance training, but did not obtain improvements with low intensities [130]. Also, in another study only those with a high percentage of IMAT improved CSA [74].

While exploring the effects of age and exercise interventions on muscle composition, CT is crucial for assessing muscle quality by quantifying muscle attenuation and fat content, based on the specific attenuation of each tissue measured in Hounsfield units (HU). Increases in these areas are linked to poorer muscle quality and higher mortality risk [132]. Age-related increases in these fat deposits have been associated with metabolic and muscular dysfunction [126]. Our systematic review elucidates that physical exercise prevents the increase of intermuscular fat and the decrease of muscle density, compared to control [71], while another study shows that exercise improves muscle attenuation without increasing IMAT [133]. The findings align with existing research, a study with a similar population showed that while muscle CSA remained unchanged, there was a reduction in subcutaneous fat and IMAT [134]. In obese older adults,

interventions including exercise and nutrition are proven to enhance subcutaneous and intermuscular fat, muscle CSA, and muscle attenuation [126, 132, 133, 135, 136].

Moreover, aging leads to a decline in muscle contractile properties, often due to the loss of type II fibers [56]. TMG measured Tc has been found to correlate with muscle fiber composition, in muscles such as vastus lateralis [56], while Dm correlates with muscle atrophy [56]. As far as we have been able to observe the vast majority of interventions focus on young populations, where a regular decrease in dm is a common post-training response to strength training [57, 96, 137, 138]. Improvements in BB Dm and Tc have also been reported [139], although in some studies Dm has improved but Tc has remained unchanged [140]. These results agree with those obtained in the systematic review [32, 96].

In the findings of our systematic review, it is observed that resistance training notably enhances muscle stiffness, whereas aerobic training maintains muscle tone and frequency [32, 78] assessed by myotonometry. Comparable populations have shown improvements in muscle tone, stiffness, and elasticity following neck stabilization exercises [141], with muscle stiffness responding more noticeably than tone or elasticity to upper-extremity rehabilitation post-stroke [142]. A field review reveals that resistance training effects on muscle are inconsistent, while plyometric training improves muscle stiffens also in pathological cases, exercise normalizes stiffness, but further study is needed [143].

Furthermore, as evidenced by the results of the review, resistance exercise increases BIA-derived PhA [79], aligning with the literature linking resistance with improvements in strength and PhA in older adults [79, 104, 144]. Likewise, these studies associate PhA with changes in muscle strength [145]. To enhance PhA, a

program of at least twelve weeks is recommended, with three weekly sessions of six to ten exercises, as applied in the intervention analyzed [104].

#### Primary multisource parameters in muscle quality assessment research

Among the articles incorporating multiple tests, some specifically combined different methodologies like MRI+US and tensiomyography+myotonometry [32, 66]. MRI and US provide detailed images of muscle composition and structure, while tensiomyography and myotonometry assess muscle mechanical properties and stiffness, respectively.

Muscle quality is characterized by functional and morphological domains; the first one aligns with indirect measurements (Table 5) of muscle function relative to mass, while the second involves direct assessments of muscle architecture [31]. Our review shows that studies often use both methods for a holistic understanding [17]. Direct measurements offer precision for clinical research, yet are costly and require specialized skills. Indirect methods are prized for their speed and practicality [31]. Employing both allows for cross-validation and a more comprehensive understanding of muscle quality, blending structural and functional insights.

Moreover, the inclusion of functional capacity tests in many articles of the systematic review [32, 68, 71, 72, 76, 79, 80, 82, 90, 91, 93, 94, 146, 147, 148] is justified by the association between muscle quality and functional capacity, especially in older adults [148]. Therefore, functional capacity tests provide valuable information on how muscle quality translates into daily practical performance.

**Table 5** Indirect measures of muscle quality

Author	Definition of indirect muscle quality assessment	Formula
Da boilt et al., 2016 [68]	Strength per unit of cross-sectional area (CSA) of the knee extensor muscle in isometric position	Strength (N) / CSA (cm <sup>2</sup> )
Goodpaster et al., 2008 [71]	Knee extensor strength per unit area of the quadriceps muscle	Strength (N) / Quadriceps area (cm <sup>2</sup> )
Greig et al., 2011 [72]	Mechanical quality of the muscle, defined as maximum voluntary contraction (MVC) per unit of muscle volume	MVC (N) / Muscle volume (l)
Nunes et al., 2019 [79]	Muscle Quality Index (MQI)=Total 1RM force divided by total skeletal muscle mass (SMM) in kilograms	1RM (kg) / SMM (kg)
Radaelli et al., 2013 [80]	Maximum dynamic strength of the knee extensors divided by the sum of the muscular thickness of the quadriceps (MT QUAsum)	Unilateral 1RM knee extension (kg) / MT QUAsum (mm)
Radaelli, et al., 2019 [82]	MQI maximum rate of torque development (MRTD) and muscle power, calculated by dividing MRTD by muscle echo intensity (MQEI)	MRTD (Nm/s) / MQEI (Nm/s/mm)
Tracy et al., 1999 [90]	The values of isometric strength and 1-RM (N and kg, respectively) were divided by muscle volume values	Strength (N or kg) / Muscle volume
Vojciechowski et al., 2021 [91]	Relationship between torque (T) and muscular cross-sectional area (CSA)	T (Nm) / CSA (cm <sup>2</sup> )

### Trends in direct muscle quality assessment tools

From the perspective of the EWGSOP, which emphasizes the importance of evaluating not just muscle quantity but also quality, our review reveals that a defined criterion for selecting one evaluation tool over another based on an individual's specific characteristics has not yet been established [30••]. This underscores the urgency of further researching the concept of muscle quality and how new technologies, combined with current physiological knowledge, can be appropriately applied to assess muscle quality depending on each individual's unique characteristics. Innovative technologies such as tensiomyography and myotonometry are emerging as important tools in this field [32•]. Phase angle measurements using BIA also show promise as a biomarker for monitoring muscle quality in older adults [103, 104]. In addition, recent advances in quantitative ultrasound techniques, such as echogenicity analysis, texture parameters, elastography and acoustic wave properties, are moving forward although so far, their clinical application has been limited [101, 149].

### Conclusions

To our knowledge, this study represents one of the most comprehensive syntheses of evidence aimed at assessing muscle quality (microscopic and macroscopic aspects of muscle architecture and composition) in older adults through direct methods following physical exercise interventions. Key findings include: (1) the results of this review reflect that the most commonly used methods for the direct assessment of muscle quality after an exercise intervention are ultrasound (US) and magnetic resonance imaging (MRI). US imaging commonly reported outcomes such as echo intensity, pennation angle, fascicle length, and cross-sectional area (CSA) in the rectus femoris (RF) and vastus lateralis (VL). MRI, primarily assessed CSA, intramuscular adipose tissue (IMAT), and fat infiltration, with a predominant focus on the quadriceps. Exercise-induced reductions in echo intensity, improvements in pennation angle, and CSA enhancements were observed with ultrasound. MRI highlighted benefits in fat infiltration and IMAT; (2) a general tendency of exercise interventions to improve or maintain muscle quality; (3) the frequent combination of direct measures of muscle quality with indirect methods and functional capacity tests in current research. The majority of the reviewed articles employ both direct and indirect methods to assess muscle quality; and (4) an emerging development of technological innovation in the design of new tools for the direct detection of muscle quality, exemplified by tools such as US and phase angle measurement,

although their clinical application remains limited in the target population.

Regarding the limitations of the study, the condition imposed to include studies, where muscle quality had to be measured directly in conjunction with exercise interventions, significantly limited the number of articles eligible for this review. Furthermore, a limitation has been observed in the inclusion of studies using phase angle as a parameter, this is because the studies did not perform a comparative analysis with muscle quality, which could have left out relevant articles. Likewise, no studies were found that employ all the direct measurement parameters of muscle quality together. The lack of a standardized protocol and the diversity in the evaluation methods used by different authors prevent an accurate and unified comparison of the results. The decision not to perform a meta-analysis on the effects of exercise on muscle quality is grounded in the notable diversity observed in the included studies. Variability in the tools used to measure muscle quality, differences in the muscles assessed, and the various aspects measured contribute to a significant level of methodological heterogeneity, compromising the necessary comparability for a robust meta-analysis.

A promising direction for future research is the development of personalized protocols for the selection of measurement tools, tailored to the specific conditions of each patient. This would include the identification of which tool is the most appropriate according to the individual profile and needs. In parallel, it is crucial to investigate advanced non-invasive techniques in sports medicine and rehabilitation to measure muscle quality with greater precision and sensitivity, which could lead to the creation of personalized physical exercise programs based on each person's specific muscle weaknesses. Furthermore, there is a need to explore the effectiveness of these tools in different muscles, determining the most effective one in which to perform the measurements in order to extrapolate the data to the diagnosis of muscle diseases in clinical settings.

### Abbreviations

BB	Biceps Brachii
BF	Biceps Femoris
BF	Biceps Femoris
BIA	Bioimpedance
BR	Brachialis
CSA	Cross-Sectional Area
CG	Control Group
CON	Low-intensity + normal speed
CT	Computed Tomography
Dm	Maximal radial displacement
DXA	Dual Energy X-ray Absorptiometry
EG	Exercise Group
EWGSOP	The European Working Group on Sarcopenia in Older People
GL	Gastrocnemius Lateralis
GM	Gastrocnemius Medialis
HITT	High-Intensity Interval Training
IMAT	Intramuscular Adipose Tissue

LST	Low-intensity + slow movement
MRI	Magnetic Resonance Imaging
MRI	Magnetic Resonance Imaging
MSK-US	Musculoskeletal Ultrasound
PA	Pennation Angle
PhA	Phase Angle
QF	Quadriceps Femoris
RF	Rectus Femoris
RT	Resistance Training
S/W	Session/Week
TA	Tibialis Anterior
Tc	Time contraction
TMG	Tensiomyography
US	Ultrasound Sonography
VI	Vastus Intermedius
VL	Vastus Lateralis
VM	Vastus Medialis

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### Authors' contributions

NV and XR conceived the idea and design for the article. NV and XR performed the literature search, data acquisition, analysis, and/or interpretation. NV, XR, AM-Z and BG-Z drafted and/or critically revised the work. All authors have read, and approved the final version of the manuscript.

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### Availability of data and materials

The systematic search queries and data charting methods employed in this study are available upon request. Additionally, our systematic review was registered on the Open Science Framework (OSF) platform on October 24, 2023, with the registration DOI [<https://doi.org/https://doi.org/10.17605/OSF.IO/3GD6Y>]. The authors are committed to fostering transparency in research, and for any inquiries or requests for specific methodological details, we welcome communication with the corresponding author.

### Declarations

#### Ethics approval and consent to participate

Not applicable.

#### Consent for publication

Not applicable.

#### Competing interests

The authors have no competing interests to declare that are relevant to the content of this article.

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### **3.2 Article II: Non invasive techniques for muscle quality functional domain monitoring in older adults: a scoping review.**

This section presents the second of two systematic reviews and four case studies included in this dissertation. It provides a summary of non-invasive methods used to indirectly assess muscle quality in older adults, addressing one of the previously identified research gaps and aligning with the dissertation's main objectives. Since the EWGSOP emphasized the importance of muscle quality in diagnosing sarcopenia in 2019, there has been increasing recognition of its relevance. This includes the analysis and measurement of skeletal muscle's morphological and functional properties, which are key indicators of muscle quality (Cruz-Jentoft et al., 2019).

While the previous review helped bridge knowledge gaps regarding the most effective non-invasive tools for assessing morphological muscle quality in older populations, an additional gap has been identified concerning indirect non-invasive tools. These tools focus on evaluating functional muscle quality. This article aims to identify such indirect non-invasive tools and explore factors such as accessibility, cost, and required training, ultimately working towards the development of simple and accessible methods for use in community settings.

To evaluate functional muscle quality, tools commonly used are designed to measure both muscle strength or power and muscle mass. These measurements are essential as they form the foundation for calculating the muscle quality index, which is derived from indirect assessments of muscle performance relative to muscle mass (Cruz-Jentoft et al., 2010; de Lucena Alves et al., 2023; Virto, Río, Méndez-Zorrilla, et al., 2024). The purpose of this scoping review is to systematically examine and summarize the current evidence on non-invasive tools for assessing functional muscle quality in older adults. This review will identify the most effective methods, as well as highlight recent trends and advancements in the field. Additionally, it aims to assess the main limitations associated with current tools and investigate the factors influencing the selection of each technique. Specifically, it will evaluate aspects such as accessibility, cost, and training requirements, with the goal of encouraging the use of simple and accessible methods in community settings. A scoping review is chosen for this work due to its broad and general approach, suitable for mapping out the wide range of available tools and evidence in this area.

Below is a table that justifies the choice of a scoping review, compares it to a systematic review and sets out the reasons why each approach was selected to best suit the needs of each of the reviews and case studies.

Table 2. Differences between scoping and systematic reviews.

Aspect	Scoping Review	Systematic Review
Approach	Broad: Exploration of non-invasive tools for measuring functional muscle quality in older adults, their principles, limitations, and contextual factors.	Specific: Evaluation of non-invasive tools for measuring muscle quality after exercise interventions, effects of exercise programmes, and advances in tools after interventions.
Principal objective	General mapping of the literature to identify available tools, limitations, and external factors affecting their implementation in the community.	Answer specific questions about the effectiveness of tools and parameters measured following exercise interventions in older adults and review recent advances in measurement technology.
Nature of the questions	Explore the big picture (what tools exist, their principles, general trends and choice factors such as cost or accessibility).	Focus on evaluating the effectiveness of interventions (effects of exercise on muscle quality) and specific details about the predominant tools and parameters in intervention studies.
Adequacy to the review	Adequate to map the field, understand the general context, and define areas for future research without conducting an exhaustive critical synthesis.	Adequate to answer concrete questions, evaluate the effectiveness of interventions, and critically analyse relevant studies around specific tools and effects of exercise programmes.
Type of Analysis	Descriptive: Identification and description of key issues, trends and knowledge gaps about non-invasive tools in the community.	Critical and Analytical: Synthesis of results and analysis of effectiveness of exercise interventions in specific studies, with emphasis on validated methods.

To achieve the referred goal, a comprehensive review was conducted to assess non-invasive techniques to indirectly measure muscle quality in older adults, analyzing 79 studies that met the inclusion criteria. This framework served as the basis for drawing conclusions on the effectiveness of various tools used to measure the functional domain of muscle quality, addressing the initial research questions. It has identified the different definitions and underlying principles associated with these definitions, as well as the measurement techniques commonly employed in the scientific literature. This comprehensive analysis not only enhances our understanding of functional muscle quality assessment but also offers practical recommendations. These recommendations are tailored to support the selection and application of assessment tools, considering factors such as budgetary constraints and the specific needs of community practice settings.

This article was submitted to the International Journal of Sports Science & Coaching (IF: 1.5 (Q2 SJR, Q3 JCR) and it is currently under review.

As we have mentioned earlier, recent updates from the EWGSOP, along with other established groups, highlight the significance of evaluating muscle quality (MQ) as a vital measure of skeletal muscle tissue's physiological characteristics, which affect both muscle strength and functional abilities (Cruz-Jentoft et al., 2019). MQ refers to the physiological capacity and performance of muscle (Cruz-Jentoft et al., 2019). MQ encompasses several factors related to muscle composition, including both the microscopic and macroscopic properties of muscle structure, as well as its functional performance in relation to muscle mass (Cruz-Jentoft et al., 2019; de Lucena Alves et al., 2023). Consequently, it is usually categorized into two main areas: morphological and functional. The morphological area involves direct assessments of muscle structure, examining both the microscopic and macroscopic traits of muscle and its composition (Cruz-Jentoft et al., 2019; de Lucena Alves et al., 2023; M. S. Fragala et al., 2015; Virto, Río, Méndez-Zorrilla, et al., 2024). In contrast, the functional area focuses on indirect evaluations of muscle performance in relation to its mass. This aspect aims to assess the efficiency of force production relative to muscle size, often quantified through a muscle quality index (Barbat-Artigas et al., 2012; Coronado-Zarco & de León, 2023; Cruz-Jentoft et al., 2019; Naimo et al., 2021). Evaluating muscle quality from a functional perspective involves analyzing performance metrics like strength and power (such as peak torque, 1RM, 5RM, isometric strength, etc.), along with quantitative measures of muscle size, including mass, lean tissue, muscle thickness, volume, and/or cross-sectional area (Barbat-Artigas et al., 2012; Coronado-Zarco & de León, 2023; Cruz-Jentoft et al., 2019; Naimo et al., 2021).

Muscular quality may be a more sensitive measure of muscular function than muscle mass alone, as age-associated changes in muscle quality typically take place before any discernible decrease in muscle mass<sup>8</sup>. This observation holds significance because changes in muscle quality may provide a more coherent explanation for the typical aging-related decreases in muscular strength and function. The fact that muscle quality is a relatively new concept and that diagnostic techniques for assessing it are not yet completely standardized (Cruz-Jentoft et al., 2019) should also be considered, highlighting the need for more study in this area. Muscle quality evaluation methods can be categorized into three main groups: the first category includes invasive methods; the second consists of direct non-invasive techniques; and the third group involves indirect non-invasive approaches that assess muscle quality through external indicators or approximations (Barbat-Artigas et al., 2012; Coronado-Zarco & de León, 2023; Correa-de-Araujo et al., 2017)(Cruz-Jentoft et al., 2019; de Lucena Alves et al., 2023; Virto, Río, Méndez-Zorrilla, et al., 2024). This scoping review will specifically concentrate on the indirect methods used to assess the functional aspect of muscle quality. These techniques are relatively simple to conduct, do not necessitate the use of invasive instruments, and serve as a valuable tool for evaluating functional muscle quality in older populations (Coronado-Zarco & de León, 2023; Correa-de-Araujo et al., 2017; Cruz-Jentoft et al., 2019).

To assess functional muscle quality, instruments typically measure both muscle strength or power and mass, which are essential for calculating the muscle quality index through indirect assessments of muscle performance in relation to muscle mass (Barbat-Artigas et al., 2012; Coronado-Zarco & de León, 2023; de Lucena Alves et al., 2023; Naimo et al., 2021). In clinical practice a variety of instruments are used for these measurements, for example in the case of strength, isometric dynamometers and MRI strength tests are used as simple measurement methods, while more advanced devices such as power meters and isokinetic analysers provide more accurate assessments (American College of Sports Medicine et al., 2009; Baltzopoulos & Brodie, 1989; Chamorro et al., 2017; Cruz-Jentoft et al., 2019; Ramirez-Campillo et al., 2022; Reid & Fielding, 2012). For clinical application, various devices are available, ranging from simpler tools like isometric dynamometers and RM strength tests to more advanced equipment such as power gauges and isokinetic testers, which provide more comprehensive assessments of strength (American College of Sports Medicine et al., 2009; Baltzopoulos & Brodie, 1989; Chamorro et al., 2017; Cruz-Jentoft et al., 2019; Ramirez-Campillo et al., 2022; Reid & Fielding, 2012). Additionally, muscle mass is typically measured through techniques such as BIA, DXA, B-mode ultrasound, CT, and MRI, each offering unique insights into muscle composition,

including lean mass, muscle thickness, and cross-sectional area (Correa-de-Araujo et al., 2017; Faron et al., 2020; Niklasson et al., 2022; Scafoglieri & Clarys, 2018; Sconfienza et al., 2018; Sergi et al., 2016). Despite strong recommendations from prominent organizations like ICFSR and EWGSOP to standardize definitions and improve assessment methods for muscle quality, determining the most effective tools for these evaluations remains a challenge. This underscores the importance of a comprehensive review to synthesize and analyze the existing evidence on non-invasive tools for assessing functional muscle quality in older adults. This review will not only evaluate the effectiveness of current methods but also highlight recent trends and advancements in the field. Furthermore, it aims to explore the practical considerations that influence the choice of tools, such as accessibility, cost, and training requirements, with the ultimate goal of promoting the use of accessible, simple methods in community settings (Correa-de-Araujo et al., 2017; Cruz-Jentoft et al., 2019).

The scoping review was conducted following the guidelines set forth by the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards. The main objective was to address several key research questions.

1. Which non-invasive techniques and their underlying concepts are employed to assess the functional domain of muscle quality in the elderly?
2. Which non-invasive techniques have been found to be the most reliable and successful for evaluating the functional domain of muscle quality in older adults?
3. Which are the primary disadvantages of the non-invasive methods used today to assess the quality of older persons' functional domain muscles?
4. What aspects, such as price, ease of use, and necessary training, affect the selection of non-invasive instruments for evaluating the quality of functional muscles, especially in community contexts, and how may easy and approachable techniques be used to promote their application in the community? What developments or trends have been noticed recently?

To ensure a thorough and systematic approach, the review adhered to the PICOS framework (participants, interventions, comparators, outcomes, and study design) to define the inclusion and exclusion criteria for studies. The review included studies focusing on healthy older adults (60 years and above) and assessed tools that measured functional muscle quality, excluding studies involving participants under 60 years or those with muscle diseases that might impact muscle quality measurement. Furthermore, studies that did not focus on the functional domain of muscle quality or employed invasive techniques were excluded.

The literature search was initiated using a tailored search strategy for PubMed, focusing on titles, abstracts, and keywords. This search strategy was then adjusted for other databases, such as Web of Science and Scopus, using boolean operators to combine relevant keywords systematically. The search was conducted up until October 2024. The search strategy was as follows, healthcare keywords: "aged" OR "old" OR "elder\*" OR "aging" OR "frail\*" OR "older" OR "senior" OR "geriatric". Technique keywords: "measure\*" OR "determine" OR "analyze" OR "evaluate" OR "sensitivity and specificity" OR "screening" OR "tool\*" OR "assess\*" OR "diagnostic accuracy". Muscle quality keywords: "muscle function" OR "muscle performance" OR "muscle functional performance" OR "muscle functional capacity" OR "muscle quality" OR "functional domain" OR "muscle quality index".

The review specifically excluded non-invasive imaging methods for monitoring muscle quality due to concerns that including these techniques could introduce bias by influencing the results. Instead, the focus was on studies that directly assessed muscle quality, ensuring a more objective approach to evaluating the available evidence.

For the purpose of eliminating duplicates and subsequently filtering them according to the predetermined inclusion and exclusion criteria, potential research were directly exported from scientific databases into Rayyan (<https://www.rayyan.ai/>). Following these procedures, 10,559 records in all were found. Figure 1 describes the study selection procedure. 6,382 records were eliminated after titles and abstracts were screened, and duplicates (n=6,591) were eliminated. 209 full-text articles remained for additional assessment. After a full-text examination for eligibility, 130 more papers were disqualified. In the end, it was decided that 79 papers qualified for the scoping review.

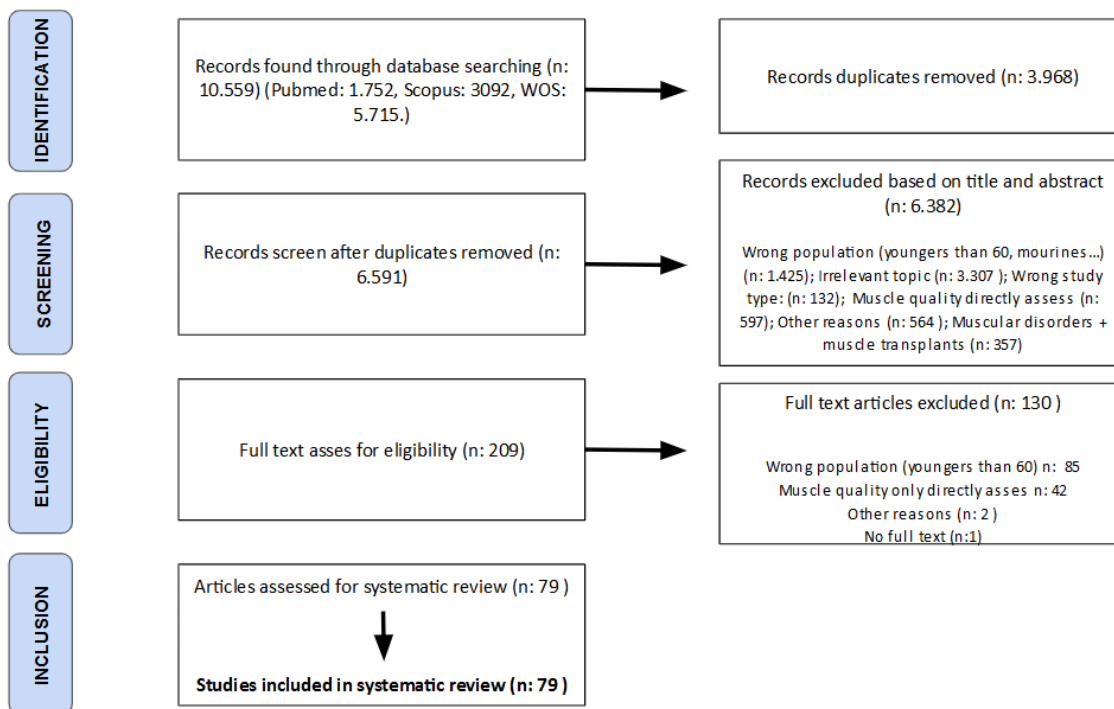


Figure 7. Flow diagram of the systematic search process.

The details of the characteristics of the studies included in this review are presented in Table 2. A total of 32,892 participants aged over 60 years were analyzed. Of these, 42 studies involved both male and female participants (n: 26,572, accounting for 80.8% of the total sample). Thirty studies consisted solely of female participants (n: 3,719, 11.3% of the total), and seven studies focused only on male participants (n: 2,601, 7.9% of the total). The studies included in this review were published between 1999 and 2024, with approximately one-third published since 2021 (n: 24, 30%).

Table 3. Descriptive features of participants, muscle quality definitions, assessment methods, targeted muscle groups, and the effectiveness and limitations of the measurement tools.

Reference and country	Participants	Muscle quality definition	Assessment methods (test and principles of measurement)	Assessment site	Advantages and disadvantages
(Abdalla et al., 2021)	94 community residents older adults (69.1% female, 69 ± 6.1 years)	MQ ratio standard (muscle strength normalized by body size).	<b>Assessment:</b> HGS, Knee extensors (KE) 1RM, isokinetic KE and peak torque. <b>Tools:</b> Strength: : isometric dynamometer (HGS), isokinetic dynamometer (inferior extremity muscle); DXA and BIA for muscle mass.	Lower and Superior extremities.	HGS and BIA are affordable and widely available, making them well-suited for both clinical and community settings, though more advanced imaging techniques offer greater specificity. Isokinetic dynamometers and DXA reliably measure leg strength and mass, but their high cost and need for specialized training restrict their use beyond clinical settings
(Abe et al., 2016)	135 active elderly males (77 ± 4 years)	Forearm MQ, ratio of HGS to forearm ulna muscle thickness (HGS/MT). Relative HGS ratio of HGS to forearm girth (HGS/forearm girth) and a ratio of HGS to body mass (HGS/body mass).	<b>Assessment:</b> HGS. <b>Tools:</b> For strength assessment: isometric dynamometer (HGS) and to muscle thickness US (B-mode).	Superior extremities.	These dynamometers are effective in assessing functional MQ and suitable for community programs, while ultrasound provides precise MQ assessments, though its high cost and reliance on operator expertise limit its accessibility in community settings.
(Baek et al., 2022)	143 older individuals (69% female, mean age 74 ± 6 years)	HGS per unit of body weight.	<b>Assessment:</b> HGS. <b>Tools:</b> For strength: isometric dynamometer (HGS); for muscle mass and body composition BIA.	Superior extremities.	HGS and BIA are affordable and widely available, making them well-suited for both clinical and community settings, though more advanced imaging techniques offer greater specificity.
(Banitalebi et al., 2020)	63 female, (65-80 years)	Formula for MQ: (Leg length×0.4 body mass×gravity×10/time sit-stand)	<b>Assessment:</b> HGS and 30 second chair stand test. <b>Tools:</b> Strength: : isometric dynamometer (HGS); for body mass: DXA.	Inferior extremity (leg).	HGS and DXA provide reliable assessments for community use, but the high cost and equipment demands of DXA may limit its accessibility.
(Barbat- Artigas et al., 2013)	1219 female (80 ± 4 years).	Muscle Quality Index (MQI): strength per unit of muscle mass. Superior extremity : HGS by superior extremities muscle mass (kPa/kg). Inferior extremity : KEstrength by inferior extremities muscle mass (kPa/kg).	<b>Assessment:</b> HGS and KEstrength (KES) test. <b>Tools:</b> Muscle strength: isometric dynamometer HGS, maximum voluntary contraction for KES; for muscle mass DXA.	Lower and Superior extremities.	MQI is easier to access, but it may not measure the entire range of muscle quality that tools like MRI or CT can capture. While DXA offers dependable assessments for community settings, its high cost and need for specialized equipment may restrict its broader use.
(Brady et al., 2014)	94 community residents older female (73.6 ± 5.4)	MQ, leg power normalized for lower-body mineral-free lean mass (watts/kg).	<b>Assessment:</b> Leg extension power. <b>Tools:</b> For leg extension power: nottingham power rig; for muscle mass, DXA.	Inferior extremity (quadriceps).	DXA accurately assesses muscle mass, but the advanced equipment needed restricts accessibility.
(Briggs et al., 2018)	17 older individuals post-hip fracture (mean age 77 ± 12 years)	MQ, isometric peak KE force by the quadriceps lean muscle mass (N/cm <sup>2</sup> ).	<b>Assessment:</b> KE isometric force. <b>Tools:</b> Muscle strength: isokinetic dynamometer and for muscle mass MRI.	Inferior extremity (quadriceps).	MRI is useful, but its community application is expensive and complicated.
(Brightwell et al., 2019)	23 healthy sedentary to low-active older	MQ, strength per unit of muscle mass. Isokinetic peak torque of the right	<b>Assessment:</b> Isokinetic (120°/s) peak torque strength test.	Inferior extremity (quadriceps).	Isokinetic dynamometers and DXA reliably measure leg strength and mass, but their high cost and need for specialized training restrict their use beyond clinical settings

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	individuals (73 ± 4 years)	leg divided by right leg lean mass (torque/kg).	<b>Tools:</b> Isokinetic dynamometer to measure muscle strength and for muscle mass DXA.		
(Brown et al., 2016)	4510 older individuals in a longitudinal cohort study (≥60 years)	MQI: Determined by sit-to-stand time, body weight, and leg length. [(L - 0.5) x body mass x g x 5=]/T sit to stand; where 0.5 (m), Leg (m), g (m/s <sup>2</sup> ).	<b>Assessment:</b> 5-repetition sit-to-stand. <b>Tools:</b> For functional strength: time analysis of 5STS; Anthropometric measurements for leg length and a digital scale for body mass.	Inferior extremities.	A practical index for mortality prediction, though less precise for detailed MQ assessment. It may help quantify age-related locomotor decline, crucial for physical function and longevity, emphasizing the need for further research to complement other methods.
(Canon & Crimmins, 2011)	867 (445 females) older individuals in a longitudinal cohort study (≥60 years).	MQ, isokinetic strength per unit muscle mass. Knee extensor strength/leg skeletal muscle mass.	<b>Assessment:</b> Knee extensor isokinetic strength. <b>Tools:</b> Kin-Com dynamometer (isokinetic strength) for strength; for muscle mass, DXA.	Inferior extremities.	Isokinetic dynamometers and DXA reliably measure leg strength and mass, but their high cost and need for specialized training restrict their use beyond clinical settings
(C.-J. Chang et al., 2021)	180 older individuals with T2DM (72.5 ± 5.3 years, 53.3% males)	MQ, HGS ratio to relative appendicular muscle mass	<b>Assessment:</b> HGS. <b>Tools:</b> Strength: : isometric dynamometer (HGS); for muscle mass, DXA.	Superior extremities	HGS and DXA provide reliable assessments for community use, but the high cost and equipment demands of DXA may limit its accessibility.
(Correa et al., 2012)	10 sedentary elderly females (67 ± 5 years)	MQ, force per unit of muscle mass. The 1RM value of the stronger leg/ muscle volume of the stronger leg (kg/cm <sup>3</sup> )	<b>Assessment:</b> KES (stronger leg). <b>Tools:</b> 1RM KE dynamometers for strength; for muscle volume US (B-mode).	Inferior extremity (quadriceps).	The 1RM test and US provide accurate muscle quality assessments, but the high cost of US and its reliance on operator expertise limit its accessibility in community settings.
(da Costa Pereira et al., 2023)	176 hospitalized older individuals (≥60 years, 43.8% females)	MQI: ratio of muscle strength to appendicular skeletal muscle mass (ASMM).	<b>Assessment:</b> HGS. <b>Tools:</b> Strength: : isometric dynamometer (HGS); BIA for muscle mass assessment.	Superior extremities	HGS and BIA are affordable and widely available, making them well-suited for both clinical and community settings, though more advanced imaging techniques offer greater specificity.
(Cramer et al., 2016)	330 sarcopenic older adults (≥65 years)	Leg strength (peak torque) relative to leg muscle mass (Nm/kg).	<b>Assessment:</b> Knee extension <b>Tools:</b> To assess muscle strength: maximal voluntary isokinetic peak torque in leg extension; for muscle mass: DXA.	Inferior extremities	Isokinetic dynamometers and DXA reliably measure leg strength and mass, but their high cost and need for specialized training restrict their use beyond clinical settings
(Cunha et al., 2018)	62 females (68.6 ± 5.0 years)	MQ, specific force per unit of muscle mass. Sum of the best 1RM values for the 3 exercises by the skeletal muscle mass.	<b>Assessment:</b> Knee extension, chest press and preacher curl. <b>Tools:</b> Muscle strength assessed by the combined 1RM of three exercises; total skeletal muscle mass measured with DXA.	Lower and Superior extremities.	These dynamometers are efficient in evaluating functional MQ and suitable for community programs, whereas DXA offers a thorough mass assessment but is restricted to clinical environments due to its high cost.
(Delmonico et al., 2008)	1367 well-functioning older individuals (726 men, 70–79 years)	For muscle quality assessment knee extensor torque per unit of thigh CSA.	<b>Assessment:</b> KE torque. <b>Tools:</b> Strength: , Kin-Com dynamometer for isokinetic strength; CT for CSA measurement.	Inferior extremities	Isokinetic dynamometry and CT provide in-depth evaluations, yet their high cost and limited practicality hinder widespread use.
(Dos Santos et al., 2024)	34 sarcopenic older females (>60 years)	Total strength (sum of the 3 1RM tests) relative to skeletal muscle mass.	<b>Assessment:</b> KE, CP and preacher curl. <b>Tools:</b> Strength: , sum of 1RM of three exercises; for total skeletal muscle mass: DXA.	Lower and Superior extremities.	These dynamometers are efficient in evaluating functional MQ and suitable for community programs, whereas DXA offers a thorough mass assessment but is restricted to clinical environments due to its high cost.
(Emerson et al., 2014)	58 healthy older individuals (71 ± 6 years, 33 females)	HGS relative to appendicular lean mass.	<b>Assessment:</b> HGS. <b>Tools:</b> Strength: : isometric dynamometer (HGS); for muscle mass, DXA.	Superior extremity	HGS and DXA provide reliable assessments for community use, but the high cost and equipment demands of DXA may limit its accessibility.
(Dalle et al., 2021)	23 community residents, non sarcopenic older	Isometric strength per unit of muscle mass.	<b>Assessment:</b> Isometric KE.	Inferior extremity	CT offers precise assessments but relies on specialized equipment, restricting its use in community settings. These dynamometers

	individuals (65-83 years)		<b>Tools:</b> Strength: : isometric dynamometer, for muscle mass CT.		effectively evaluate functional MQ and are practical for community programs.
(M. S. Fragala et al., 2014)	23 older individuals (61-85 years)	For muscle quality the ratio of strength to body mass. Leg extension strength/lean quadriceps muscle mass (kg/kg).	<b>Assessment:</b> KE test. <b>Tools:</b> Strength: : PLLE Power Lift KE machine for muscle mass and body composition: DXA.	Inferior extremities.	DXA accurately assesses muscle mass, but the advanced equipment needed restricts accessibility.
(M. S. Fragala et al., 2015)	25 older individuals (70.6 ± 6.1 years)	MQI: Determined by sit-to-stand time, body weight, and leg length. MQI= ((leg length x 0.4) x body mass x gravity x 10)/ time sit to stand.	<b>Assessment:</b> 5 Sit-to-stand (STS). Leg length <b>Tools:</b> STS performance, to measure body mass and leg length DXA.	Inferior extremities	MQI is suitable for community use, reliably detecting improvements and reflecting functional MQ, with potential in clinical and community care. However, DXA's high cost and equipment needs limit its accessibility.
(Gadelha, Neri, Nóbrega et al., 2018)	246 community-dwelling older females (68.1 ± 6.2 years)	Peak torque per unit of thigh muscle thickness.	<b>Assessment:</b> KE test. <b>Tools:</b> Isokinetic dynamometer for stronger leg strength; US (B-mode) to measure muscle thickness.	Inferior extremity (stronger leg thigh).	Isokinetic dynamometers and US are effective for accurate muscle quality assessments, but their high cost and dependence on operator expertise limit their accessibility in community settings.
(Gadelha, Neri, Bottaro et al., 2018)	167 females (68.1 ± 6.2 years)	Ratio of peak torque to thigh muscle thickness.	<b>Assessment:</b> KE test. <b>Tools:</b> Isokinetic dynamometer for stronger leg strength; US (B-mode) to measure muscle thickness.	Inferior extremity (stronger leg thigh).	Isokinetic dynamometers and US are effective for accurate muscle quality assessments, but their high cost and dependence on operator expertise limit their accessibility in community settings.
(Ghasemikaram et al., 2021)	43 older men with osteosarcopenia (78 ± 4 years)	1. Maximum isokinetic hip/leg extensor strength (MILES) per unit of mid-thigh intra-fascia volume. 2. MILES/ thigh muscle mass.	<b>Assessment:</b> KE. <b>Tools:</b> Strength: : isokinetic leg press; for muscle volume MRI; for muscle mass DXA.	Inferior extremity	MRI offers accurate volume measurements, it is more costly and less widely available; isokinetic dynamometers and DXA reliably measure leg strength and mass, but their high cost and need for specialized training restrict their use beyond clinical settings
(Goodpaster et al., 2006)	1880 older individuals (73.5 ± 2.8 years, 51.6% females)	Isokinetic torque per unit of leg lean mass (Nm/kg)	<b>Assessment:</b> Knee extensor isokinetic strength. <b>Tools:</b> Strength: ; Kin-Com dynamometer (isokinetic strength); for muscle mass: DXA.	Inferior extremities	Isokinetic dynamometers and DXA reliably measure leg strength and mass, but their high cost and need for specialized training restrict their use beyond clinical settings
(Hairi et al., 2010)	1705 older men (≥70 years)	MQ, ratio of strength per unit of mass in lower and upper extremities.	<b>Assessment:</b> HGS and quadriceps strength. <b>Tools:</b> For strength: Jamar isometric dynamometer, spring gauge on both legs separately measuring inferior extremity muscle); for muscle mass: DXA	Upper and Inferior extremities (quadriceps)	HGS and DXA provide reliable assessments for community use, but the high cost and equipment demands of DXA may limit its accessibility.
(Herda & Nabavizadeh, 2021)	65 healthy older individuals (66.5 ± 7.09 years)	Upper and lower body muscle strength (1RM) relative to respective lean mass.	<b>Assessment:</b> 5RM bench press and 5RM leg press. <b>Tools:</b> Strength assessment included bench press (free-weight and half-rack) and leg press (45° plate-loaded hip sled); lean mass measured via DXA.	Upper and Inferior extremities	These dynamometers are efficient in evaluating functional MQ and suitable for community programs, whereas DXA offers a thorough mass assessment but is restricted to clinical environments due to its high cost.
(Jerez-Mayorga et al., 2020)	28 older females (66.2 ± 5.6 years)	MQI: Determined by sit-to-stand time, body weight, and leg length. MQI= ((leg length x 0.4) x body mass x gravity x 10)/ time sit to stand	<b>Assessment:</b> 5 STS and Leg length. <b>Tools:</b> 5STS performance; for body mass BIA, leg length was measured manually.	Inferior extremities	MQI is suitable for community environments, offering reliable sensitivity to detect improvements and reflecting functional muscle quality, making it a valuable tool for both clinical and community care. However, more specialized imaging methods exist.
(Katsiaras et al., 2005)	1512 older individuals (70–79 years)	Muscle-specific torque, defined as peak torque relative to cross-sectional area	<b>Assessment:</b> KE and knee flexors.	Inferior extremities	Isokinetic dynamometry and CT provide in-depth evaluations, yet their high cost and limited practicality hinder widespread use.

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		(strength/CSA), was used as a muscle quality index.	<b>Tools:</b> Strength: , isokinetic dynamometer in knee extensors and flexors; for CSA CT.		
(Kennis et al., 2013)	72 older men (60-80 years)	MQ: ratio of muscle strength to muscle volume (Nm/cm <sup>3</sup> ) 1. MQ isometric strength/vol 2. MQ concentric strength/vol	<b>Assessment:</b> KE. <b>Tools:</b> Strength was assessed unilaterally using isokinetic and concentric KE measurements on a Biodex System 3 dynamometer, volume via CT.	Upper and Inferior extremities (separately)	Isokinetic dynamometry and CT provide in-depth evaluations, yet their high cost and limited practicality hinder widespread use.
(Nonaka et al., 2020)	170 older females (aged 65-79 years)	Muscle quality assess by leg strength relative to mass (kg/kg).	<b>Assessment:</b> KE. <b>Tools:</b> Strength assessed via hand-held dynamometer at the ankle; muscle mass measured with BIA.	Inferior extremities	HGS and BIA are affordable and widely available, making them well-suited for both clinical and community settings, though more advanced imaging techniques offer greater specificity.
(Koster et al., 2011)	2307 well functioning older individuals, (70–79 years)	Muscle quality: muscle strength divided by leg lean mass (Nm/kg).	<b>Assessment:</b> Knee extensor isokinetic strength. <b>Tools:</b> Sstrength assessed via Kin-Com dynamometer (isokinetic strength); for muscle mass: DXA.	Inferior extremities	Isokinetic dynamometers and DXA reliably measure leg strength and mass, but their high cost and need for specialized training restrict their use beyond clinical settings
(Liao et al., 2018)	56 older females (67.3 ± 5.1 years)	1. MQ upper extremity, handgrip strength by arm lean mass (kg/kg). 2. MQ lower extremity, strength of isometric quadriceps by leg lean mass (N/kg).	<b>Assessment:</b> HGS and knee extension. <b>Tools:</b> Strength: isometric dynamometer (HGS) and handheld dynamometer (leg); mass: DXA.	Upper and Inferior extremities (separately)	HGS and DXA provide reliable assessments for community use, but the high cost and equipment demands of DXA may limit its accessibility.
(Lopez et al., 2020)	24 older females (66.3 ± 5.8 years)	Isometric MQ: Ratio of maximum isometric contraction to plantar flexor thickness. Dynamic MQ: Ratio of plantar flexor strength at 30°/s to muscle thickness.	<b>Assessment:</b> Plantar flexor isometric and dynamic strength. <b>Tools:</b> Strength: isokinetic dynamometer (MVIC) and dynamic plantar flexor assessment at 30°/s.; US (B-mode) to measure muscle thickness.	Inferior extremities	Isokinetic dynamometers and US are effective for accurate muscle quality assessments, but their high cost and dependence on operator expertise limit their accessibility in community settings.
(Maltais et al., 2019)	1679 older individuals (75.3 ± 4.4years)	1. Muscle quality: HGS per unit of body weight (kg/kg) 2. MQ: HGS divided by arm fat free mass (kg/kg).	<b>Assessment:</b> HGS. <b>Tools:</b> Strength: isometric dynamometer (HGS); muscle mass DXA.	Superior extremities (arm).	HGS and DXA provide reliable assessments for community use, but the high cost and equipment demands of DXA may limit its accessibility.
(McCormack et al., 2013)	60 apparently healthy older individuals (70.7 ± 6.2 years)	Muscle quality assess by relative strength with grip strength normalized to arm lean mass (kg/kg).	<b>Assessment:</b> HGS. <b>Tools:</b> Strength: isometric dynamometer (HGS); for arm muscle lean mass DXA.	Superior extremities (arm).	HGS and DXA provide reliable assessments for community use, but the high cost and equipment demands of DXA may limit its accessibility.
(Michel et al., 2024)	184 older individuals (73.6 ± 6.83 years, 81% females)	MQ: Ratio of KE strength normalized to fat-free mass (Nm/kg).	<b>Assessment:</b> KE. <b>Tools:</b> Strength, isokinetic dynamometer for knee extensors; for fat-free mass, Sergi's equation.	Inferior extremities	Isokinetic dynamometers provide precise assessments of leg strength and mass, but their high cost and need for specialized equipment and training restrict their use outside clinical environments.
(Mistic et al., 2007)	55 healthy older individuals (69.3 ± 5.5 years)	MQ and leg strength (sum of peak extension and flexion torque measured by isokinetic dynamometer) adjusted for leg mineral-free lean mass.	<b>Assessment:</b> Isokinetic leg extension and flexion. <b>nstrument:</b> Strength: isokinetic dynamometer; DXA body composition.	Inferior extremities	Isokinetic dynamometers and DXA reliably measure leg strength and mass, but their high cost and need for specialized training restrict their use beyond clinical settings

(Moore et al., 2014)	786 adults (66.3 years)	MQ, knee-extension strength per muscle CSA.	<b>Assessment:</b> KE. <b>Tools:</b> Strength: isokinetic dynamometer in knee extensors and flexors; for CSA CT.	Inferior extremities	Isokinetic dynamometry and CT provide in-depth evaluations, yet their high cost and limited practicality hinder widespread use.
(Müller et al., 2020)	35 older men (65.8 ± 3.9 years)	MQ, specific tension formula, ratio between the KE1RM/2 and the sum of the squared quadriceps femoris muscles (N/cm <sup>2</sup> ).	<b>Assessment:</b> KE. <b>Tools:</b> Strength, 1RM test; for quadriceps femoris volume US (B-mode) derived muscle thickness.	Inferior extremities	The 1RM test and US provide accurate muscle quality assessments, but the high cost of US and its reliance on operator expertise limit its accessibility in community settings.
(Neri et al., 2021)	222 community residents females (≥60 years).	MQ, muscle strength per unit of muscle mass. Specific torque (ratio of peak knee extension torque to leg lean mass of the same limb, expressed in Nm/kg.	<b>Assessment:</b> KE. <b>Tools:</b> Strength, isokinetic dynamometer; for lean mass, DXA.	Inferior extremities	Isokinetic dynamometers and DXA reliably measure leg strength and mass, but their high cost and need for specialized training restrict their use beyond clinical settings
(Neri et al., 2020)	246 community residents females (≥60 years).	MQ, muscle strength per unit of muscle mass. Specific torque (ratio of peak knee extension torque to leg lean mass of the same limb, expressed in Nm/kg.	<b>Assessment:</b> KE. <b>Tools:</b> Strength: , isokinetic dynamometer; for lean mass, DXA.	Inferior extremities	Isokinetic dynamometers and DXA reliably measure leg strength and mass, but their high cost and need for specialized training restrict their use beyond clinical settings
(Neto et al., 2023)	64 obese older females (67.05 ± 5.46 years)	Field MQI: highest value divided by the subject's body mass index. Laboratory MQI: ratio of grip strength to total arm muscle mass in kilograms measured by DXA.	<b>Assessment:</b> HGS. <b>Tools:</b> Strength: isometric dynamometer (HGS); for arm muscle lean mass DXA (body composition).	Superior extremities (arm).	HGS and DXA provide reliable assessments for community use, but the high cost and equipment demands of DXA may limit its accessibility.
(Neto et al., 2022)	88 obese females (69.4 ± 6.06 years)	1. Laboratory MQI: ratio of predicted 1RM leg extension to total lower limb muscle mass in kilograms measured by DXA. 2. Field MQI: ratio of predicted 1RM leg extension divided by BMI.	<b>Assessment:</b> KE. <b>Tools:</b> Strength: leg extension via 10RM test; for lean mass, DXA.	Inferior extremities	These dynamometers are efficient in evaluating functional MQ and suitable for community programs, whereas DXA offers a thorough mass assessment but is restricted to clinical environments due to its high cost.
(Nogueira Paranhos Amorim et al., 2021)	220 octogenarians (≥80 years)	MQ, ratio of HGS to arm muscle mass (kg/kg).	<b>Assessment:</b> HGS. <b>Tools:</b> Strength: isometric dynamometer via HGS; DXA for the arm muscle lean mass.	Superior extremities (arm).	HGS and DXA provide reliable assessments for community use, but the high cost and equipment demands of DXA may limit its accessibility.
(Nunes et al., 2019)	66 older females with previous RT experience (68.8 ± 4.6 years)	MQI: Total Strength 1RM (sum of load in kg from 1RM tests in CP, KE, PC) divided by total body skeletal muscle mass.	<b>Test:</b> Chest press (CP), KE(KE) and preacher curl (PC). <b>Tools:</b> Strength: 1RM test assessed on CP, KE, and PC; for skeletal muscle mass, Kim et al. proposed a formula for lean soft tissue values based on BIA.	Upper and Inferior extremities (together)	These dynamometers are effective in assessing functional MQ and suitable for community programs, while BIA is affordable and accessible for community settings but lacks the accuracy of imaging techniques.
(Oh et al., 2017)	38 older females (≥70 years)	MQ: ratio of strength to muscle mass. Ratio of isokinetic knee torque to leg lean mass (Nm/kg).	<b>Assessment:</b> KE. <b>Tools:</b> Strength: isokinetic dynamometer; DXA for lean mass.	Inferior extremities	Isokinetic dynamometers and DXA reliably measure leg strength and mass, but their high cost and need for specialized training restrict their use beyond clinical settings

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(Osuka et al., 2022)	156 older females (65-79 years)	Functional MQ: muscle strength to muscle mass ratio (muscle thickness).	<b>Assessment:</b> KE. <b>Tools:</b> isometric knee extensor strength in the stronger leg using a handheld dynamometer; for muscle mass B-mode ultrasound.	Inferior extremities (quadriceps).	These dynamometers are effective in assessing functional MQ and suitable for community programs, while ultrasound provides precise MQ assessments, though its high cost and reliance on operator expertise limit its accessibility in community settings.
(Park et al., 2006)	2618 older individuals (70-79 years)	MQ: muscle strength relative to regional muscle mass (Nm/kg). Specific force of the leg normalized to leg muscle mass or specific force of the arm adjusted for arm muscle mass.	<b>Assessment:</b> HGS and KE. <b>Tools:</b> Strength: Isometric dynamometer (HGS) and isokinetic dynamometer for KE strength and for arm or leg muscle mass assessment DXA.	Upper and Inferior extremities (separately).	Isokinetic dynamometers and DXA reliably measure leg strength and mass, but their high cost and need for specialized training restrict their use beyond clinical settings.
(Pancera et al., 2024)	30 stable inpatients (68±8 years)	Muscle quality of the stronger leg: ratio of isometric quadriceps peak torque (PT) to leg lean mass (Nm/kg).	<b>Assessment:</b> KE. <b>Tools:</b> Strength measured by computerized dynamometer and BIA for muscle mass.	Inferior extremities.	HGS and BIA are affordable and widely available, making them well-suited for both clinical and community settings, though more advanced imaging techniques offer greater specificity.
(Pinto et al., 2014)	36 sedentary elderly females (66.0 ± 8 years)	MQ, strength relative to muscle mass. Determined by dividing the 1RM knee extension value by the total quadriceps femoris muscle thickness.	<b>Assessment:</b> KE stronger leg. <b>Tools:</b> Strength: 1RM in knee extension test; for quadriceps femoris volume B-mode ultrasound derived muscle thickness.	Inferior extremities (quadriceps).	These dynamometers are effective in assessing functional MQ and suitable for community programs, while ultrasound provides precise MQ assessments, though its high cost and reliance on operator expertise limit its accessibility in community settings.
(Radaelli et al., 2019)	26 adult females (64.8 ± 3.2 years)	MQ, maximal strength produced per unit of muscle mass. Calculated by dividing maximal rate of torque development by muscle quality echo intensity.	<b>Assessment:</b> KE. <b>Tools:</b> Strength: , isokinetic dynamometer; for muscle echo intensity B-mode ultrasound	Inferior extremities.	Isokinetic dynamometers and DXA reliably measure leg strength and mass, but their high cost and need for specialized training restrict their use beyond clinical settings.
(Radaelli et al., 2014)	27 postmenopausal females (67.6 ± 5.1 years)	MQ, knee extension 1-RM value of the stronger leg was divided by the MT of the quadriceps of the stronger leg.	<b>Assessment:</b> KE stronger leg. <b>Tools:</b> Strength: , 1RM test in knee extension; for quadriceps femoris volume US (B-mode) derived muscle thickness.	Inferior extremities (quadriceps).	These dynamometers are effective in assessing functional MQ and suitable for community programs, while ultrasound provides precise MQ assessments, though its high cost and reliance on operator expertise limit its accessibility in community settings.
(Rava et al., 2017)	32 older females (≥65 years)	1. Upper limb MQ: handgrip strength normalized to arm lean mass (kg/kg). 2. Lower limb MQ: isometric quadriceps strength relative to leg lean mass (kg/kg).	<b>Assessment:</b> HGS and isometric leg extension. <b>Tools:</b> Strength: HGS via isometric dynamometer, custom-built isometric dynamometer for leg strength assessment; DXA for muscle mass evaluation.	Upper and Inferior extremities (separately).	These dynamometers are effective for assessing functional MQ and suitable for community programs, while DXA provides precise MQ data; however, its cost and equipment requirements may limit its use in community settings.
(Reinders et al., 2015)	2725 older individuals (74.8 ± 4.7 years)	MQ, the proportion of muscle strength to muscle cross-sectional area.	<b>Assessment:</b> KE stronger leg. <b>Tools:</b> Strength: 1RM knee extension and isokinetic dynamometer; leg muscle area assessed via CT.	Inferior extremities.	Isokinetic dynamometry and CT provide in-depth evaluations, yet their high cost and limited practicality hinder widespread use.
(Ribeiro et al., 2022)	34 older females	1.MQI: 1RM load from the chest press (CP), knee extension (KE), and preacher curl (PC) normalized to fat-free mass.	<b>Assessment:</b> Chest press (CP), knee extension (KE) and preacher curl (PC). <b>Tools:</b> Strength: , 1RM test assessed on CP, KE, and PC performed in this exact order and DXA for fat free mass.	Upper and Inferior extremities (together and	These dynamometers are effective for assessing functional MQ and suitable for community programs, while DXA provides precise MQ data; however, its cost and equipment requirements may limit its use in community settings.

		2. Superior extremity MQ: 1RM from PC relative to arm lean mass. 3. Inferior extremity MQ: 1RM from KE relative to leg lean mass.		separately )	
(Ribeiro et al., 2016)	25 physically independent older females (67.6 ± 5.1 years)	1.MQI: 1RM load from the chest press (CP), knee extension (KE), and preacher curl (PC) normalized to fat-free mass. 2. Superior extremity MQ: 1RM from PC relative to arm lean mass. 3. Inferior extremity MQ: 1RM from KE relative to leg lean mass.	<b>Assessment:</b> Chest press (CP), knee extension (KE) and preacher curl (PC). <b>Tools:</b> Strength: , 1RM test assessed on CP, KE, and PC performed in this exact order and DXA for fat free mass.	Upper and Inferior extremities (together and separately )	These dynamometers are effective for assessing functional MQ and suitable for community programs, while DXA provides precise MQ data; however, its cost and equipment requirements may limit its use in community settings.
(Rondanelli et al., 2014)	159 older individuals admitted in physical medicine and rehabilitation division (80.3 years, 107 females)	MQ, strength relative to muscle mass.	<b>Assessment:</b> Isometric leg extension test and HGS. <b>Tools:</b> Strength: handgrip strength (HGS) and leg extension assessed via isometric dynamometer; muscle mass measured using DXA.	Superior extremities (for both arms)	These dynamometers effectively assess functional MQ and are suitable for community programs, while DXA provides precise MQ data but may be less accessible due to its cost and equipment requirements.
(Salas-Groves et al., 2024)	47 older individuals (mean 70 years)	For muscle quality, muscle strength normalized to lean body mass (kg/kg).	<b>Assessment:</b> HGS. <b>Tools:</b> For strength assessment Camry Digital Hand Dynamometer and DXA to measure muscle mass.	Superior extremity	HGS and DXA provide reliable assessments for community use, but the high cost and equipment demands of DXA may limit its accessibility.
(Schroeder et al., 2011)	88 older individuals (≥65 years)	MQ, maximal composite strength score in kilograms divided by total lean mass measured by DXA in kilograms (kg/kg).	<b>Assessment:</b> Bilateral leg press, leg flexion and extension, latissimus pull-down, and CP. . <b>Tools:</b> Strength: , 1RM test in LP, LE, LF, LPD and CP; for lean mass DXA.	Inferior extremities	These dynamometers effectively assess functional MQ and are suitable for community programs, while DXA provides precise MQ data but may be less accessible due to its cost and equipment requirements.
(M.-W. Seo et al., 2020)	59 older females (≥65 years)	MQ is defined as maximal contraction per muscle mass measured as CSA.	<b>Assessment:</b> KE stronger leg. <b>Tools:</b> Strength: isokinetic dynamometer via KE test, 1RM test in KE and CT for leg muscle CSA.	Inferior extremities	Isokinetic dynamometry and CT offer detailed assessments but are expensive and less feasible for broad application.
(Shin et al., 2012)	72 older individuals (69.5 ± 6.1 years)	MQ, muscle strength (maximal voluntary contraction) relative to mineral-free lean mass (MFLM). 1. MQ Upper legs: sum of knee extension MVC and knee flexion MVC divided by MFLM of the upper legs. 2. MQ Ankle: sum of MVC for ankle dorsiflexion and plantarflexion divided by MFLM of the lower leg.	<b>Assessment:</b> Knee extension and flexion and ankle plantarflexion and dorsiflexion. <b>Tools:</b> Strength: Isokinetic dynamometer used for assessing knee extension, knee flexion, ankle dorsiflexion, and ankle plantarflexion; for lean mass measurement, DXA.	Inferior extremities	Isokinetic dynamometers and DXA reliably measure leg strength and mass, but their high cost and need for specialized training restrict their use beyond clinical settings

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		*Strength from both legs combined and normalized by the total MFLM.		
		MQI: muscle strength/ muscle mass. <b>Upper body:</b> 1. Field MQI: HGS/BMI 2. Lab MQI: HGS/arm lean mass (DXA) <b>Lower body:</b> 3. Lab MQI: 10RM leg extension/lean mass (DXA)	<b>Assessment:</b> HGS and leg extension. <b>Tools:</b> Strength: Isometric dynamometer (HGS) and 10 RM from the leg extension exercise; for muscle and lean mass evaluation, DXA.	Upper and Inferior extremities (separately) These dynamometers effectively assess functional MQ and are suitable for community programs, while DXA provides precise MQ data but may be less accessible due to its cost and equipment requirements.
(Silva PR, 2021)	39 older females (69.0 ± 6.2 years)			
(Spira et al., 2016)	838 older individuals (60- 82 years)	MQ: HGS in relation to arm muscle mass.	<b>Assessment:</b> HGS. <b>Tools:</b> Strength: for HGS Smedley Hand Dynamometer and DXA for muscle mass.	Superior extremity HGS and DXA provide reliable assessments for community use, but the high cost and equipment demands of DXA may limit its accessibility.
(Stotz et al., 2023)	74 older individuals (76.8 ± years, 38 men)	Trunk muscle quality as strength relative to lean mass: Absolute trunk flexion and extension torque divided by lean tissue mass.	<b>Assessment:</b> Trunk flexion and extension. <b>Tools:</b> For strength measurement trunk flexion and extension via isokinetic concentric dynamometer; for lean tissue mass Inbody (BIA).	Trunk Isokinetic devices provide reliable targeted measurements but are expensive for regular community use. BIA is affordable and accessible, making it ideal for community and clinical settings, though it lacks the ability to offer detailed assessments.
(Straight et al., 2015b)	96 community residents older females (73.9 ± 5.6 years)	MQ, leg extension power relative to lower body mineral-free lean mass (W/kg).	<b>Assessment:</b> KE. <b>Tools:</b> Muscle power via Nottingham power ring and lean mass via DXA.	Inferior extremities DXA accurately assesses muscle mass, but the advanced equipment needed restricts accessibility.
(Sui et al., 2022)	342 older men (60-96 years)	MQ: HGS in relation to arm lean mass.	<b>Assessment:</b> HGS. <b>Tools:</b> Strength: HGS via isometric dynamometer; DXA for muscle mass and body composition assessment.	Superior extremity HGS and DXA provide reliable assessments for community use, but the high cost and equipment demands of DXA may limit its accessibility.
(Tracy et al., 1999)	23 older individuals (65- 75 years)	MQ, strength relative to muscle volume (kg/cm <sup>3</sup> ). Isometric and 1-RM strength values (N and kg, respectively) divided by muscle volume (cm <sup>3</sup> ).	<b>Assessment:</b> KE. <b>Tools:</b> Strength: 1RM strength test, isometric force production, and isokinetic peak torque were measured for the knee extensors; muscle mass and volume were assessed using MRI.	Inferior extremities (quadiceps) Isokinetic devices provide reliable targeted assessments but are expensive, while MRI is highly effective yet costly and too complex for community use.
(Vilaça et al., 2014)	75 older females (65-80 years)	MQ, ratio of muscle strength to lean mass. 1. Superior extremity : HGS/ lean mass of the dominant Superior extremity (kg/kg). 2. Inferior extremity : bilateral KES / lean mass of the Inferior extremity (kg/kg).	<b>Assessment:</b> HGS and knee extension. <b>Tools:</b> Strength via portable hydraulic dynamometer and 1RM via KE test; for muscle composition and mass, DXA.	Upper and Inferior extremities These dynamometers effectively assess functional MQ and are suitable for community programs, while DXA provides precise MQ data but may be less accessible due to its cost and equipment requirements.
(Vilaça et al., 2013)	77 active older females (65-80 years)	MQ, ratio of muscle strength to lean mass. 1. Superior extremity : HGS/ lean mass of the dominant Superior extremity (kg/kg). 2. Inferior extremity : bilateral KES (lean mass of the Inferior extremity (kg/kg).	<b>Assessment:</b> HGS and KE. <b>Tools:</b> Strength via portable hydraulic dynamometer and 1RM via KE test; for muscle composition and mass, DXA.	Upper and Inferior extremities These dynamometers effectively assess functional MQ and are suitable for community programs, while DXA provides precise MQ data but may be less accessible due to its cost and equipment requirements.

(Virto, Río, Muñoz-Pérez, et al., 2024)	1253 older individuals (78.1 ± 5.8 years)	MQI: HGS (kg) divided by relative skeletal muscle mass (kg).	<b>Assessment:</b> HGS. <b>Tools:</b> Strength assessed by Camry EH101 electronic handheld dynamometer (HGS) and BIA for muscle mass.	Upper and Inferior extremities	HGS and BIA are affordable and widely available, making them well-suited for both clinical and community settings, though more advanced imaging techniques offer greater specificity.
(Vojciechowski et al., 2021)	46 older females (69 ± 4 years)	MQ, quadriceps peak torque to quadriceps CSA.	<b>Assessment:</b> Knee extension and flexion, ankle dorsiflexion and plantarflexion. <b>Tools:</b> Strength: Isokinetic dynamometer for assessing knee extension, knee flexion, ankle dorsiflexion, and ankle plantarflexion; MRI for cross-sectional area measurement.	Inferior extremities	Isokinetic devices provide reliable targeted assessments but are expensive, while MRI is highly effective yet costly and too complex for community use.
(Volpato et al., 2012)	835 older individuals (65+ years)	MQ: ratio of ankle strength (dorsiflexion + plantarflexion) per muscle area (kg/cm <sup>2</sup> ).	<b>Assessment:</b> Ankle dorsiflexion and plantar flexion. <b>Tools:</b> Strength: Handheld dynamometer for muscle strength; muscle cross-sectional area measured at 66% of the tibial length, starting from the tibiotarsal joint, using peripheral quantitative CT.	Inferior extremities (ankle, plantar)	These dynamometers effectively evaluate functional muscle quality and are suitable for community programs, while pQCT offers detailed density analysis but is costly and less accessible for community settings.
(Walsh et al., 2022)	25 not institutionalized older individuals (66 ± 9 years)	1. Upper leg MQ: the total peak torque of knee flexors and extensors divided by upper leg muscle mass. 2. Lower leg MQ: the total maximum torque of ankle plantar flexors and dorsiflexors divided by lower leg muscle mass. 3. Total leg MQ: the sum of all strength measurements divided by the combined muscle mass of the upper and lower leg (Nm/kg).	<b>Assessment:</b> Knee flexors and extensors test, ankle plantarflexion and dorsiflexion test. <b>Tools:</b> Strength: isokinetic dynamometer and DXA to measure muscle mass.	Inferior extremities	Isokinetic dynamometers and DXA reliably measure leg strength and mass, but their high cost and need for specialized training restrict their use beyond clinical settings
(M. Yamada et al., 2017)	347 healthy older individuals (81 ± 7 years, 247 females)	MQ: KE torque divided by the quadriceps femoris MT (Nm/cm).	<b>Assessment:</b> Knee extension <b>Tools:</b> Strength: isokinetic dynamometer for KE and quadriceps femoris US (B-mode) for muscle thickness.	Inferior extremities (quadriceps)	Isokinetic dynamometer and ultrasound provide accurate muscle quality assessments, but their expense and reliance on skilled operators reduce their accessibility in community settings.
(Yamaguchi et al., 2022)	340 older individuals with T2DM (≥65 years)	MQ: HGS normalized to skeletal muscle mass (kg/kg)	<b>Assessment:</b> HGS. <b>Tools:</b> Strength: HGS via isometric dynamometer and BIA to measure muscle mass.	Superior extremities	HGS and BIA are affordable and widely available, making them well-suited for both clinical and community settings, though more advanced imaging techniques offer greater specificity.
(Yoon et al., 2016)	269 older men (65+ years)	MQ: ratio of strength measured to the entire corresponding leg muscle mass in kg measured by DXA.	<b>Assessment:</b> KE. <b>Tools:</b> Strength: isokinetic dynamometer for KE test and DXA for mass	Inferior extremities	Isokinetic dynamometers and DXA reliably measure leg strength and mass, but their high cost and need for specialized training restrict their use beyond clinical settings
(X. Yu et al., 2024)	475 older individuals (≥60 years)	MQ: HGS normalized to skeletal muscle mass (kg/kg)	<b>Assessment:</b> HGS. <b>Tools:</b> Strength: HGS via isometric dynamometer and BIA to measure muscle mass.	Superior extremities	HGS and BIA are affordable and widely available, making them well-suited for both clinical and community settings, though more advanced imaging techniques offer greater specificity.

In line with findings from the literature (Coronado-Zarco & de León, 2023; de Lucena Alves et al., 2023) the results of this review show significant variation in the definitions of muscle quality. Definitions regarding functional muscle quality mainly entail indirect evaluations of muscle performance in relation to muscle mass, generally defined as strength per unit of muscle mass. Although 70 research have embraced this definition, which is based on the same basic idea of the strength-to-mass ratio, heterogeneity results from the differences in how strength and muscle mass are measured. As a result, even when a comparable conceptual framework for muscle quality is used, different measuring methods lead to inconsistent results, which emphasizes the necessity of methodological standardization to improve study comparability. The variation shown in functional muscle quality evaluations is mostly caused by the range of instruments used to quantify muscle mass and strength. The literature study found that 16 research used handheld dynamometers to measure HGS, one of the non-invasive methods used to quantify muscle strength. Twenty-three studies utilized isokinetic dynamometers, six employed handheld isometric dynamometers, and one used both techniques for knee extension. Furthermore, ten studies evaluated strength using RM, four evaluated leg power and eleven examined combined upper and lower extremity strength.

Assessing muscle force output is a crucial aspect of clinical evaluation, and dynamometry is considered one of the most reliable techniques for objectively measuring strength. This method quantifies and provides precise measurements of force, torque, or power in the course of muscle contractions, making it the primary laboratory-based approach for strength assessment. Several methods of dynamometry exist, each designed to meet specific evaluation requirements. The literature identifies isokinetic and handheld (isometric) dynamometry as the main types. Isokinetic dynamometry is widely regarded as the gold standard due to its high validity and reliability in measuring muscle force. These advanced machines offer a range of metrics related to muscle force, enabling precise measurements at different angles and speeds while reducing potential issues in the measurement process (Baltzopoulos & Brodie, 1989; R. C. Li et al., 2006; Stark et al., 2011). Nevertheless, isokinetic devices are costly and lack portability, limiting their application in routine clinical practice (Baltzopoulos & Brodie, 1989; R. C. Li et al., 2006). In contrast, isometric dynamometers, such as handheld devices (HHD), are portable, which enhances their accessibility in therapeutic settings due to their ease of use and lower cost compared to isokinetic machines. While they provide a more limited range of data, primarily offering a practical method for measuring isometric muscle strength and power, their lower cost may justify their widespread clinical use. Although HHD are considered reliable and valid, they offer less detailed information compared to isokinetic systems, even though correlations between the two types of measurements have been reported (Beere et al., 2022; Bohannon, 2006; Chamorro et al., 2017; Grootswagers et al., 2022; Martin et al., 2006; Stark et al., 2011; Surburg et al., 1992).

In contrast, one of the most commonly employed field tests for assessing strength is the one repetition maximum (1RM) test, which is defined as the heaviest weight that can be lifted once while maintaining proper technique. This test serves to accurately evaluate the maximum force for a particular movement, being straightforward, safe, cost-effective, and considered the benchmark in non-laboratory settings. Moreover, it follows patterns similar to those seen in regular training sessions or everyday activities, thus enabling the assessment of strength in multi-joint exercises (American College of Sports Medicine et al., 2009; Grgic et al., 2020; Levinger et al., 2009; Medicine et al., 2018).

Assessing power is essential for evaluating a person's capacity to generate force quickly, which results from the combination of force and velocity (American College of Sports Medicine et al., 2009). Power can be quantified through the use of isokinetic dynamometers or other specialized techniques, such as the Nottingham Power Rig and the PLEE Power Lift, which are employed in the studies reviewed in this article. Both instruments offer high accuracy in assessing explosive power by combining force and velocity. When comparing the two, the Nottingham Power Rig is especially effective for clinical populations or tests involving isolated leg movements, while the PLEE Power Lift is principally designed to assess athletic performance

during functional movements, making it more difficult to execute safely with older populations (Bassey & Short, 1990; Hurst et al., 2018; Reid & Fielding, 2012; van der Woude et al., 2022).

Several non-invasive techniques can be used to assess muscle mass. In the studies reviewed, DXA was the most commonly used, appearing in 44 studies, followed by ultrasound in 11 studies, BIA in 12, MRI in 4, and CT in 8. Both MRI and CT are regarded as the gold standard for muscle composition assessment, with MRI being especially recommended by EWGSOP2 (5). These approaches allow for qualitative and quantitative measurements of body composition, with a strong capacity to differentiate between tissue types, such as intramuscular fat, muscle mass, cross-sectional dimensions, and other structural properties (Faron et al., 2020; Niklasson et al., 2022; Oba et al., 2021). While CT is faster and more affordable, it involves radiation exposure, whereas MRI, although free of radiation, is more expensive and requires higher technical proficiency. Although these methods are strongly correlated in clinical settings for evaluating muscle quantity and quality, their high costs, the need for specialized equipment, and trained personnel limit their routine use in community practice (Faron et al., 2020; Niklasson et al., 2022; Oba et al., 2021).

DXA is another widely used technique for assessing muscle composition, and it is the most commonly employed method in clinical settings for evaluating body composition and diagnosing sarcopenia (Albano et al., 2020; Cruz-Jentoft et al., 2019). This is supported by the findings of the review, which revealed that 56% of the studies analyzed used DXA to assess muscle mass. Although, there is ongoing debate in the literature regarding whether DXA should be considered the "gold standard." While DXA is regarded as a precise, reliable, reproducible, and readily accessible imaging method for quantifying lean mass, appendicular muscle mass, fat, and bone mineral density, it also serves as a useful indicator of the muscle strength-muscle mass relationship, it does not assess muscle composition at a more detailed structural level. Additionally, it is influenced by hydration levels, relatively costly, and lacks portability (Albano et al., 2020; Blake & Fogelman, 2007; Cruz-Jentoft et al., 2019; Jain & Vokes, 2017; Klement et al., 2023).

Ultrasonography is becoming more widely acknowledged as a quick, non-invasive, and easily accessible way to evaluate the musculoskeletal system, allowing for the measurement of qualitative as well as quantitative muscle parameters (Correa-de-Araujo et al., 2017; Lopez et al., 2018; Perkisas et al., 2018; Sconfienza et al., 2018). The use of ultrasound has been shown to have strong interclass correlation coefficients and to be comparable with alternative imaging modalities in recent systematic reviews evaluating its validity and reliability for skeletal muscle evaluation (Correa-de-Araujo et al., 2017; Cruz-Jentoft et al., 2019; Lopez et al., 2018; Neira Álvarez et al., 2021; Perkisas et al., 2018; Sconfienza et al., 2018). While continuous attempts at standardizing these metrics, their high operator dependency highlights the need for more study to improve their lack of reference and clinical usefulness (Correa-de-Araujo et al., 2017; Lopez et al., 2018; Perkisas et al., 2018; Sconfienza et al., 2018). Significantly, new research has started to show robust relationships between parameters obtained from ultrasonography and other muscle mass reference measurements (Neira Álvarez et al., 2021; Prell et al., 2024).

BIA is a valuable non-invasive approach for estimating skeletal muscle mass, either total or appendicular, by assessing the electrical conductivity of the body and utilizing predictive models. Although it is a fast, accessible, and non-invasive method, its precision largely depends on the specific predictive model used and can be influenced by factors such as hydration status (Beaudart et al., 2020; Distefano & Goodpaster, 2018; Kyle et al., 2003; Sergi et al., 2016). When compared to more established techniques such as DXA and CT, BIA may either slightly overestimate or underestimate muscle mass, but overall, it shows a strong level of agreement with these reference methods (Achamrah et al., 2018; Cruz-Jentoft et al., 2019; Ribeiro et al., 2022; Zuo et al., 2024).

One of the main difficulties with the tools mentioned is the lack of universally accepted assessment standards, which complicates the process of identifying the most effective and validated techniques. The most reliable and well-supported tools for evaluating the functional aspect of MQ are those that provide accurate measurements of multiple facets of muscle function (such as strength and power), while also accounting for the structural features of the muscle (such as muscle mass). The tools employed must be dependable, reproducible, and capable of delivering objective and clinically relevant data that accurately reflect the muscle's capacity to perform functional tasks. In this regard, methods like CT, MRI, and DXA are considered more precise for evaluating the compositional and structural aspects of muscle. MRI and DXA are potentially more practical than CT, as they do not involve radiation and are more easily accessible in some clinical environments. On the other hand, US and BIA might provide more convenient and budget-friendly options, particularly when quick and non-invasive evaluations are needed, though they tend to have slightly reduced precision (Correa-de-Araujo et al., 2017; Cruz-Jentoft et al., 2019; Sconfienza et al., 2018; Sergi et al., 2016). When assessing strength, isokinetic dynamometry, the 1RM test, and handheld isometric dynamometers are used, each differing in terms of precision, cost, and practicality. Isokinetic dynamometry provides the highest accuracy but is limited by its expense and lack of portability. The 1RM test is cost-effective and straightforward but does not offer the detailed metrics found in isokinetic machines. Handheld dynamometers are more accessible and affordable but offer fewer comprehensive data (American College of Sports Medicine et al., 2009; Baltzopoulos & Brodie, 1989; Chamorro et al., 2017; Grootswagers et al., 2022; Martin et al., 2006; Medicine et al., 2018). Each method relies on different technologies and targets specific facets of functional MQ, highlighting the need for careful selection depending on the assessment objectives and available resources.

The lack of established standards and substantial methodological variability are the main limitations of the non-invasive techniques currently used to evaluate the functional domain of muscle quality in older persons. This unpredictability makes it difficult to compare studies directly and makes it more difficult to determine which instrument is best for this goal. Notably, the variety of assessment methodologies has been cited as a challenge in other muscle quality publications and reviews as well (Correa-de-Araujo et al., 2017; de Lucena Alves et al., 2023; Virto, Río, Méndez-Zorrilla, et al., 2024).

The EWGSOP emphasizes the significance of evaluating muscle amount and quality<sup>5</sup>. Our review does point out that there is currently no clear standard for choosing a particular evaluation tool based on an individual's characteristics (Correa-de-Araujo et al., 2017; Cruz-Jentoft et al., 2019). The selection of non-invasive methods for evaluating the functional domain of muscle quality is influenced by multiple aspects. Cost, accessibility, and the degree of training needed to utilize the technology efficiently are some of these. Despite their high cost, restricted accessibility, and requirement for specialized personnel, reliable and verified techniques like DXA and MRI are commonly utilized in clinical settings. Even though these direct approaches yield trustworthy data, their restricted accessibility makes it difficult for them to be widely used, particularly in non-clinical settings (Correa-de-Araujo et al., 2017; Cruz-Jentoft et al., 2019; Sabatino et al., 2024). Consequently, more straightforward, portable, and cost-effective techniques like BIA or ultrasound are becoming increasingly popular in everyday clinical practice, although they tend to have a moderate or lower level of accuracy compared to the advanced methods previously discussed (Perkisas et al., 2018). The growing integration of portable ultrasound and BIA devices in community settings underscores their potential to provide accessible and affordable solutions in these contexts (Cruz-Jentoft et al., 2019; Nagae et al., 2023). These approaches offer an effective way to bridge the gap between clinical and community environments, making muscle quality assessments more attainable, particularly when resources are limited. Whereas higher-cost techniques are frequently confined to clinical applications, simpler and more economical alternatives are better suited for community use, where ease of use and affordability are crucial for broad adoption (Cruz-Jentoft et al., 2019; Sabatino et al., 2024). The emphasis on accessible tools is particularly significant because muscle quality changes often occur before other functional impairments, and identifying these changes early may serve as a

more sensitive indicator of muscle function, potentially preventing further health deterioration (de Lucena Alves et al., 2023; Kuschel et al., 2022).

Since changes in muscle quality often manifest earlier than alterations in other functional variables, it is crucial to extend the assessment of this parameter to the community level (de Lucena Alves et al., 2023; Kuschel et al., 2022). This covers a wide spectrum of applications, from health promotion programmes and community activities to integration into training and fitness centres specifically designed for older people. As noted above, accessibility and speed of measurement are critical, especially in contexts where the volume of individuals is high and the resources available are limited. In this sense, the development and use of tools that are fast, accurate and economically viable could represent a key solution (de Lucena Alves et al., 2023). Formulas for measuring functional quality, estimated from indirect assessments of muscle performance in relation to muscle mass, offer a promising alternative (Correa-de-Araujo et al., 2017). When muscle assessments are performed using accessible tools, these formulas could be effectively incorporated into community settings, enabling large-scale monitoring and promotion of muscle health. Among the most affordable and commonly used tools for assessing muscle strength are handheld dynamometers, suitable for both upper and lower limbs, including 1RM evaluations. For muscle mass measurement, the most accessible options in community settings are US and BIA, with BIA being the simplest and most practical choice for widespread application.

A number of new developments in the past few years have brought attention to the growing use of readily available instruments, such the MQI, for functionally evaluating the connection amongst muscle mass and strength. Significant progress is being made in community-based implementations thanks to these innovative techniques, which include using BIA and US for this strength measurement.

## 4 Methods

*There's no substitute for hard work. If you work hard and prepare yourself, you might get beat, but you'll never lose. – Nancy Lieberman.*

This chapter elucidates the methodology of each of the studies that make up the thesis. Encompassing the four case studies, the first one presents an approach and preliminary results, the completion of which enables the subsequent three studies. The objective of this chapter is to clarify the protocol and general methodology of the studies constituting the thesis.

### 4.1 Overall methodology.

Before initiating the thesis work and the accompanying articles, a comprehensive work plan was established, detailing a specific methodology. This methodology is illustrated in Figure 1, which summarizes the process followed during the development of the systematic review and the three case studies.

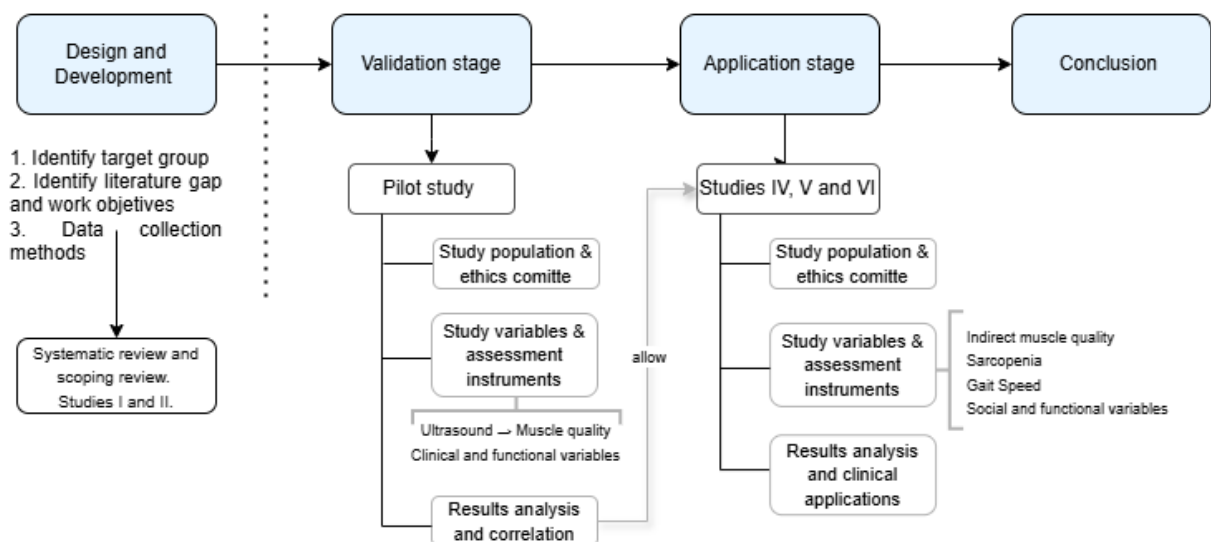


Figure 8. Summary of methodology stages.

The key aspects of the design and development phase involve determining the essential questions and objectives within the identified literature gap. Additionally, the study group and data collection methods have been established based on the clinical characteristics to be measured and the study's stage. Specifically, the study population consists of adults over 65 years old, with or without sarcopenia and frailty. The measurement instruments will vary depending on the study phase, ranging from direct methods of muscle quantification to indirect measures.

Upon completing the initial design phase, the validation phase begins. In this phase, a pilot study is conducted to correlate direct muscle quality quantification tools with relevant functional and clinical variables. If a correlation is found, this will allow the use of indirect muscle quality measures obtained through functional tests, as these are simpler and could facilitate the assessment of muscle quality in clinical practice. In order to ensure the appropriateness of the studies, the first case study was approved by the ethical committee, the appropriate study variables were selected, and data collection was performed by professionals.

After completing the pilot study, the obtained results were then applied in the subsequent three case studies to further investigate the relationship between muscle quality and functional outcomes in older adults. Considering all these criteria and establishing the collaborative channels required to engage with the selected sample of participants, diverse methodologies were employed across all the studies. A description of the procedures used in each of them can be found in the following section.

## **4.2 Methodology of case study I:**

### **4.2.1 Participants**

For this initial study, participants were consecutively recruited from the scheduled patient list of the Falls Unit and the outpatient clinics at the University Hospital of Albacete. A total of 66 participants were enrolled, comprising 55 women (83.3%) and 11 men (16.7%), all of whom met the inclusion criterion of being aged 70 years or older. The inclusion and exclusion criteria will be detailed in

Table 5.

*Table 4. Case study I participants*

<b>Type of sampling</b>	<b>Sample size</b>	<b>Gender distribution</b>
Consecutive sampling	N: 66	Females: 55 Males: 11

Table 5. Inclusion and exclusion criteria.

Criteria	Details
<b>Inclusion criteria</b>	
Age	Age of at least 70 years.
Gender	Either gender.
Informed consent	Ability to provide informed consent.
Functional tests	Ability to perform all the functional tests.
Hospital exercise cohort	Ability to participate in the physical exercise program (for hospital exercise cohort only).
<b>Exclusion criteria</b>	
Expected survival	Expected survival of <1 year.
Barthel Scale score	Barthel Scale score <70.
Cognitive impairment	Moderate-to-severe cognitive impairment.
Refusal to participate	Refusal to participate.
Medical conditions	Medical conditions that may compromise or impede follow-up assessments.
Existing exercise program	Older adults already enrolled in regular physical exercise programs.
<b>Termination criteria</b>	
Participation refusal	Refusal to continue participation.
Complications	Complications during or between examinations and intervention.

## 4.2.2 Clinical variables and assessment tools

Data processing will be carried out independently of the recruitment and follow-up of the cohort in this preliminary study. Furthermore, only anonymised data will be transmitted to the data evaluation center. Specifically, data evaluation will take place at the University of Deusto.

In terms of data collection for the study variables, each will be explained in detail below, starting with the primary variable, the ultrasound evaluation. Ultrasound aims to assess muscle quality and mass using the portable linear scanner L7 HD3 (Clarius Mobile Health Corp., Vancouver, BC, Canada), designed for point-of-care ultrasound (POCUS). The scanner incorporates an imaging package designed to enhance B-mode image quality for musculoskeletal examinations, along with a research package for capturing raw backscattering ultrasound data. To conduct the ultrasound examination, patients were positioned supine on a bed with knees fully extended and relaxed. The ultrasound transducer was positioned perpendicular to both the longitudinal and transverse axes of the quadriceps rectus femoris to capture both transverse and longitudinal images. Placement of the transducer was standardized at the midpoint between the upper pole of the patella and the anterior superior iliac spine along the length of the femur. Each imaging session comprised 12 B-scan frames, including three transverse and three longitudinal views for both the right and left thighs.

During the examination, morphometric ultrasound measurements are recorded using the scanner's interface. These include:

- Transverse view measurements of the rectus femoris:
  - Thickness (mm) at the mid-section point
  - Cross-sectional area (CSA, cm<sup>2</sup>)
  - Perimeter (mm) of the muscle surface
- Longitudinal view measurement of the rectus femoris:
  - Pennation angle (°)

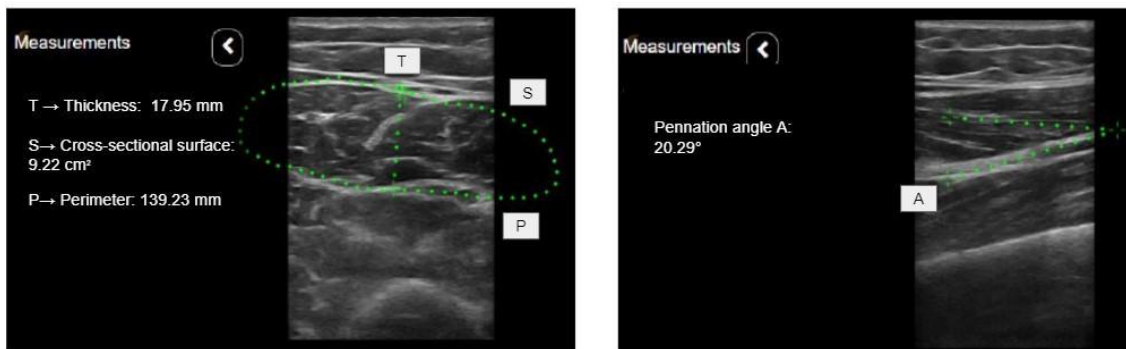


Figure 9. Ultrasound measurements of rectus femoris include (A) thickness, cross-sectional area, and perimeter of the rectus femoris in transverse view, and (B) pennation angle in longitudinal view.

Ultrasound measurements were conducted by trained geriatricians with prior experience in performing ultrasound examinations. Furthermore, to ensure accurate imaging acquisition and analysis during the study, all ultrasound images underwent supervision by a qualified radiologist. The radiologist assessed their appropriateness and approved each collected file.

Among the other evaluation instruments, Table 6 provides an overview of the tools used to gather data across health domains within the study cohort. These domains include anthropometry, frailty, sarcopenia, disability, physical function, nutrition and demographic. Each instrument or scale is designed specifically to assess aspects of health status, providing a range that indicates the severity or level of each condition evaluated. This compilation facilitates a comprehensive assessment of individuals' health and well-being, supporting clinical research and healthcare interventions.

Table 6. Clinical variables and assessment tools

Domain	Assessment/Tool	Range/Description
<b>Anthropometry</b>	BMI (Body Mass Index)	Below 18.5: Underweight; 18.5 – 24.9: Healthy Weight; 25.0 – 29.9: Overweight; 30.0 and Above: Obesity
	DXA (Dual-energy X-ray absorptiometry)	-
<b>Frailty</b>	FRAIL Scale	0-5 (0: not frail, 5: very frail)
	Frailty Phenotype	0-5 ( $\geq 3$ : frail, 1-2: pre-frail or intermediate, 0: not frail)
<b>Sarcopenia</b>	SARC-F Scale	0-10 (higher score indicates higher risk of sarcopenia)
<b>Disability</b>	Charlson Comorbidity Index	0-1 (no comorbidity), 2 (low comorbidity), $\geq 3$ (high comorbidity)
	Barthel Index (Activities of Daily Living)	0-100 (100: total independence)
	Lawton and Brody Index (Instrumental Activities of Daily Living)	0-8 women, 0-5 men (higher score indicates higher independence)
<b>Physical Function</b>	Short Physical Performance Battery (SPPB)	0-12 (higher score indicates better physical function)
	Gait Speed Test (4m test)	Seconds (lower time indicates better physical function)
	Grip Strength with Jamar Dynamometer	Kilograms (higher strength indicates better physical function)
<b>Demographic variables</b>	Age, sex, gender...	-

### 4.2.3 Statistical Analysis

In the statistical analysis conducted, the correlation between ultrasound morphometric parameters and clinical variables was assessed in a hospital-based subset of 66 participants. Correlation coefficients were used to examine the relationships between ultrasound parameters and clinical measures during the baseline examination. Significant weak correlations were noted when the coefficient was ( $r < 0.4$ ), while moderate and strong correlations were observed when ( $r > 0.4$ ). All reported correlations were assessed with a statistical significance level of  $P < 0.05$ .

### 4.2.4 Ethics

The study from which the data for this case study I was obtained has been approved by the Research Ethics Committee of Albacete, Spain, under reference number CEIm-2021-51 (Annex 1). The research will be conducted following the ethical principles for medical research involving human subjects as stated in the Declaration of Helsinki by the World Medical Association. Prior to participation, all participants will provide written informed consent. Their data will be managed according to the Health Insurance Portability and Accountability Act (HIPAA) guidelines, ensuring that no personally identifiable patient information, other than the unique trial identification number, will be included in the metadata associated with the ultrasound and biomarker data. This data will be uploaded to a HIPAA-compliant cloud service provided by the ultrasound system manufacturer, allowing for centralized evaluation by the research team.

## 4.3 Methodology of studies II, III and IV

In the methodology section of this thesis, the explanation of the participants, clinical variables, ethical committee and data collection procedures of case studies II, III and IV have been presented together. This approach was chosen because these case studies share the same database and the same group of participants. However, the statistical analyses are treated separately to address the specific objectives and analytical approaches specific to each study. This structure allows for a comprehensive presentation of the shared elements between studies while highlighting the different methodological considerations of the statistical analyses.

### 4.3.1 Participants

The participants for these three articles were chosen via a non-probabilistic convenience sampling method from among older adults enrolled in the "Health for the Elderly" program, supported by the Bilbao City Council. In total, 1253 individuals (89.5% women), aged over 60 years, with a mean age of  $78.1 \pm 5.8$ , were recruited.

*Table 7. Case study II, III and IV participants.*

Type of sampling	Sample size	Gender distribution
Non-probabilistic convenience	N: 1253	Females: 1121 Males: 132

### 4.3.2 Clinical variables and assessment tools

Participants were examined at specified centers and times according to the program organized by the Bilbao City Council, with evaluators attending daily. Due to the study's large participant cohort, supplementary personnel were recruited to aid in data collection. To ensure impartiality and uphold data integrity, individuals from the Higher-Level Training Cycle in Teaching and Socio-sports Animation underwent specialized training conducted by fitness professionals. This training covered the necessary tests and subsequent data collection procedures. The following tests were conducted to gather the data.

#### **Anthropometry:**

Segmental bioimpedance analysis was performed using the Tanita BC-601 Segment analyzer (Tanita Corp., Tokyo, Japan). This method provides data on weight (W), body fat percentage (fat %), and muscle mass in kilograms (Kg\_Muscle). The Tanita BC-601 Segment is recognized as a reliable and non-invasive technique that delivers highly accurate measurements ( $R2 = 0.98$ ) (Y. Yamada et al., 2021). Furthermore, measurements of height were taken using the Tanita HR 001 Leicester portable stadiometer.

#### **Functional assessment:**

Functional assessment involves the systematic evaluation of physical performance through standardized batteries of tests. In these studies, we will employ three specific tests to comprehensively measure functional capabilities.

**The Short Physical Performance Battery (SPPB):** The SPPB is a highly reliable and valid clinical functional assessment tool frequently used to evaluate functional mobility in community-dwelling older adults (Santamaría-Peláez et al., 2023). It objectively measures balance, lower extremity strength, and functional capacity through three specific domains: balance assessment (in standing, semi-tandem, and tandem positions), a 4-meter gait assessment (timed walk over 4 meters at a normal pace), and the five-repetition chair stand test (5STS) completed as quickly as possible. Each component is scored from 0 to 4, with 0 being the lowest score. The composite score, ranging from 0 to 12 points, is obtained by summing the individual component scores (Guralnik et al., 1994).

For the balance assessment, participants are required to maintain unsupported standing for 10 seconds in three progressively challenging positions: feet together, semi-tandem, and full tandem (Guralnik et al., 1994). The 4-meter gait assessment uses a soft tape measure and stopwatch to measure the time taken to walk the distance at a normal pace. The 5STS involves performing five repetitions of rising from a chair of 49 cm height as quickly as possible, timed using a stopwatch (Alcazar et al., 2018).

**Manual Grip Strength:** The hand grip strength of participants was measured using the Camry EH101 electronic hand dynamometer, which is certified as medical equipment by the Spanish Agency for Medicines and Health Products. During testing, individuals maintained a posture with slight shoulder abduction (approximately  $10^\circ$ ), full elbow extension, and the forearm and hand in a neutral position (Suni, J., Husu, P., & Rinne, M., 2009). Each participant underwent two trials, and the highest recorded value was used for analysis. This dynamometer, chosen for its excellent reliability and validity, is recognized as a dependable, cost-effective, and practical device for assessing grip strength in geriatric clinical environments (Huang et al., 2024).

**Relative Power and Absolute Power:** Mechanical power, a product of strength and speed, plays a crucial role in functional assessments of physical performance (Siglinsky et al., 2015). The 5STS test serves as a tool for evaluating lower extremity muscle power in clinical or field settings (Alcazar et al., 2018). From the 5STS results, both absolute and relative lower limb power were derived (Baltasar-Fernandez et al., 2021; Ferrari et al., 2016).

The mean absolute power was calculated using the equation formulated by Alcazar et al., 2018, which incorporates performance metrics from the 5STS (measured as time to complete five sit-to-stand repetitions), along with factors such as body mass, body height, and chair height (Alcazar et al., 2018). For relative data normalization, the calculated absolute power was adjusted relative to body weight.

### **Muscle Quality Index:**

To indirectly assess muscle quality, the method of dividing handgrip strength by relative skeletal muscle mass, as proposed by Barbat-Artigas et al. and Chang et al. was utilized (Barbat-Artigas et al., 2012; C.-J. Chang et al., 2021). Muscle quality was categorized based on the criteria established by Barbat-Artigas et al. (2012). For men, the muscle quality categories were defined as normal (greater than 1.53), low (greater than 1.36 but less than or equal to 1.53), and poor (less than or equal to 1.36). For women, the categories were normal (greater than 1.53), low (greater than 1.35 but less than or equal to 1.53), and poor (less than or equal to 1.35) (Barbat-Artigas et al., 2012).

### **Socioeconomic information:**

The socioeconomic and physical environment of a region are interconnected with health statistics and have a direct impact on the population, so this variable has been considered (Molero Jurado & Pérez Fuentes, 2011). For this purpose, the Euskadi 2021 socioeconomic index was used, created using the same approach as the MEDEA project (Domínguez-Berjón et al., 2008). The definition of this variable is based on the average personal income (in euros) for each neighbourhood in the municipality of Bilbao. As a result, three socioeconomic levels have been identified: low income (<20,000 euros), medium income (20,000 - 30,000 euros), and high income (>30,000 euros), depending on the neighbourhood from which each individual comes (Eustat, 2023).

### 4.3.3 Statistical Analysis case study II

This section details the process of preparing data for the analysis of the second case study, with the aim of developing a predictive algorithm and selecting relevant features for sarcopenia and MQI. Machine learning techniques were selected because they are widely used in clinical settings for diagnosing and predicting diseases. Many studies have utilized ML to identify key factors in predicting sarcopenia and frailty (Kang et al., 2019; Tarekegn et al., 2020; Zupo et al., 2023).

Before commencing the analysis, data subsets were processed for the MQI and sarcopenia tests. After data processing, machine learning (ML) feature selection was employed to identify the most relevant features for training predictive models. This approach is particularly effective in addressing the challenge of small sample sizes commonly encountered in medical studies. Specifically, four feature selection methods were utilized in this study: Spearman correlation, Ordinary Least Squares (OLS), Random Forest (RF), and Support Vector Machine (SVM). Each method generated data subsets that were subsequently used for classification tests.

Following the classification tests, the selected features were ranked and aggregated. This step aimed to evaluate the model's performance with different numbers of features from the aggregated list. Consequently, data subsets were created using the first four features, the first eight features, and the entire list of features from the aggregated list. These subsets were then compared in classification tests, along with those created from each individual selection method, to determine if including more features improves the model's performance.

To identify the most effective method for predictive modelling of sarcopenia and MQI, data subsets were created from the feature selection techniques. Eight ML algorithms were employed: K-nearest Neighbors (KNN), Gradient Boosting (GB), Decision Tree (DT), Gaussian Naive Bayes (NB), Stochastic Gradient Descent (SGD), Random Forest (RF), Multi-Layer Perceptron (MLP), and Support Vector Machine (SVM), all implemented with the Sci-Kit Learn library.

### 4.3.4 Statistical Analysis case study III

The initial dataset contained 1,253 cases and 16 original variables (see Table 1). Derived variables such as the Muscle Quality Index (MQI), MQI\_max, relative muscle mass, body mass index (BMI), 4-meter walking speed, walking test points, mean power, relative power, squat test score, total Short Physical Performance Battery (SPPB) score, frailty classification based on SPPB, and sarcopenia status were calculated. To enhance data quality for MQI analysis, several data preprocessing steps were conducted, leading to the exclusion of 31 individuals due to missing data ( $n = 14$ ) or implausible values ( $n = 17$ ), resulting in 1,222 participants.

MQI is traditionally calculated from right-hand grip strength, assuming it as the dominant hand. However, in this study, 425 older adults showed greater grip strength in the left hand, with 200 showing a difference greater than 10%. Therefore, incorporating the maximum grip strength from either hand (MQI\_max) was found to be more accurate, and MQI\_max was used as the primary variable for analysis.

The sample included 1,091 women and 131 men, totalling 1,222 participants. Significant sex-based differences were observed in several key variables, particularly MQI and the prevalence of conditions such as sarcopenia and frailty (see Tables 20, 21, and 22). Due to these differences, separate analyses for men and women were conducted. Initial models suggested strong interactions between sex and variables, leading to the decision to estimate sex-stratified models.

After an initial test, the regression model was expanded to include nearly all independent variables, and separate models were built for each sex due to observed disparities.

### **Women Model:**

The first model for women included age, BMI, fat mass, muscle mass, 4-meter gait speed, balance test (EQ3), ID2, and squat test performance. BMI was used instead of weight and height due to collinearity. A Generalized Additive Model (GAM) was employed to handle non-linear relationships, and most variables were included linearly. However, 4-meter walking speed and squat test performance showed nonlinearity. For the 4-meter walk, the relationship was linear once walk time was converted to gait speed (m/s). The squat test revealed a saturation effect, where longer times were associated with lower MQI\_max values, up to a threshold of 13.7 seconds, beyond which the relationship levelled off. Squat test performance was categorized into three levels to improve model interpretability. Redundant variables like weight and height were excluded, as were EQ1 (all participants reached the maximum score) and EQ2 (no effect). The SPPB composite score was also excluded as its components were already accounted for.

### **Male Model:**

For men, similar procedures were followed, and it was found that all variables, including chair squat time, could be included linearly, except for relative power, which showed a nonlinear pattern. Despite this, the model with chair squat time was selected for its simplicity, as the model with relative power produced similar results.

In both models, the analysis was performed using R software 4.2.2, with the mgcv package for the GAM models.

## **4.3.5 Statistical Analysis case study IV**

This section outlines the data preparation process for the analysis of the fourth case study. To commence data analysis, Levene's test was conducted to assess variance homogeneity, while the normality of continuous variables was examined using Kolmogorov–Smirnov, Cramer-von Mises, and Anderson-Darling tests. Pearson's  $\chi^2$  test was employed to explore potential dependencies between variables, followed by Cramér's V to determine effect size (ES), categorized as "small" ( $< 0.2$ ), "medium" (0.2 to 0.6), or "large" ( $> 0.6$ ). Subsequently, correspondence analysis was performed to investigate relationships between variables.

The correlation analysis aimed to establish relationships among quantitative variables by assessing their strength using R2 and aimed to detect multicollinearity among independent quantitative variables to prevent biases in the interpretation of regression coefficients. Subsequently, a regression analysis was performed to identify the most suitable explanatory variables for the final regression model, with a specific focus on gait speed as the dependent variable. Following the regression analysis, the inclusion of the categorical variable (Socioeconomic environment) led to conducting a one-way ANOVA to determine variations in gait speed across different socioeconomic groups. Statistical analyses were conducted using R version 4.2.2 67 and RStudio version 2022.12.0.353 68 (Rstudio Team, 2022).

For internal validation, k-fold cross-validation (10 folds, five replicates) was used to avoid overfitting, removing data with standardized residuals (SRE)  $\geq 3$ . The final regression model included 1209 participants after outlier analysis. Power analysis included 1209 participants, establishing a medium ES ( $f^2 = 0.54$ ) with 99% power at  $\alpha = 0.05$  for future multiple linear regressions utilizing G\*Power software based on  $R^2 = 0.35$  and seven predictors.

#### **4.3.6 Ethics**

The present research project adhered to the Helsinki Declaration by the World Medical Association concerning ethical principles for medical research involving human subjects (General Assembly of the World Medical Association, 2014). Data collection was conducted anonymously, ensuring confidentiality rights were respected by securely storing personal information and adhering strictly to the Organic Law 3/2018 of December 5, regarding the Protection of Personal Data and the Guarantee of Digital Rights (Spanish Government, 2018).

The project, from which case studies II, III and IV were derived, received approval from the Ethics Committee of the University of Deusto (Annex 2), reference ETK-32/18-19. Prior to participation, participants provided written informed consent, understanding the general objectives of the articles, the voluntary nature of their involvement, and the anonymity of their participation. Participants were also informed of their right to withdraw from the study at any time.

## 5 Results

*Those who think they have no time for exercise will sooner or later have to find time for illness. - Edward Stanley.*

This chapter presents the four case studies (one pilot study and three articles) that form the core of this dissertation, following the two systematic reviews that have provided an in-depth understanding of the topic at hand. These studies were designed to validate the hypothesis of this work, addressing research questions that arose from identifying gaps in the literature. Each study in this section aims to objectively determine the validity of this hypothesis. The studies are included in the format in which they were published in four different impact factor journals. For ease of reference, each article is preceded by a summary of its main contributions and objectives, its role within the overall thesis work, and details of where and when it was published.

Table 8 shows a summary of the main conclusions of each of the publications, which respond to the objectives and hypotheses set out in this project. The case study is not shown in the table because it is not presented as an article in this doctoral thesis.:

Table 8. Summary of the articles and results presented that make up the thesis.

Type of article	Article	Objective	Conclusions
1. Systematic review	Virto, N., Ríó, X., Méndez-Zorrilla, A., & García-Zapirain, B. (2024). Non invasive techniques for direct muscle quality assessment after exercise intervention in older adults: a systematic review. <i>BMC geriatrics</i> , 24(1), 642. <a href="https://doi.org/10.1186/s12877-024-05243-3">https://doi.org/10.1186/s12877-024-05243-3</a>	1	There is significant diversity in the methods of direct assessment of muscle quality, mainly using ultrasound and magnetic resonance imaging; and a consistent positive trend in exercise interventions, indicating their efficacy in improving or preserving muscle quality. However, the lack of standardized assessment criteria poses a challenge given the diversity within the studied population and variations in methodologies.
2. Scoping review	<i>Under review, pending publication.</i> Virto, N., Ríó, X., Méndez-Zorrilla, A., & García-Zapirain, B. Non invasive techniques for muscle quality functional domain monitoring in older adults: a scoping review.	2	This review highlights the heterogeneity in MQ, particularly in the methods used to assess muscle strength and mass. A variety of non-invasive tools are available for assessing MQ, with handheld dynamometers and 1RM tests being practical for community use, while isokinetic dynamometers and power assessments are more specialized. For muscle mass, MRI, DXA, and CT are highly accurate but costly, whereas BIA and ultrasound offer more accessible and cost-effective alternatives for community settings.
3. Observational Descriptive	Virto, N., Dequin, D. M., Ríó, X., Méndez-Zorrilla, A., & García-Zapirain, B. (2024). Exploring determinant factors influencing muscle quality and sarcopenia in Bilbao's older adult population through machine learning: A comprehensive analysis approach. <i>PloS one</i> , 19(12), e0316174.	4	Exploring the factors that affect sarcopenia and MQI in older adults, this study highlights that relative power, age, weight, and the 5STS are significant determinants. While considering these clinical markers and using a holistic approach, this can provide crucial information for designing personalized and effective interventions to promote healthy aging.
4. Observational Descriptive	<i>Under review, pending publication.</i> Virto, N., Ríó, X., Méndez-Zorrilla, A., & García-Zapirain, B. Functional muscle quality and its determinants in older adults: analysis of key factors and their influences.	5	Suggests possible sex-specific differences in factors influencing MQI in older adults, with muscle mass, fat mass, and functional performance (gait speed, squat time, and balance) being significant predictors in women, whereas age, BMI, squat time, and balance were relevant in men. The smaller male sample and lower variability in their performance measures may have influenced the model's predictive power. These findings underscore the importance of considering gender-specific characteristics in MQ assessment, highlighting the need for further research to enhance generalisability.
5. Observational Descriptive	Virto, N., Ríó, X., Muñoz-Pérez, I., Méndez-Zorrilla, A., & García-Zapirain, B. (2024). Gait speed in older adults: exploring the impact of functional, physical and social factors. <i>Retos</i> , 61, 552-566. <a href="https://doi.org/10.47197/retos.v61.109902">https://doi.org/10.47197/retos.v61.109902</a>	6	Exploring the factors that affect walking speed in older adults, this study highlights that age, relative power and balance are significant determinants. These clinical markers provide crucial information for designing personalized and effective interventions to promote healthy aging.

\*The case study is not shown in the table because it is not presented as an article in this doctoral thesis.

Table 9 shows the characteristics of the journals in which the above-mentioned articles have been published.

*Table 9. Journal Quality Index.*

<b>Journal</b>	<b>eISSN</b>	<b>Country</b>	<b>Category</b>	<b>IF</b>	<b>Q</b>	<b>Editorial</b>
BMC Geriatrics	1471-2318	England	Medicine: Geriatrics and Gerontology	3.4 (2023)	SJR: Q1 <b>JCR</b> JCI: Q1 JIF: Q2	Springer Nature
Plos One	1932-6203	United States	Multidisciplinary		SJR: Q1 <b>JCR</b> JCI: Q1 JIF: Q1	PLOS
Retos	1579-1726	Spain	<b>Health Professions:</b> Physical Therapy, Sports Therapy and Rehabilitation  <b>Medicine:</b> Orthopedics and Sports Medicine	1.2	SJR: Q2  JCR: Q3	

*Note:* ISSN: International Standard Serial Number; IF: Impact Factor (JCR 2024); Q: quartile

Last, Table 10 specifies the exact participation of each of the authors in each article. Subsequently, each article is accompanied by an abstract.

*Table 10. Participation of the authors in each of the articles.*

Contribution	Paper 1	Paper 2	Paper 3	Paper 4	Paper 5
Conceptualisation	N.V	N.V	N.V	N.V	N.V
Data collection	N.V	N.V	X.R	X.R	X.R
Formal analysis	N.V	N.V	N.V and D.D.	N.V	N.V., X.R., I.M
Research	N.V	N.V	N.V and X.R	N.V and X.R	N.V and X.R
Methodology	N.V	N.V	N.V., X.R., D.D	N.V	N.V., X.R., I.M
Supervision	X.R, A.M.Z, B.G.Z	X.R, A.M.Z, B.G.Z	X.R, A.M.Z, B.G.Z	X.R, A.M.Z, B.G.Z	X.R, A.M.Z, B.G.Z
Validation	N.V and X.R	N.V and X.R	N.V., X.R, A.M.Z, B.G.Z	N.V., X.R, A.M.Z, B.G.Z,	N.V., X.R, A.M.Z, B.G.Z
Initial drafting of the article	N.V	N.V	N.V., X.R., D.D	N.V. and X.R	N.V
Writing-revising and editing	N.V., X.R., A.M.Z., B.G.Z	N.V., X.R., A.M.Z., B.G.Z	N.V., X.R., D.D., A.M.Z., B.G.Z	N.V., X.R., A.M.Z., B.G.Z	N.V., X.R., I.M., A.M.Z., B.G.Z

*Nota:* N.V= Naiara Virto; X.R. = Xabier R o; A.M.Z = Amaia Mendez Zorrilla; B.G.Z= Bego a Garcia Zapirain; D.D: Danielle Dequin; I.M: Iker Mu oz.

## 5.1 Case Study I: Pilot Study

This research builds upon the findings of two previous studies (systematic reviews) on muscle quality in older adults, extending the analysis to the study of direct methods, particularly the use of ultrasound, within the framework of this thesis. The two initial studies have established a solid theoretical foundation by identifying non-invasive methods to assess both functional and morphological aspects of muscle quality, laying the groundwork for the next steps in the investigation. On the one hand, the first systematic review focused on identifying the most effective non-invasive tools for assessing morphological muscle quality in older adults, highlighting ultrasound as a key direct method. On the other hand, the second review completed the theoretical analysis of muscle quality quantification by evaluating and determining indirect methods for assessing muscle quality, also known as functional muscle quality. Functional muscle quality is based on muscle performance in relation to muscle mass and is obtained through indirect assessments that measure functional capacity in specific health contexts.

The first systematic review lays the foundation for the use of ultrasound as a direct method for analyzing morphological muscle quality. This leads us to the need to explore the correlations between the geometric variables of the rectus femoris derived from ultrasound and clinical and functional variables, in order to explore the sensitivity of direct muscle quantification tools and compare the potential correlation with functional variables. This approach paves the way for the potential use of these functional measures as indirect indicators of muscle quality. Currently, these muscle quality parameters are predominantly used in research settings and not routinely in clinical and community practice, mainly due to the technical challenges associated with their measurement (Buckinx et al., 2018; Masanés et al., 2017; McGregor et al., 2014; Treviño-Aguirre et al., 2014). This is why we are looking for ways to overcome these limitations by exploring simpler and more accessible assessment tools that could bridge the gap between research and practical application.

To this end, a pilot study was conducted on a cohort of 66 older adults, revealing that the geometric variables derived from ultrasound images of the rectus femoris muscle significantly correlate with clinical and functional indicators. This finding provides compelling evidence of the potential for ultrasound-based assessments to capture meaningful aspects of muscle health in older populations. Moreover, it lays the groundwork for the use of these functional measures as indirect indicators of muscle quality, which could contribute to the development of more accessible assessments for muscle quality quantification in older adults, both in clinical and community settings.

### 5.1.1 Pilot Study I:

The assessment of muscle quality and mass in clinical and research settings typically relies on quantitative methods, as examined in our prior study (systematic review). Our analysis highlighted that the most frequently employed approaches for evaluating morphological muscle quality are direct measurement techniques, which capture both microscopic and macroscopic characteristics of muscle architecture, composition, and structure (Cruz-Jentoft et al., 2019). Among the non-invasive tools identified for directly assessing muscle quality, ultrasound (US) was the most commonly utilized, followed by magnetic resonance imaging (MRI). In contrast, computed tomography (CT), tensiomyography (TMG), myotonometry, and bioelectrical impedance analysis (BIA) were used less frequently.

Given the increasing focus on identifying sarcopenia and frailty, two related yet distinct conditions that often develop during the ageing process, there is a growing need for accessible and reliable tools to assess muscle quality (Davies et al., 2018; Oviedo-Briones et al., 2021; Reijnierse et al., 2016). In line with this, international health organizations now emphasize the importance of incorporating muscle quality evaluation into sarcopenia diagnostics, acknowledging that muscle function and composition play a critical role beyond simple mass measurements.

Muscle deterioration is associated with negative health outcomes, yet these can be prevented, delayed, or even reversed through timely detection and appropriate interventions, such as tailored exercise programs and nutritional strategies (Casas-Herrero et al., 2022; X. Chen et al., 2014; Landi et al., 2015). To address this, it is crucial to have precise and reliable tools to assess muscle quality and its relevance to frailty (Davies et al., 2018; Oviedo-Briones et al., 2021; Reijnierse et al., 2016). Among the available options, ultrasound has emerged as a widely used technique due to its affordability, noninvasive nature, and rapid application in musculoskeletal assessments (Patil & Dasgupta, 2012; Sconfienza et al., 2018). Traditional B-mode ultrasound imaging is currently used to estimate muscle morphology and mass by analyzing parameters such as muscle thickness, cross-sectional area, pennation angle, echo intensity, and fascicle length (López Jiménez et al., 2023; Perkisas et al., 2018; Ramírez-Fuentes et al., 2019). Nevertheless, despite being portable and cost-effective, these assessments remain largely inaccessible in community settings. Despite its portability and cost-effectiveness, the use of ultrasound remains limited in community settings due to financial constraints and a lack of accessibility, hindering its widespread application for assessing morphological muscle quality in older adults (Paris & Mourtzakis, 2021; Sanabria et al., 2019). This limitation highlights the need to further understand the morphological aspects of muscle quality to optimize assessment techniques.

The morphological domain of muscle quality focuses on the direct assessment of muscle architecture and composition, considering both its microscopic and macroscopic structural characteristics. Unlike approaches centered on functional performance, this domain primarily examines the physical properties and structural configuration of muscle tissue (Coronado-Zarco & de León, 2023; Cruz-Jentoft et al., 2019; de Lucena Alves et al., 2023; M. S. Fragala et al., 2014). Within the composition dimension, factors such as muscle density, lipid infiltration, fat content, and water distribution are analyzed. In contrast, architectural characteristics are closely related to the muscle's contractile capacity. Key architectural features influencing muscle force generation include muscle fiber length (fascicle length) and their angular arrangement relative to the direction of force produced by the entire muscle (pennation angle) (Correa-de-Araujo et al., 2017). Advanced B-mode ultrasound techniques have facilitated detailed assessments of muscle architecture, allowing accurate measurements of fascicle length, pennation angle, cross-sectional area and echo intensity, all of which are indicators of muscle composition (Correa-de-Araujo et al., 2017; M. Fragala et al., 2015; Perkisas et al., 2018; Virto, Río, Méndez-Zorrilla, et al., 2024). Finally, the assessment of muscle quality from a morphological perspective also involves examining muscle ultrastructure (M. Fragala et al., 2015; Ochala et al., 2007; Šimunič et al., 2018).

Therefore, understanding the relationship between morphological muscle quality and functional outcomes is crucial for evaluating the potential of functional assessments as accessible alternatives to morphological measurements, particularly in community settings. In line with this, the aim of this study is to establish correlations between ultrasound-derived geometric variables, which serve as indicators of morphological muscle quality, and functional measures. By exploring these correlations, future research may better integrate muscle quality assessment based on functional performance, thereby facilitating its broader implementation in clinical and community settings.

In line with the study's objectives, the findings reveal correlations between ultrasound-derived geometric variables and functional measures, suggesting that functional assessments may serve as viable proxies for evaluating morphological muscle quality in community-based settings.

Table 11. Preliminary correlations at baseline visit for hospital cohort (n=66).

Correlations (p value)	Thickness	Cross sectional area	Pennation angle
SARC-F (Strength, Assistance with walking, Rising from a chair, Climbing stairs, and Falls)	-0.098 (0.353)	-0.236 (0.023)	-0.158 (0.108)
Grip strength	0.240 (0.021)	0.372 (0.000)	0.105 (0.321)
Short Physical Performance Battery total	0.288 (0.005)	0.355 (0.001)	0.197 (0.044)
Gait speed	0.168 (0.112)	0.327 (0.002)	0.241 (0.014)
Frailty Phenotype (Fried)	-0.101 (0.339)	-0.211 (0.043)	-0.044 (0.680)
FRAIL (short five-questions assessment of Fatigue, Resistance, Aerobic capacity, Illnesses and Loss of weight)	-0.125 (0.237)	-0.284 (0.006)	-0.034 (0.731)

<sup>a</sup>Significant moderate and strong correlations ( $r > 0.4$ ); <sup>b</sup>Significant correlations ( $P < .05$ ); <sup>c</sup>Significant weak correlations ( $r < 0.4$ ).

Significant but weak correlations were identified between functional variables (gait speed, handgrip strength, and the SPPB) and morphometric parameters obtained by ultrasound (CSA, muscle thickness, and PA of the rectus femoris). However, it is important to note that, within the context of our research, the focus is particularly on the relationship and correlation of functional variables with geometric parameters, specifically CSA and PA, as these are the two markers that most directly reflect morphological muscle quality.

Based on this analysis and the information gathered from the initial systematic review, it is noteworthy that geometric parameters measured by ultrasound, such as pennation angle and CSA, show correlations with functional variables. These results serve as a foundational baseline for the possibility of using functional variables as a basis to calculate muscle quality in a functional manner, thereby developing a simpler and more accessible formula to effectively assess muscle quality in community settings.

It is important to highlight that previous studies using ultrasound (US) measurements have also identified a relationship between morphological muscle quality and strength, functional variables, or functional performance, supporting the usefulness of these correlations (Bartley & Studenski, 2017; Benton et al., 2021; Lopez et al., 2020; Patil & Dasgupta, 2012; Ramírez-Fuentes et al., 2019; Scanlon et al., 2014; Sconfienza et al., 2018; Whang et al., 2025). Furthermore, when morphological muscle quality is measured with different tools such as CT or MRI, these relationships are also found (Cameron et al., 2023; Cleary et al., 2015; Farrow et al., 2021; Klupp et al., 2019; Millor et al., 2020; Oba et al., 2021).

In conclusion, this study validates the relationship between morphological muscle quality and functional variables, which allows for the exploration and justification of using functional measurements as an accessible alternative to assess muscle quality in community settings.

## 5.2 Case Study II: Article III: Exploring determinant factors influencing muscle quality and sarcopenia in Bilbao's older adult population through machine learning: A comprehensive analysis approach.

This study represents the next step in the analysis of muscle quality in older adults, as addressed within the framework of this thesis. Preliminary studies have provided a solid theoretical basis by identifying non-invasive tools for the assessment of muscle quality, both functional and morphological, setting the bases for more advanced research. In this regard, the findings from the pilot study, conducted on a cohort of 66 older adults, demonstrated that geometric variables derived from ultrasound imaging of the rectus femoris muscle (a relevant measure within the morphological domain of muscle quality) show significant correlations, albeit weak, with clinical and functional indicators. This result is particularly noteworthy as it aligns with previous findings suggesting that functional measures could serve as proxy indicators of muscle quality. While not a direct substitute, these functional assessments could provide a viable alternative for estimating muscle quality in clinical and community settings, supporting the exploration of more accessible and practical indirect methods (Barbat-Artigas et al., 2012).

These tools, being more accessible and less complex than direct measures, would not only streamline the evaluation process but also enhance their integration into routine clinical and community practice. In this way, one of the key aims of this thesis would be achieved: to improve the accessibility and feasibility of muscle quality assessment, thereby increasing its applicability in both clinical and community settings.

The functional domain involves evaluating muscle performance indirectly in relation to its mass (Barbat-Artigas et al., 2012; Coronado-Zarco & de León, 2023; de Lucena Alves et al., 2023). The objective in this domain is to measure the efficiency with which a muscle produces force in proportion to its size, often expressed as a muscle quality index. This approach has gained increasing support in the literature as a more accessible method for quantifying functional muscle quality. As a strategy in line with these trends, both the findings of our scoping review and the results of the aforementioned case study further corroborate the feasibility of using functional measures to assess muscle quality, reinforcing the rationale for adopting this method in resource-limited community settings.

With this in mind, this study aims to investigate the determinants of muscle quality and sarcopenia in older adults, as well as their relationship with functionality and general health. To achieve this, anthropometric, functional and socioeconomic factors associated with muscle quality and sarcopenia will be analysed using machine learning approaches to identify key determinants for possible integration into clinical practice. Analysis data will be obtained using indirect and non-invasive muscle quality assessment tools and advanced techniques, such as machine learning, will be used to uncover critical patterns that influence muscle quality in older adults.

This approach aims not only to deepen our understanding of the factors that influence muscle quality, but also to propose innovative ways to integrate these tools into clinical practice. By recognizing that proxy measures can be derived from functional indicators, this study aims to optimize assessment strategies and advance towards more accessible and effective interventions. In doing so, it not only expands the knowledge base on muscle quality and sarcopenia but also explores their potential to transform current assessment and treatment methods. Ultimately, by identifying the factors influencing muscle quality and sarcopenia in this cohort of older adults in Bilbao, we aim to uncover key determinants that impact these variables. This knowledge will facilitate the development of exercise programs tailored to promote healthy aging, grounded in a deeper understanding of the underlying pathophysiology.

In this study, 1,253 older adults with a mean age of  $78.13 \pm 5.78$  years participated voluntarily. Functional, anthropometric, geriatric pathology and socioeconomic tests were

examined to identify determinants of sarcopenia and the Muscle Quality Index (MQI) using machine learning techniques. The key predictors for both conditions include relative power, age, weight, and the 5STS. Since no single factor alone is sufficient to predict either condition, the study highlights the importance of a comprehensive approach, considering all selected features, to better understand and address sarcopenia and MQI in older adults.

This paper is published in the journal PLoS ONE (IF: 2.9 [Q1 SJR and JCR]) and was accepted on the 31th of December of 2024. It includes the original full version of the manuscript.

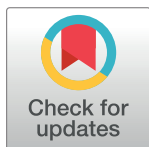
## RESEARCH ARTICLE

# Exploring determinant factors influencing muscle quality and sarcopenia in Bilbao's older adult population through machine learning: A comprehensive analysis approach

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## Abstract

### Background

Sarcopenia and reduced muscle quality index have garnered special attention due to their prevalence among older individuals and the adverse effects they generate. Early detection of these geriatric pathologies holds significant potential, enabling the implementation of interventions that may slow or reverse their progression, thereby improving the individual's overall health and quality of life. In this context, artificial intelligence opens up new opportunities to identify the key identifying factors of these pathologies, thus facilitating earlier intervention and personalized treatment approaches.

### Objectives

investigate anthropomorphic, functional, and socioeconomic factors associated with muscle quality and sarcopenia using machine learning approaches and identify key determinant factors for their potential future integration into clinical practice.

### Methods

A total of 1253 older adults (89.5% women) with a mean age of  $78.13 \pm 5.78$  voluntarily participated in this descriptive cross-sectional study, which examines determining factors in sarcopenia and MQI using machine learning techniques. Feature selection was completed using a variety of techniques and feature datasets were constructed according to feature selection. Three machine learning classification algorithms classified sarcopenia and MQI in each dataset, and the performance of classification models was compared.

### Results

The predictive models used in this study exhibited AUC scores of 0.7671 for MQI and 0.7649 for sarcopenia, with the most successful algorithms being SVM and MLP. Key factors in predicting both conditions have been shown to be relative power, age, weight, and

the 5STS. No single factor is sufficient to predict either condition, and by comprehensively considering all selected features, the study underscores the importance of a holistic approach in understanding and addressing sarcopenia and MQI among older adults.

## Conclusions

Exploring the factors that affect sarcopenia and MQI in older adults, this study highlights that relative power, age, weight, and the 5STS are significant determinants. While considering these clinical markers and using a holistic approach, this can provide crucial information for designing personalized and effective interventions to promote healthy aging.

## Introduction

Aging is marked by a progressive loss of physical and physiological capacities, resulting in a decline in functions and heightened vulnerability to death [1]. This deterioration stands as the primary risk factor for major human pathologies [2]. The concurrent increase in life expectancy, coupled with a growing elderly population, raises substantial concerns about public health [3]. Consequently, a rising demand emerges for the development of effective solutions to address age-related pathologies, with frailty and sarcopenia taking center stage among the most prevalent geriatric conditions [4, 5]. The universal decline in both muscle quantity and quality with age further intensifies these concerns, highlighting the acute necessity for targeted interventions and tools to mitigate the consequences of age-related muscular deterioration [6].

Frailty and sarcopenia are related yet distinct conditions associated with aging. While sarcopenia primarily affects the musculoskeletal system, frailty is a more multifactorial syndrome [7]. According to the European Working Group on Sarcopenia in Older People (EWGSOP-2), the first criterion indicating the probable presence of sarcopenia is the characteristic decrease in muscle strength, while the reduction in muscle mass and quality confirms the diagnosis. In cases where inferior physical performance is identified, sarcopenia is categorized as severe [8]. The EWGSOP-2 underscores the significance of assessing not just the quantity of muscle, but also its quality [8]. Muscle quality (MQ) encompasses both microscopic and macroscopic alterations in muscle architecture, as well as the functional output per unit of muscle mass [9].

An essential sign of an older adult's general health is the overall condition of their muscles [10]. Age-related declines in muscle mass and quality are prevalent for everyone, leading to frailty and sarcopenia, reduced independence, compromised quality of life, and heightened mortality risk [6, 9]. It is imperative to comprehend factors influencing muscle quality, alongside actively maintaining and regulating it, to stave off declines in muscle mass, strength, and regenerative capabilities [11].

One of the possible strategies that maintains optimal health during aging is regular physical activity, as aging, even in healthy individuals, is associated with a progressive decline in muscular, neural and cognitive function, leading to deficits in functionality [12]. These interventions result in an improvement of the features of sarcopenia and muscle quality by optimizing changes in body composition, improving strength and mobility, increasing physical activity levels and improving the cardiorespiratory system, among others [13–15].

The mentioned geriatric pathologies have been given special attention due to their prevalence among older individuals and the adverse events they generate [4, 16]. Additionally, early detection holds significant potential, enabling the implementation of interventions that may slow or reverse progression, reduce health costs, and enhance quality of life [8, 16].

In community and clinical settings, developing specific machine learning (ML) models tailored to predict sarcopenia and MQ based on the characteristics of the studied population is presented as a crucial asset. Machine learning, a subset of artificial intelligence, is a computational technique that enables computers to automatically learn from data to identify patterns and make predictions in order to identify key factors contributing to the risk of health concerns such as MQ and sarcopenia [17]. Machine learning is commonly applied in clinical settings for disease diagnosis and prognosis [18]. Several studies have used ML to discover important factors for predicting sarcopenia and frailty [3, 19, 20]. Enhancing the detection of physiological, environmental, social, and lifestyle factors contributing to frailty and sarcopenia in older individuals will refine prediction models and enhance healthcare system policies and practices [21].

Artificial intelligence opens new opportunities to advance personalized medicine and understand relevant characteristics in pathophysiology, with recent research demonstrating its effectiveness [21, 22]. Utilizing these developments in personalized medicine using ML permits the identification of complex patterns in large datasets, the anticipation of health risks, and aids in the design of intervention strategies. Integrating these techniques into clinical practice, this study aims to investigate anthropomorphic, functional and socioeconomic factors associated with muscle quality and sarcopenia, using ML approaches.

## Methods

### Study design and population

This descriptive cross-sectional study investigates dynamometric, anthropometric, and Short Physical Performance Battery (SPPB) test outcomes, including balance, gait speed test and chair stand test alongside socioeconomic index data. Participants were selected from the "Health for the Elderly" program sponsored by the Bilbao City Council. Inclusion criteria for participants encompass being aged 60 or older, currently enrolled in the "Health for the Elderly" program, and voluntarily participating, with the inability to walk independently serving as the exclusion criteria. Most of the patients are of Basque origin, sharing similar demographic, racial, and body characteristics. This homogeneity in the sample may limit the generalizability of the model, as it does not adequately capture the variability found in a more diverse population. The data collection of the study was approved by the University of Deusto Ethics Committee (reference # ETK-32/18–19), started on May 1st, 2019 and finished on May 31st, 2019 and written informed consent was obtained from each participant prior to study.

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### Measurement protocol

**Manual grip strength.** A Camry EH101 electronic hand dynamometer, approved as medical equipment by the Spanish Agency for Medicines and Health Products, was used to measure hand grip strength. The testing protocol involved individuals adopting a posture with a slight shoulder abduction (approximately 10°), with the elbow in full extension and the forearm and hand in a neutral position [23]. Each participant underwent two tests, with the higher recorded value used for analysis. The CAMRY EH101 dynamometer, employed in this study,

demonstrated excellent reliability and validity. This device stands out as a reliable, cost-effective, and practical tool for evaluating grip strength in geriatric clinical settings [24].

**Anthropometry.** Body composition variables were analyzed using segmental bioimpedance with the Tanita BC-601 segment analyzer. This approach yields information regarding body fat percentage, weight, and muscle mass (kg). The Tanita BC-601 is a reliable non-invasive method that offers precise measurements [25]. Furthermore, the Tanita HR 001 Leicester portable stadiometer was utilized for measuring height.

**Socioeconomic index.** The socioeconomic and physical environment of a region are interconnected with health statistics, exerting a direct impact on the well-being of the elderly population [26]. The Euskadi 2021 socioeconomic index was created using the same approach as the MEDEA project [27]. This variable's definition is based on the average personal income (in euros) for each type of financial category throughout city neighbourhoods in the municipality of Bilbao in 2021. As a result, three socioeconomic indices, low rent (<20,000 euros), medium rent (>20,000 and <30,000 euros), and high rent (>30,000 euros), have been identified [28].

**Functional assessment: SPPB.** The Short Physical Performance Battery (SPPB) is a commonly used clinical assessment tool renowned for its strong reliability and validity, reporting an excellent inter-rater reliability and test-retest reliability [29, 30]. The SPPB consists of three components: a balance assessment (including standing, semi-tandem, and tandem positions), a four-meter walk test (measuring the time taken to walk four meters at a normal pace), and a five-repetition sit-to-stand test (5STS) performed as rapidly as possible [31]. Each component is scored from zero to four, with zero representing the lowest score. Moreover, a combined score, which ranges from zero to 12 points, is calculated by adding together the scores obtained from the three components [31].

**Relative power.** The 5STS test, utilized to assess lower extremity muscle power in clinical or field environments, demonstrates good intra-rater, inter-rater, and test-retest reliability, making it a dependable measurement tool suitable for both experienced and inexperienced raters [32]. To compute the mean absolute value, the equation developed by Alcazar et al., 2018 was utilized, taking into account performance in the 5STS (measured as time to complete five STS repetitions), body mass, body height, and chair height [33]. To standardize the data, the result was divided by body weight [33].

**Muscle Quality Index (MQI).** In this research, muscle quality was indirectly evaluated using the method proposed by Barbat-Artigas et al. and Chang et al. [34, 35], which involves dividing handgrip strength by relative skeletal muscle mass. The classification of muscle quality was based on the thresholds established by Barbat-Artigas et al. (2012). Participants are categorized into normal (>1.53), low (>1.36 and  $\leq$ 1.53) and poor ( $\leq$ 1.36) muscle quality for men, and normal (>1.53), low (>1.35 and  $\leq$ 1.53) and poor ( $\leq$ 1.35) muscle quality for women [35].

Within the data this feature is referred to as *cut off points* with integer values one through three; one corresponding to normal muscle quality and three corresponding to poor muscle quality. This feature is subsequently used for feature selection and classification tests of MQI.

**Sarcopenia.** For sarcopenia tests the feature *sarcEWGSOP* was used as the dependent variable. This feature represents the level of sarcopenia with integer values zero through two: zero corresponding to the absence of sarcopenia, one with moderate presence, and two with severe sarcopenia, as defined by EWGSOP-2 [8]. The calculation of sarcopenia levels was carried out using the gender-specific cut-off values for males and females, according to the EWGSOP-2 criteria.

**Frailty.** Frailty in older adults can be operationally defined using the Short Physical Performance Battery (SPPB), which provides a total score ranging from 0 to 12 points. This score

enables the classification of frailty into four categories: non-frail (10–12 points), pre-frail (7–9 points), mild to moderate frailty (4–6 points), and severe frailty (0–3 points) [31].

**Data preparation and preprocessing.** We prepared the data for analysis, including separate processes for the MQI and sarcopenia tests. The raw dataset contained 1,253 individual entries with 39 features. The key preprocessing steps involved data cleaning, filtering relevant variables, applying one-hot encoding to nominal variables, and scaling ordinal variables to ensure comparability. A normalised and standardised dataset was then created to facilitate feature selection using support vector machines.

*Specific processing for MQI.* Seventeen variables were selected for MQI tests: *socioeconomic index (3)*, *age*, *weight*, *bmi*, *fat mass*, *balance 1*, *balance 2*, *balance 3*, *gait speed (m/s)*, *4m test*, *5STS*, *mean power*, *relative power*, *SPPB*, *frailty*, *groups*, *sarcopenia (v)*. One-hot encoding was applied to nominal variable *sarcopenia (v)*. Ordinal features *socioeconomic index (3)*, *frailty*, and *groups* were scaled.

*Specific processing for sarcopenia.* Eleven variables were selected for sarcopenia tests: *socioeconomic index (3)*, *sex*, *age*, *height*, *weight*, *bmi*, *fat mass*, *muscle*, *5STS*, *relative power*, *points balance*. *Socioeconomic index (3)* was scaled.

**Feature selection methods.** Feature selection in ML is the process of selecting features relevant for training a prediction model. Feature selection provides many benefits, including reducing computation time, improving prediction performance, and a better understanding of the data in machine learning [36, 37]. A common problem within medical ML studies is small sample size [38]. Feature selection techniques have been shown to provide possible solutions to this, while also helping medical researchers identify the underlying mechanisms that relate to diseases [39, 40].

Four methods were employed in this study for feature selection: Spearman correlation, Ordinary Least Squares (OLS), Random Forest (RF), and Support Vector Machine (SVM). A subset of the data was created using the chosen features from each method. These subsets are subsequently used for classification tests.

*Spearman correlation.* Spearman correlation was used as a filter method to select a subset of the features based on the relationship between the features and the target class. We chose to use Spearman correlation because it is suited to handle data such as the one used in this study which contains both non-normally distributed continuous data and ordinal data [41]. The strength of the relationship between the features and target class was measured using the correlation coefficient. Previous works were utilized for interpreting the correlation coefficient [41, 42].

The following steps were followed to select features using Spearman correlation:

1. Compute the correlation between all variables with the target variable.
2. Select those with an absolute value of the correlation coefficient above a threshold of 0.3. Anything less was considered a weak correlation.
3. Check selected variables for correlation with each other. From each pair of features that are strongly correlated, remove the one that is less correlated with the target. Anything with a coefficient above 0.5 is considered strongly correlated.

*OLS.* An OLS wrapper method was used by iteratively selecting a subset of features and passing it to the model. Based on feature performance another set of features is selected or the process terminates [43]. Feature performance was evaluated based on p-value. The feature with the highest p-value was removed from the selected features. This process was repeated until there were no more features with a p-value above 0.5.

*Random forest.* An embedded method with a random forest ML model was employed to extract features based on importance. Embedded methods use intrinsic properties of the

classifier to select the subset of features [43]. We used the meta-transformer *SelectFromModel* from *Scikit-Learn* to select features based on importance weights. Feature importances were computed as the mean and standard deviation of accumulation of the impurity decrease within each tree in the random forest [44].

**SVM.** Feature selection using SVM recursive feature elimination was performed using a linear kernel, inspired by previous work [45]. Features were ranked using the sum of the absolute value of the coefficients. In this process, the feature with the lowest rank is removed and a model is trained on the remaining features. When evaluating the weights of the features we found that the lowest ranked 35% of features had a significantly lower weight. Therefore, we decided to repeat the process until less than 65% of the features remain.

**Aggregated select features and importance rank.** The selected features were ranked and aggregated to create a list of features. The purpose was to investigate model performance with a different number of features from this aggregated list of selected features.

Feature rank is calculated as follows:

1. Each feature is given a rank per selection method. If it is not chosen for a method, it is given the rank of “last place”. For example, in the MQI dataset there are 17 features, and any unchosen feature is given a rank of 17.
2. The *rank sum* for each feature is the sum of all rankings across all methods.
3. The aggregated feature rank is calculated as *one* divided by *rank sum*.

Subsets of data were then created based on the first four, first eight, and the full list of the features from the select feature list. These subsets were then compared in classification tests, alongside the subsets created from each individual selection method, to investigate if using more features provides a better performing model.

**Sarcopenia and MQI classification modeling using machine learning.** Using the subsets of data created from feature selection techniques mentioned above we aimed to see if a particular method for selecting features was ideal to establish a prediction model for both sarcopenia and MQI. For the tests, we used eight ML algorithms including K-nearest Neighbors (KNN), Gradient Boosting (GB), Decision Tree (DT), Gaussian Naive Bayes (NB), Stochastic Gradient Descent (SGD), Random Forest (RF), Multi-Layer Perceptron (MLP), and Support Vector Machine (SVM). All of the models employed come from the Sci-Kit Learn library. Generally, deep learning (DL), a subfield of ML, offers multiple benefits over traditional ML methods [46]. However, when training on small datasets, such as in our case, ML models are preferred over DL models, since a dataset with less than 100,000 samples is considered insufficient for DL [47].

**Classification experiments.** Two steps were employed to compare classification results using the different feature selection methods: baseline test and hyperparameter tuning. All tests were completed using a total of nine datasets. This includes the four subsets of data created to compare classification performance across feature selection methods, as well as the three subsets using the aggregated select features. Classification results are compared against the full dataset as well as a normalized version of the dataset as a baseline. In all tests we chose to perform cross validation instead of a train-test split. Previous works show that, with small datasets such as ours, a train-test split can lead to unreliable test metrics, and therefore cross-validation as a better option [48, 49].

**Baseline test.** For the baseline performance tests we trained a total of 16 models using the aforementioned ML algorithms: eight models for prediction of sarcopenia and eight for MQI. Classifier performance was reported using accuracy, area under ROC curve (AUC) and f1-score. Each model was evaluated based on prediction AUC using test samples from the

data. Accuracy is included because it is a commonly reported metric in ML. Our analysis focuses on AUC to compare models due to its ability to handle multiclass classification with class imbalances [50]. F1-score, the harmonic mean between precision and recall, is also reported as it is a common metric in multiclass classification tasks [51]. In both cases we used macro averaging, the arithmetic mean of the score of each class, to not give extra weight to larger classes. For example, a high Macro-F1 value indicates that the algorithm has good performance across all classes [51]. To determine the performance of a given model with each subset of the data created using feature selection, we conducted a five-fold cross-validation, resulting in the average performance across all folds.

Standard parameters were chosen for the baseline experiments, with non-standard parameters used in only a few cases. For all models that have the parameter *random\_state* we gave a value of 42 to improve result reproducibility. To ensure reproducibility of models that do not have this parameter, we also set a seed in the environment to 42. For MLP it was necessary to set the value of *max\_iter* to 5000, as the standard input 200 was not sufficient for convergence. For SVM we used a linear kernel for the baseline experiments, to see if the data are linearly separable before moving on to more complex kernels. To allow for the ability to compute AUC for certain classifiers, we set probability to True for SVM, and used the *log\_loss* function for SGD.

Multilayer perceptrons and SVMs are both sensitive to feature scales [52]. For MLPs standardization is used to increase model performance and decrease the number of epochs required for model convergence [53]. Therefore, all tests involving MLP and SVM include a pipeline with a step to standardize the data before they are fed to the model. The pipeline utilized *StandardScaler* from *Sci-Kit Learn*.

*Hyperparameter tuning and final results.* Default hyperparameters are not guaranteed to give optimal performance [54]. Therefore, using the results of the baseline experiments we selected the three best performing models for further tests to discover the optimal hyperparameters. The three models that we found to have the highest AUC scores for both sarcopenia and muscle quality prediction tasks include RF, SVM, and MLP. With these models we ran hyperparameter tuning using *GridSearchCV* from *Scikit-Learn*, with a five-fold cross-validation. The hyperparameter options tested are shown in Table 1 in [S1 File](#). The best performing models from this stage gave us the final classification results.

## Results

### Participant characteristics

A total of 1253 patients aged 60 or older were included in this study: 1121 being female and 132 male. [Table 1](#) shows the anthropometric and functional measurements of the study

**Table 1. Anthropometric and functional measurements of the study participants.**

Variable	Mean $\pm$ SD	Med [Min-Max]
Age	78.13 $\pm$ 5.78	79 [60–93]
Handgrip Strength (right)	20.7 $\pm$ 6.57	20 [6–55]
Muscle Mass (kg)	39.37 $\pm$ 5.58	38 [24–65]
Fat Mass (kg)	38.02 $\pm$ 5.98	39 [15–64]
BMI	28.44 $\pm$ 4.08	28 [16–46]
Gait Speed (m/s)	0.99 $\pm$ 0.25	0.99 [0.33–2.94]
Mean Power ( <i>weight</i> $\times$ <i>BMI</i> )/5STS	121.71 $\pm$ 44.5	116.7 [29.24–352.13]
Relative Power ( <i>mean power</i> /kg)	1.8 $\pm$ 0.53	1.74 [0.5–4.46]
SPPB	9.75 $\pm$ 1.68	10 [4–12]
MQI	1.25 $\pm$ 0.37	1.2 [0.33–3.46]

<https://doi.org/10.1371/journal.pone.0316174.t001>

**Table 2. Prevalence of disease within the study population.**

Variable	Healthy	Moderate	Severe
Sarcopenia ( <i>sarcEWGSOP</i> )	513	587	153
MQI ( <i>cut off points</i> )	215	201	837
Frailty	748	451	54

<https://doi.org/10.1371/journal.pone.0316174.t002>

participants. The degree of disease present within the study population, including MQI, frailty, and sarcopenia is shown in Table 2. Most patients (837) had a poor level of muscle quality, with 201 showing moderate degradation and 215 presenting with healthy MQI. Regarding sarcopenia 513 patients presented as healthy, with 587 showing moderate and 153 showing severe sarcopenia. 748 patients were found to have normal levels of frailty, with 451 showing moderate and 54 showing more advanced levels of frailty.

### Feature selection

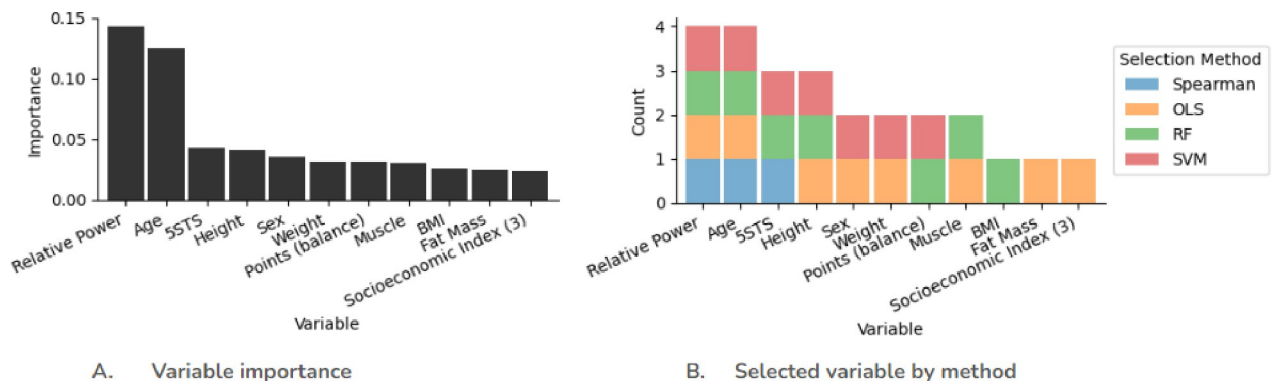
**Sarcopenia feature selection frequency and ranking.** The calculated importance of the selected features for sarcopenia are shown in Fig 1A. *Relative power* and *age* have a relatively close level of importance for sarcopenia, with an over 50% drop in importance for the next highest ranking feature, *5STS*. The aggregated select features includes all of the features from the full sarcopenia dataset, thereby not reducing the number of features.

**MQI feature selection frequency and ranking.** The calculated importance of each of the features within the aggregated select features for MQI is shown in Fig 2A. The variables in the x-axis are displayed in order of importance, with *relative power* being the most important feature. After *relative power*, the importance of each feature drops by over 50%.

### Classification results

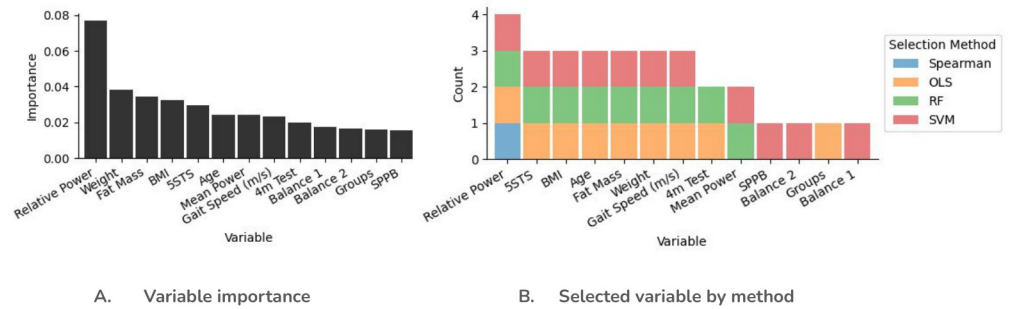
The results of the models are compared using the AUC score for both MQI and sarcopenia classification. Each of the eight ML models was trained on nine datasets separately. Through this we can compare the various selection methods for each disease classification task. A detailed list of the features included in each dataset are shown in Table 4 for MQI and Table 5 for sarcopenia in S1 File.

**Baseline results.** The three models that perform best for both tasks across all datasets are MLP, RF, and SVM. The NB models had similar results to the other highest performing models when classifying sarcopenia, but quite poorer performance when classifying MQI, as shown



**Fig 1. Calculated importance of selected features for sarcopenia.**

<https://doi.org/10.1371/journal.pone.0316174.g001>



**Fig 2. Calculated importance of the features selected based on relevance to MQI.**

<https://doi.org/10.1371/journal.pone.0316174.g002>

in Figs 3 and 4. The relatively high AUC values indicate that the models are good at distinguishing between classes by assigning a higher probability to the correct class. Accuracy results are overall higher for MQI prediction, indicating that the models’ ranking ability align closer to their overall ability to classify correctly. The complete performance metrics reported for each test for the baseline experiments are shown Table 6 for sarcopenia and Table 7 for MQI in S1 File.

**Hyperparameter tuning results.** The hyperparameters investigated are as follows: *n\_estimators* and *max\_features* for RF, *hidden\_layer\_sizes*, *activation*, and *learning\_rate* for MLP, and *C*, *kernel*, and *degree* for SVM. The best hyperparameters found for each model and dataset combination are shown in Table 2 for sarcopenia and Table 3 for MQI in S1 File. The results of hyperparameter tuning are shown in Fig A. for sarcopenia and Fig 5B. for MQI. The y-axis in all subplots shows the mean test AUC across all folds using only one of the datasets, with the same process being repeated for each of the nine datasets.

**RF hyperparameters.** A random forest fits a number of DT classifiers on various sub-samples of the dataset and uses averaging to improve the predictive AUC score. The parameter *n\_estimators* controls the number of trees in the forest. Increasing the number of trees

	SVM	NB	KNN	RF	MLP	GB	DT	SGD
Dataset								
Spearman Select	0.7369	0.7446	0.6512	0.7076	0.7418	0.7140	0.5807	0.7255
OLS Select	0.7552	0.7449	0.6456	0.7359	0.7550	0.7387	0.5883	0.7389
RF Select	0.7476	0.7510	0.6521	0.7369	0.7495	0.7223	0.5775	0.7391
SVM Select	0.7575	0.7468	0.6606	0.7378	0.7582	0.7332	0.5821	0.7459
Aggregated First 4	0.7038	0.7439	0.6341	0.7050	0.7402	0.7152	0.5885	0.7240
Aggregated First 8	0.7585	0.7477	0.6514	0.7444	0.7546	0.7355	0.5995	0.7405
Aggregated All	0.7508	0.7467	0.6664	0.7376	0.7528	0.7382	0.5908	0.7462
Full	0.7508	0.7467	0.6664	0.7376	0.7528	0.7382	0.5908	0.7462
Full Normalized	0.7525	0.7468	0.6880	0.7457	0.7508	0.7296	0.5843	0.7564

**Fig 3. Baseline results for sarcopenia classification, shown in AUC.**

<https://doi.org/10.1371/journal.pone.0316174.g003>

	SVM	NB	KNN	RF	MLP	GB	DT	SGD
Dataset								
Spearman Select	0.5306	0.6859	0.6091	0.6156	0.6828	0.6646	0.5926	0.6856
OLS Select	0.7189	0.7084	0.6718	0.7311	0.7663	0.7377	0.5937	0.7553
RF Select	0.7260	0.7060	0.6644	0.7352	0.7649	0.7378	0.5850	0.7554
SVM Select	0.7281	0.7018	0.6579	0.7363	0.7603	0.7372	0.6041	0.7563
Aggregated First 4	0.7289	0.7122	0.6500	0.6994	0.7553	0.7259	0.5883	0.7501
Aggregated First 8	0.7231	0.7134	0.6644	0.7374	0.7572	0.7442	0.5847	0.7538
Aggregated All	0.7281	0.7018	0.6579	0.7401	0.7561	0.7360	0.5941	0.7569
Full	0.7279	0.6698	0.6655	0.7297	0.7570	0.7320	0.6080	0.7492
Full Normalized	0.6830	0.6830	0.6631	0.7322	0.7488	0.7332	0.5953	0.7491

Fig 4. Baseline results for MQI prediction, shown in AUC.

<https://doi.org/10.1371/journal.pone.0316174.g004>

improves AUC, but also the computation time. It can be seen in both Fig 5A.1. and 5B.1. that model performance increases as this value increases.

*Max\_features* is the number of features to consider when looking for the best split. Empirically good values often depend on the type of task. For both MQI and sarcopenia classification, ‘sqrt’ is the best value across the majority of the datasets.

*MLP hyperparameters.* The number of neurons in the neural network are represented by *hidden\_layer\_sizes*, with the *i*th value in the tuple representing the number of neurons in the *i*th layer. For either classification task a larger network does equate to better results, with the best framework for sarcopenia being (100,) or (200,) depending on the dataset, and the best for MQI being (10,10,10) or (200,).

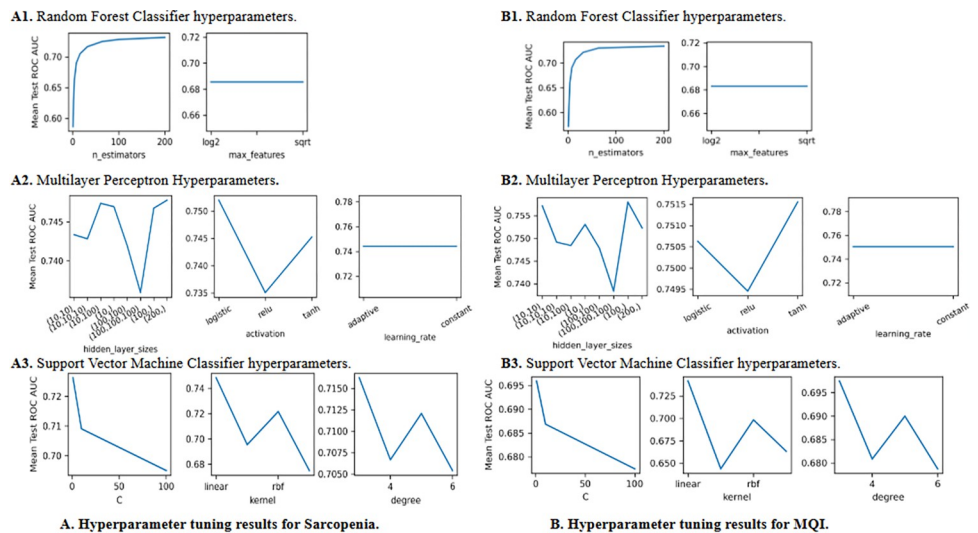


Fig 5. Hyperparameter tuning results for sarcopenia and MQI.

<https://doi.org/10.1371/journal.pone.0316174.g005>

The *activation* parameter represents the activation function for the hidden layer. For sarcopenia a logistic function is shown to be the best activation function, whereas tanh is better for MQI classification.

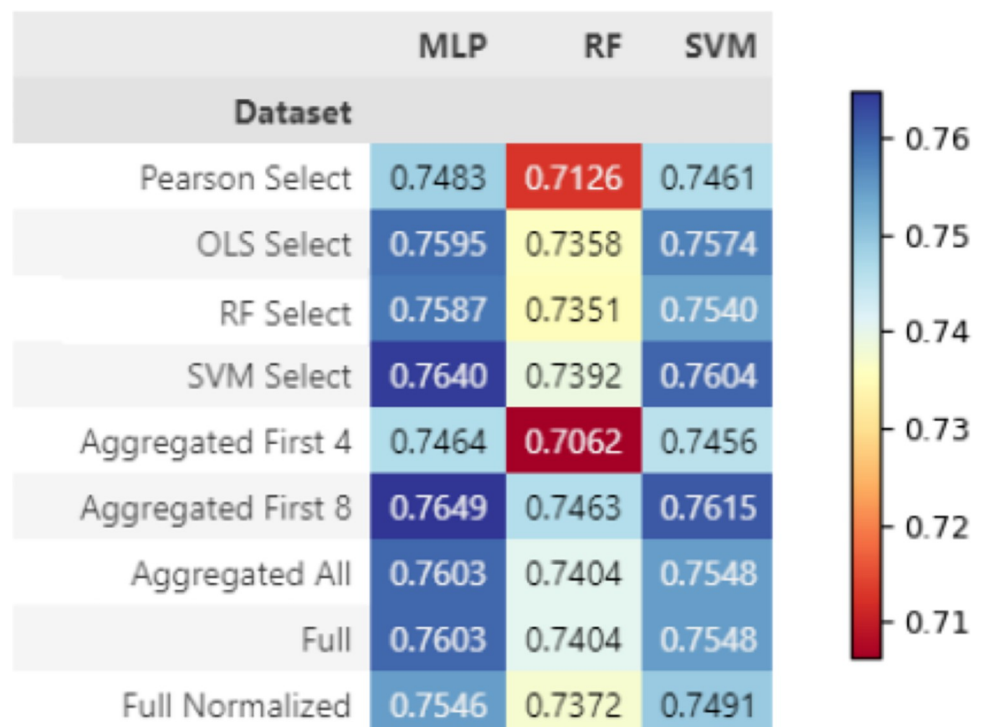
The *learning\_rate* represents the schedule for weight updates. A higher value leads to faster learning by determining the step size taken into the gradient direction in backpropagation. Too small learning rate can lead to very slow learning and increased computation time, while too large a value can lead to early convergence with poor performance. The average test score shown in Fig 5A.2. and 5B.2. do not show a difference between adaptive or constant with the dataset displayed. However, as shown in Table 2 and Table 3 in S1 File a constant learning rate is best.

*SVM hyperparameters.* C is the regularization parameter. It controls the tradeoff of generalizability and overfitting by modifying the width of the margin of the hyperplane between classes. A smaller number corresponds to a larger margin, which will generalize better to unseen data. In the case of sarcopenia and MQI classification the results show a smaller value for C being ideal.

The parameter *kernel* specifies the kernel type to be used in the algorithm. The results show a linear algorithm to be the best for both sarcopenia and MQI classification.

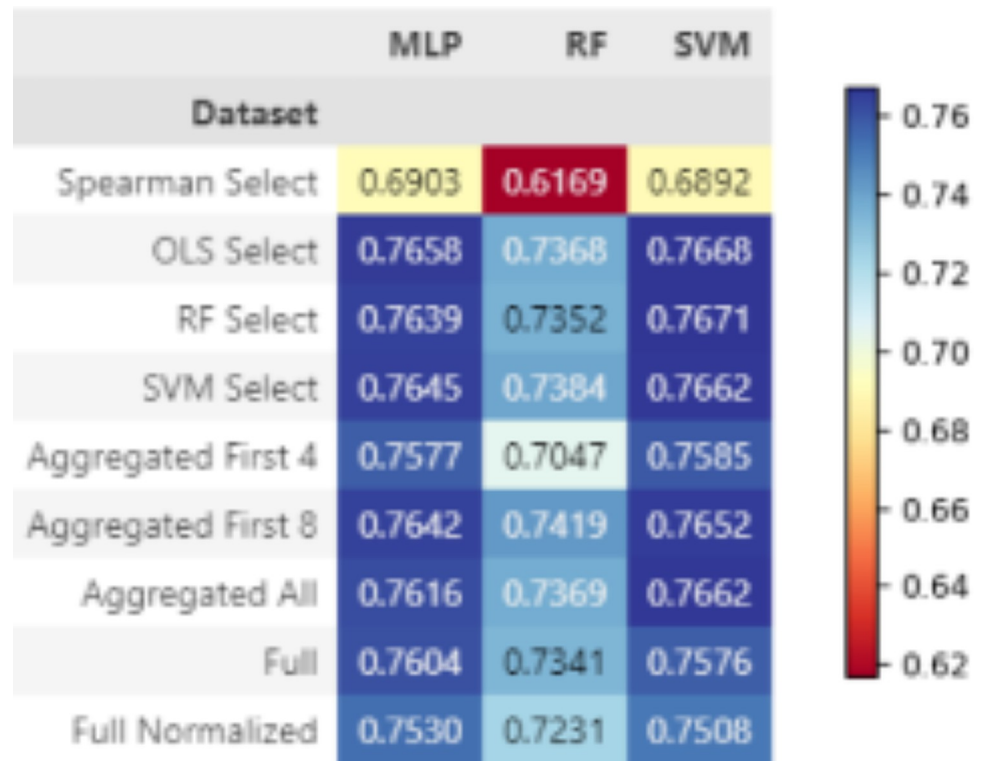
When using a polynomial kernel, *degree* specifies the degree of the function. There is not a significant difference in performance using different polynomial degrees, as shown in Fig 5A.3. and 5B.3, however, the best value across all datasets is a degree of three.

**Final sarcopenia classification results.** The AUC score of sarcopenia classification for each dataset and model combination are shown in Fig 6. Multilayer perceptrons perform best for sarcopenia classification. The highest AUC score was 0.7649, which is held by an MLP trained on the dataset containing the first 8 variables in the aggregated select features dataset. The SVM selected data has worked well for training a MLP on this task, with a similar AUC of



**Fig 6. Final sarcopenia classification results shown in AUC across all dataset and model combinations.**

<https://doi.org/10.1371/journal.pone.0316174.g006>



**Fig 7. Final classification results shown in AUC across all dataset and model combinations for MQI.**

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0.7640. The complete performance metrics reported for each test are shown in Table 8 for sarcopenia in [S1 File](#).

*Final MQI classification results.* The AUC results for each dataset and model combination are shown in [Fig 7](#). The best AUC score achieved for MQI classification was 0.7671, which was given by an SVM trained on the RF selected features. Multilayer perceptrons and SVMs overall perform well at this task with very similar results using all datasets, except for when trained on the Spearman selected dataset. The complete performance metrics reported for each test are shown in Table 9 for MQI in [S1 File](#).

## Discussion

This study aimed to investigate anthropomorphic, functional, and socioeconomic factors associated with muscle quality and sarcopenia, using machine learning approaches. We performed several experiments using feature selection and classification to build predictive models for MQI and sarcopenia and find underlying risk factors. The prediction models showed an AUC performance of 0.7649 for sarcopenia and 0.7671 for MQI, using few features. There was little variation between feature selection methods, highlighting the importance of the features we had originally selected to inspect for both conditions. The explored prediction models have shown a slight increase in predictive power when estimating sarcopenia over MQI. Furthermore, we have demonstrated SVMs and MLPs to have higher overall AUC in predicting each condition. Utilizing an aggregation of feature selection techniques, we were able to investigate the variables most associated with sarcopenia and MQI. For sarcopenia we have found *relative power* and *age* to be the most influential features, with *relative power* being the most significant for predicting muscle quality.

We investigated four approaches to feature selection, which largely agree on selected features. Spearman correlation and SVM methods both use a threshold, which is one cause for the discrepancy present in the features selected. There is not a set rule regarding which threshold should be used for either method. Previous studies using the correlation coefficient make use of different thresholds based on the specific field of research [42, 55]. When using SVM for feature selection there are a variety of approaches to selecting a threshold, including a threshold based on the percentage of features [56], dataset complexity, or other empirically proven threshold values [57]. Determining an appropriate threshold is not a simple task, with too high a threshold possibly removing relevant risk factors for disease and too low including those that are unrelated [58]. One study has suggested automatically selecting a threshold based on model performance [55]. Future work investigating MQI and sarcopenia feature selection could automate the threshold selection process and derive a deeper insight into risk factors for each disease.

From a clinical and data science perspective we believed it was crucial to avoid including pre-established diagnostic variables for feature selection and model training tasks. For our experiments we removed the variables that form part of the clinical diagnostic batteries of each disease, such as *handgrip* and *gait speed (m/s)* in the case of sarcopenia. Incorporating these variables in our dataset could cause both feature selection and model training tasks to replicate the existing diagnostic process rather than helping us to discover other potentially relevant characteristics that could be associated with sarcopenia or MQI. One related study compared sarcopenia prediction amongst different ML algorithms and reported accuracies of 91.7% and upward [59]. However, that study included features such as *handgrip* and *gait speed* in the training data. If we re-run our classification test and add these features to our training data, we also can report higher AUC scores, such as 96.49% when training a RF to predict sarcopenia. However, this does not provide us further insight into understanding sarcopenia. By removing these variables, we were able to investigate underlying and potentially unknown risk factors, thus contributing to a deeper understanding of each disease and improved clinical intervention strategies.

By training prediction models on the different datasets, we were able to further evaluate the importance of each feature for both sarcopenia and MQI. Spearman correlation selected the least number of features for both MQI and sarcopenia; one and three features respectively. With MQI there is marked performance increase when including up to the first four most important features. Performance remains the same as more of the selected variables are used in training, indicating that the variables beyond the first four in the list do not provide significant information. However, prediction is best when using the full, unfiltered dataset. With sarcopenia the performance increases up until and including use of the full dataset. This demonstrates the collective importance of each of these features in our relatively low-dimensional data, where we had already reduced from the original 39 features. The optimal prediction performance for sarcopenia and MQI can be ensured by considering the selected features collectively. In other words, sarcopenia and MQI need to be explained by comprehensively considering all selected features.

### Relevant features for sarcopenia

In our study the variables selected using machine learning that influence sarcopenia, as shown in Fig 1, are the following:

- *Relative power* is the largest contributing factor in the identification of sarcopenia. Sarcopenia is initially identified by low muscle strength and confirmed by diminished muscle quantity or quality. The severity is established when low physical performance is also detected [8].

Muscle power is defined as the result of muscle force multiplied by contraction velocity [60]. Furthermore, it stands out as one of the most dependable indicators of muscle function, showing a robust correlation with functional strength performance among older individuals [13, 60, 61]. Age-related decline in muscle power happens at a faster rate compared to the loss of strength and mass [62, 63], likely due to a decrease in the size of type II fibers or atrophy of the remaining fibers, among other contributing factors [62–64]. Given its tendency to decline early on, muscle power emerges as a feature in the evolution of sarcopenia, as its decline can serve as a key marker of the loss of functionality, muscle mass, and strength associated with this condition. Additional studies corroborate muscle power as a predictor in the assessment of sarcopenia [65, 66].

- *Age* is an influential feature. Sarcopenia, traditionally exclusively associated with the aging process, is now recognized as a multifactorial phenomenon that may manifest in earlier stages of life [8]. However, it remains closely related to aging and its effects, which involve a decline in muscular, neuronal and cognitive function [8, 67]. Beyond the age of 50, a gradual loss of muscle mass (1–2% annually) and strength (1.5–5% annually) is evident [68]. Hand-grip strength and walking speed, two dependent variables in the sarcopenia model, also decline with age in both sexes [8, 67], emphasizing the importance of age as a determining factor [13].
- The *5STS* test is also regarded as a feature describing sarcopenia, as the time to complete the test provides insight into strength and locomotor capacity and can be used as a proxy for the strength of leg muscles [8, 69]. As noted above, muscle strength is prioritized as the main parameter for assessing probable sarcopenia within the diagnostic framework, underlining its pivotal role [8, 70].
- *Height, weight* and *BMI* are features relevant to sarcopenia. BMI is calculated by dividing a person's weight in kilograms by the square of their height in meters [71]. It is well recognized that individuals with sarcopenia frequently have lower BMIs, both worldwide [72] and within Spanish populations [73, 74]. In addition, BMI is highlighted in other studies as an important feature in several prediction models [75, 76]. This relationship can be explained by the fact that an increase in BMI, usually accompanied by an increase in both muscle mass and body fat in adults, is associated with lower mortality and a reduced risk of cardiovascular diseases [72, 74]. Furthermore, it may be advantageous to be slightly overweight [77]; while excess body fat has been associated with increased all-cause and disease mortality, people with low, lean body mass have higher mortality rates [72, 74]. As BMI only considers total body mass and not body composition, it may not be a suitable indicator for older people as it does not distinguish between fat and muscle mass [72, 78].
- *Fat mass* is also regarded as a feature describing sarcopenia. In older populations, it may be advantageous to be slightly overweight [77]. However, obesity and excess fat mass exacerbate the risk of sarcopenia, as fat infiltration into the muscle reduces physical function [72, 74]. Additionally, this fat mass is associated with metabolic issues that can affect sarcopenia, and it has differing effects depending on gender. In women, very low percentages of body fat can detrimentally affect muscle status since adipose tissue is an essential endocrine organ that regulates hormonal levels [72, 79]. Excess fat mass also contributes to health conditions, but these impact both genders and entail heightened risks of sarcopenia [72, 80].
- Another influential factor is *sex*, with studies revealing sex-specific etiopathogenic patterns in age-related sarcopenia [61, 81]. Although the diagnostic tools are the same, the cut off points vary between genders [8]. Epidemiological data on the prevalence of sarcopenia

among elderly men and women are also contradictory, although many highlight a higher prevalence in men [82, 83]. These differences in risk factors between sexes emphasize the importance of considering sex as a predictive factor when assessing and predicting sarcopenia in older adults.

- *Balance* is another factor influencing sarcopenia. The severity of sarcopenia is determined by physical performance, a multidimensional concept that encompasses not only muscular aspects but also the central and peripheral nervous systems, including balance [8]. Muscle weakness, sarcopenia, and frailty are correlated with an incapacity to maintain balance and results from different studies indicate inferior balance capabilities among those with sarcopenia [84, 85]. Additionally, maintaining balance is crucial to prevent falls, and from a pathophysiological perspective, sarcopenia and decreased balance could increase the risk of falls, thereby worsening the initial pathological condition [85, 86].
- To confirm sarcopenia once the loss of strength has been identified, the loss of *muscle mass* becomes a relevant factor [8]. This progressive age-related process results in substantial declines in both the functional and quantitative aspects of muscle, leading to significant muscle loss [87], and lower muscle mass ratios are linked with sarcopenia [72, 88]. This underscores the importance of preserving muscle mass and strength, given the elevated mortality risk associated with muscle disorders [72, 88]. In addition, there are gender differences that influence the mechanisms of age-related muscle loss; men tend to experience higher absolute rates of muscle loss than women, possibly due to greater initial mass and varied responses to anabolic and catabolic stimuli [89, 90].
- *Socioeconomic index* is also noted as a feature influencing sarcopenia. It is consistent with the literature, as the prevalence of better health and functional outcomes tends to be found in individuals with higher income and education [91, 92].

### Relevant features for MQI

In our study the variables selected using machine learning that influence MQI, as shown in Fig 2, are the following:

- The results highlight the importance of *relative power* in the assessment of MQI. Muscle quality index is defined as the muscular force per unit of muscle mass [35], thus highlighting the functional relevance of muscle architecture and the characteristics of musculoskeletal tissue [93]. The production of maximum force, a key indicator in muscular function, is influenced by morphological factors, muscular architectural features and neural factors [35]. Relative power is an important component of MQI, since it captures the functional importance of the muscular architecture, determining force production capacity and physical function [94]. Several studies find that muscle quality influences muscle power [95, 96] and that reduction in muscle quality is associated with a decrease in strength and power in aged individuals [97]. The loss of muscle power might suggest a decline in muscle quality, as it reflects the organization of neuromuscular factors and the muscle's ability to produce force, which cannot be fully explained by the reduction in muscle mass alone [35].
- *Fat mass, weight and BMI* have also been shown to be important features describing MQI. Obesity characterized by an excessive accumulation of body fat mass increases the infiltration of fat into muscle, lowering physical function and an unfavorable burden on muscle quality [8, 98]. Research has found negative associations between fat mass and obesity with MQI [98, 99]. Other studies have also observed these associations in individuals with

pathologies, as higher body fat is linked to MQI deterioration [100]. The same applies to BMI, as elevated BMI has been associated with increased fat infiltration into skeletal muscle. This occurs when BMI is high due to elevated fat mass and decreased muscle mass [100, 101]. However, BMI is not able to distinguish between fat and muscle mass [100, 101]. Additionally, as people age, instead of the loss of muscle mass and strength resulting in weight loss, muscle is often replaced by visceral fat, leading to a preservation of weight but increased muscle weakness [102].

- Another influential feature is the *5STS test*, a commonly employed functional test to assess lower body strength, power, and functional capacity [103, 104]. Although MQI is considered a more comprehensive measure of muscle quality than muscle strength alone, this indirect measure of muscle quality is based on a ratio between overall strength and muscle mass, which may explain why it influences the assessment. Therefore, the 5STS provides valuable information about the lower limb that complements the evaluation of MQI [104, 105]. Additionally, several studies have correlated higher MQ with increased strength, function, and physical performance [94, 106].
- *Gait speed*, also regarded as a feature describing MQI, is seen as a crucial indicator of health and functional condition in elderly individuals [107]. Various walking speed tests are available, with one common option being the 4m gait speed test [108]. Gait speed, indicating physical function and mobility, may be influenced by muscle quality. Good MQ suggests stronger muscles relative to mass, potentially leading to an improvement in walking speed and overall physical performance. This is supported by various studies, which demonstrate that muscle quality significantly impacts walking speed [109, 110]. However, it is worth noting that not all findings align in the same direction, as some articles have found no significant relationship between gait velocity and muscle quality [111].
- *Age* emerges as an influential feature in MQI. The aging process induces neural and morphological alterations in the human musculoskeletal system, leading to a decline in muscular parameters [112]. This reduction in muscular parameters subsequently contributes to the loss of MQI. Various factors contribute to this loss, including compositional changes such as fat infiltration or fibrosis, diminished aerobic capacity, and alterations in metabolism and neural activation [95, 113].
- *Balance* also emerges as an important feature in MQI. However, the literature presents controversy regarding the associations between balance and MQI, tending to link them with dynamic balance and fear of falling rather than static balance [114, 115].

## Conclusion

This research aimed to explore the determinant factors influencing muscle quality and sarcopenia in the older adult population of Bilbao through a machine learning approach. The study encompassed a thorough analysis of participant characteristics, feature selection processes, and classification results to unveil the intricate relationships between various anthropometric, functional, and socioeconomic factors with muscle quality index (MQI) and sarcopenia.

The predictive models used in this study exhibited accuracy rates of 72.78% for MQI and 74.14% for sarcopenia using limited features, with the most successful algorithms being SVM and MLP. This underscores the importance of the features that were used to train the models as well as the effectiveness of machine learning approaches in understanding complex health conditions.

The exploration of feature selection methodologies revealed the collective importance of selected features in predicting both sarcopenia and MQI accurately. Notably, this investigation highlights the pivotal role of features such as *relative power*, *age*, *weight*, and the *5STS test* in predicting both conditions. However, no single factor is sufficient to predict either condition, and by using more features we are able to achieve better predictive results. By comprehensively considering all selected features, the study underscores the importance of a holistic approach in understanding and addressing sarcopenia and MQI among older adults.

The study has several limitations; firstly, the number of patients in the database is small, which limits the ability to obtain results. In addition, the profile of the users is not as diverse as the general world population, as most of the patients are Basque, with similar demographic, racial and body characteristics. This homogeneity in the sample reduces the generalisability of the model, as it does not adequately reflect the variability of a more diverse population, which could lead to biases in the results and limitations in the applicability of the conclusions to a global context.

This research contributes to advancing our understanding of the determinants of muscle quality and sarcopenia, offering valuable insights for developing targeted intervention strategies and improving clinical outcomes in older adult populations. Moving forward, further research endeavors could focus on refining feature selection methodologies, exploring additional factors influencing muscle quality and sarcopenia, and devising tailored interventions to mitigate the burden of these conditions on public health.

## Supporting information

### S1 File.

(DOCX)

### S2 File. Data.

(XLSX)

**S3 File. Code repository.** The repository can be found at [https://github.com/dmdequin/sarcopenia\\_and\\_machine\\_learning](https://github.com/dmdequin/sarcopenia_and_machine_learning).

(DOCX)

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### **5.3 Case Study III: Article IV: Functional muscle quality and its determinants in older adults: analysis of key factors and their influences.**

This study builds upon previous research on muscle quality in older adults within the framework of this thesis. In Article III, we developed a predictive algorithm and identified the most relevant features associated with muscle quality and sarcopenia. However, we did not assess the direction and magnitude of these key features of muscle quality, which would be essential to improve their translation into practice in clinical and community settings.

Building on previous findings, this study takes a further step in advancing the understanding of muscle quality in older adults. While our previous work identified the most relevant features through feature selection, this study aims to determine the magnitude of their effect. Specifically, it seeks to answer key questions such as: To what extent do these factors influence muscle quality? And how can the age-related decline in muscle quality be more effectively assessed and managed in both clinical and community settings, given its longstanding underdiagnosis and undertreatment?. By estimating the effect size and direction through regression analysis, we aim to pinpoint the key variables that should be prioritized. This understanding will help lay the groundwork for more targeted and effective interventions.

To this end, this study analyzes the direction and magnitude of key variables associated with muscle quality in older adults using regression models. By quantifying their impact, we aim to clarify how these variables influence muscle quality and their relationship with functional capacity and overall health. Gaining a deeper understanding of these associations will enhance the implementation of muscle quality assessments in both clinical and community settings, ultimately facilitating the development of more personalized and effective interventions for older populations.

To achieve this, the final sample for analysis consisted of 1,222 participants, with 1,091 females and 131 males. Significant differences between males and females were found in several key measures, including the MQI and the prevalence of geriatric conditions such as sarcopenia and frailty. Given these differences, separate analyses were conducted for each gender. The regression model for females included age, BMI, muscle mass, fat mass, 4-meter walking speed, chair squat time, balance test, and socioeconomic background (divided into two groups), with an  $R^2 = 0.3321$ . For males, the model included age, BMI, chair squat time, and balance, resulting in an  $R^2 = 0.2427$ . This difference is likely due to the smaller sample size of males and their generally better health status, which led to less variability in performance measures.

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In this study, we will emphasize indirect non-invasive methods for evaluating muscle quality, with a focus on the functional domain, which reflects the muscle's performance relative to its mass (de Lucena Alves et al., 2023). This perspective considers the role of muscle architecture, the force generating capacity and general tissue properties (Naimo et al., 2021). Although there are multiple ways to assess the functional domain of muscle quality (de Lucena Alves et al., 2023), one widely accepted approach is the Muscle Quality Index (MQI) (M. Fragala et al., 2015). Developed by Barbat-Artigas et al., the MQI is determined by calculating the ratio of hand grip strength to relative skeletal muscle mass (Barbat-Artigas et al., 2012). Many studies have consistently used this method to accurately evaluate the quality of muscles (Baek et al., 2022; Chiles Shaffer et al., 2017; Emerson et al., 2014; Nunes et al., 2019; Yoda et al., 2012; You et al., 2023). Furthermore, as previously mentioned, the reviews and the case study conducted allow us to highlight the correlation between morphological variables of muscle quality assessed by ultrasound and functional variables, which are crucial for evaluating functional muscle quality. This supports the use of indirect non-invasive methods for assessing muscle quality, making it accessible for evaluating muscle quality in our sample.

While it is well established that muscle quality is affected by multiple factors, including genetics, comorbidities, and nutrition (Davis et al., 2021; Dubé & Laveneziana, 2018; Xia et al., 2024), this study concentrates on examining the influence of functional factors. We aim to clarify the direction and magnitude of their effects, as these aspects are not yet well defined. Gaining insight into these relationships is crucial for designing targeted interventions and preventive strategies to preserve and enhance muscle quality in older adults.

A comprehensive description of the methodology employed in this study is provided in the previous chapter.

Table 12 provides an overview of the participants' demographic information. The overall sample consisted of 1222 individuals, with a breakdown of 1091 women and 131 men. Gender-based differences were identified across multiple assessments, including key MQI-related variables and the occurrence of conditions like sarcopenia and frailty (Table 12 and Table 13). In light of these disparities, distinct analyses were carried out for men and women.

*Table 12. Average values of the measured variables by gender.*

	Women (SD)	Men (SD)
n	1,091	131
Hand Right	19.3 (4.55)	32.1 (6.3)
MQI	1.2 (0.29)	1.8 (0.37)
MQI_max	1.2 (0.28)	1.8 (0.36)
Age	78.0 (5.88)	78.9 (5.18)
Height	1.5 (0.06)	1.6 (0.06)
Weight	66.2 (10.09)	76.0 (10.33)
Fat Mass	38.7 (5.4)	31.3 (6.17)
Muscle	38.1 (4.01)	49.6 (6.02)
BMI	28.5 (4.12)	28.2 (3.32)
4m	4.4 (1.26)	4.1 (1.17)
Sit to Stand test	14.8 (4.41)	14.0 (3.52)
Relative Power	1.7 (0.5)	2.2 (0.61)
EQ2	9.9 (0.81)	9.9 (0.91)
EQ3	8.6 (3.32)	9.0 (2.69)
SPPB	9.7 (1.69)	10.1 (1.52)

Table 13. Prevalence of health conditions in the study population by gender.

Condition	Women (n = 1091)	Men (n = 131)
<b>Sarcopenia</b>		
Healthy	386 (35.3%)	110 (84.6%)
Moderate	550 (50.4%)	19 (14.6%)
Severe	156 (14.3%)	1 (0.8%)
<b>MQI</b>		
Healthy	110 (10.1%)	91 (70.0%)
Moderate	175 (16.0%)	22 (16.9%)
Severe	807 (73.9%)	17 (13.1%)
<b>Frailty</b>		
Healthy	643 (58.9%)	88 (67.7%)
Moderate	399 (36.5%)	40 (30.8%)
Severe	50 (4.6%)	2 (1.5%)

In the final model, an Ordinary Least Squares (OLS) regression analysis was conducted, incorporating all variables in their linear form to assess their impact on MQI\_max. For females, the regression model included factors such as age, BMI, muscle mass, fat mass, 4m walking speed, chair squat duration, balance performance, and socioeconomic status (split into two categories). This model demonstrated a strong fit, with an  $R^2$  of 0.3321. In contrast, for males, the regression model considered age, BMI, chair squat time, and balance, yielding an  $R^2$  of 0.2427. The lower explanatory power in the male model is likely due to the smaller sample size and the generally better health status of the male participants, leading to reduced variability in performance across these measures.

Table 14. Regression outcomes using MQI\_max as the criterion in the women's model  $R^2 = 0.3321$ .

	Estimate	Std. Error	t value	Pr(> t )
(Intercept)	1.5262	0.1532	9.96	0.0000
Age	-0.0098	0.0013	-7.48	0.0000
BMI	-0.0565	0.0035	-16.24	0.0000
Fat Mass	0.0257	0.0021	12.10	0.0000
Muscle Mass	0.0234	0.0025	9.38	0.0000
4m test speed (m/s)	0.1308	0.0349	3.75	0.0002
Squat test (3 quartiles)	0.0511	0.0102	5.00	0.0000
Balance 3	-0.0416	0.0181	-2.30	0.0218
ID2	-0.0443	0.0147	-3.01	0.0027

Table 15. Regression outcomes using *MQI\_max* as the criterion in the male's model  $R^2 = 0.2427$ .

	Estimate	Std. Error	t value	Pr(> t )
(Intercept)	4.0633	0.5608	7.25	0.0000
Age	-0.0137	0.0056	-2.43	0.0166
BMI	-0.0428	0.0086	-4.96	0.0000
Squat test (3 quartiles)	-0.0171	0.0082	-2.08	0.0396
Points EQ 3	0.1349	0.0557	2.42	0.0170

To assess the linearity assumption, the *gvlma* linearity test was conducted, analyzing the residuals for any consistent patterns. All tests were successfully passed, indicating that the assumption of linearity was valid and no adjustments to the model were necessary. In the case of the male model, all tests were met except for the heteroscedasticity test. To address this, robust standard errors (White's correction) were applied to the models. While the results remained mostly consistent, the Relative Power with threshold variable was found to be marginally non-significant at the 5% significance level ( $p = 0.058905$ ).

Building on the previous analysis, the factors influencing *MQI\_max* in older adults were further explored using Ordinary Least Squares (OLS) regression analysis, adding every variable to a linear model. For the female group, the final regression model incorporated variables such as age, BMI, muscle mass, fat mass, 4-meter walking speed, chair squat duration, balance test performance, and socioeconomic status (grouped into two categories), showing a strong fit ( $R^2 = 0.3321$ ). On the other hand, for males, the model included only age, BMI, chair squat duration, and balance, yielding a lower explanatory value ( $R^2 = 0.2427$ ). This difference can likely be attributed to the smaller number of male participants and their generally better health, which led to less variation in their performance data. Nonetheless, these results underscore the importance of both physical capabilities and body composition factors in understanding muscle quality, particularly in females, where a wider range of variables played a role in explaining the outcomes.

The sample of women was significantly larger and displayed more health challenges compared to their male counterparts. On the other hand, the male participants not only had better overall health but were also fewer in number, which might explain the reduced number of significant predictors identified in their model. For example, almost all men scored well on EQ2 and EQ3, with just two participants performing poorly on EQ2. Likewise, only a small number of men showed suboptimal results in the physical assessments. This uniformity in the male group, both in terms of health and sample size, may have constrained the detection of meaningful correlations, as the limited variation in health status and the smaller sample size likely hindered the identification of substantial relationships between the variables.

Studies routinely demonstrate that elderly men are much less likely than women to participate in health promotion programs, with participation percentages often matching or slightly higher than those seen in this study (Howell et al., 2023; Ory et al., 2014; Smith et al., 2014; Smith & Ory, 2014). This lower engagement can be attributed to a combination of biological, socio-economic, and cultural factors that influence both genders' healthcare access and behaviors (Anderson et al., 2016; European Institute for Gender Equality, 2024; Howell et al., 2023). Men are culturally less inclined to seek assistance, often perceiving it as a sign of weakness. Contributing factors include societal expectations, environments within programs perceived as female-oriented, and the overwhelming presence of female participants and facilitators (Anderson et al., 2016; Howell et al., 2023). Consequently, the limited involvement of men in these programs represents a significant societal issue, reducing their chances to enhance their health. Potential solutions may involve endorsements from male community figures,

advertisements targeting men, and modifying program structures to better resonate with them (Anderson et al., 2016; Howell et al., 2023). The relatively small and homogeneous male sample in this study hampers the detection of meaningful associations. A majority of male participants had no difficulty in health assessments, suggesting they were healthier than the general elderly male population (Abizanda Soler et al., 2011; Cabrero-García et al., 2012; Ríó et al., 2021). This could imply that men attending health promotion programs are healthier than the broader male elderly demographic, exhibiting a more robust profile.

As mentioned earlier, men typically perform better in functional assessments, reflected in the lower occurrence of conditions such as frailty and sarcopenia. In this study, more than 84% of men were classified as healthy concerning sarcopenia, with 67% showing no signs of frailty, and fewer than 2% experiencing severe cases of either condition. While frailty and sarcopenia are often linked to aging and have similarities, they are two different conditions: frailty is a multifactorial condition that involves deficits across numerous physiological systems, while sarcopenia mainly impacts the musculoskeletal system (Davies et al., 2018; Reijnierse et al., 2016). It has been shown in a number of research studies that older persons with frailty had a higher prevalence of sarcopenia than frailty (Davies et al., 2018; Mijnarends et al., 2015; Nishiguchi et al., 2015), and our population reflects this pattern. This is consistent with previous research showing that among older persons living in the community, sarcopenia is more common (1-29%) than frailty (12%) (Cruz-Jentoft et al., 2014; Falaschi, 2021; O’Caoimh et al., 2018)(55–57). Women, on the other hand, have worse health indicators, with a significantly higher incidence of frailty and sarcopenia. Specifically, 50.4% of women were categorized with moderate sarcopenia, 14% with severe sarcopenia, 36.5% with moderate frailty, and 4.6% with severe frailty.

Moreover, the findings suggest that the deterioration of muscle quality is notably more widespread than the geriatric conditions mentioned, affecting both men and women. This is likely due to the fact that the decline in muscle quality associated with aging occurs before significant muscle mass loss, making it a more sensitive marker of muscle function (Barbat-Artigas et al., 2012; de Lucena Alves et al., 2023; Straight et al., 2015b). As people age, muscle strength and power deteriorate swiftly, however power deteriorates the most, exacerbating the loss of muscle quality. Research indicates that the main driver of muscle weakness in older adults is the decline in muscle quality, rather than a reduction in muscle mass (Riviati & Indra, 2023). Therefore, variations in muscle quality could provide a more accurate explanation for the decline in muscle strength and function associated with aging. Our results align with this trend, as the loss of MQI in both women and men surpasses the prevalence of the geriatric conditions described earlier (Table 2). Moreover, existing evidence suggests that the rate of decline in muscle quality is greater than that of sarcopenia, which is consistent with our findings (Straight et al., 2015b) This highlights the importance of evaluating and tracking muscle quality, as it reflects physiological changes that occur before the development of aging-related diseases. It emphasizes the need to identify critical factors and assess their effects in order to create effective preventive interventions.

The effect of age on MQI is particularly noteworthy. In the regression analysis, a significant negative correlation between age and MQI was observed. The impact of age was moderately reduced in women ( $-0.010$ ) compared to men ( $-0.014$ ), meaning that for each additional year, MQI decreases by 0.010 units for women and 0.014 units for men, with other variables held constant. These results are in keeping with earlier research indicating that the gradual deterioration of metabolic, neurological, and muscular processes leads to a decrease in MQI with age (Abe et al., 2016; Delmonico et al., 2008; Goodpaster et al., 2006; Hairi et al., 2010; Newman et al., 2003; Straight et al., 2015b). Furthermore, gender-based differences in this process have been documented, with men experiencing a more pronounced and faster loss of muscle mass compared to women (de Jong et al., 2023; Tay et al., 2015; Zamboni et al., 2003). Although men generally possess higher muscle mass initially, they lose muscle at a faster rate and suffer almost double the strength loss in comparison to women (Cruz-Jentoft et al., 2019; Gheller

et al., 2016; Goodpaster et al., 2006; Tay et al., 2015). Additionally, studies have found that the quality of arm muscles decreases more sharply in men than in women (Lynch et al., 1999). However, women tend to maintain muscle quality better as they age, especially when it comes to eccentric peak torque (Lindle et al., 1997).

The performance on balance tests influences the Muscle Quality Index (MQI), as a positive correlation is observed between balance and MQI. This is most evident when comparing the 892 women who get the best score possible in the three balance tests to the 215 women who failed to do so. Those who attained the highest points demonstrated an MQI value approximately 0.0422 units higher than those who did not, with other variables controlled. In men, the relationship follows a similar trend, but the effect is more pronounced in the highest score group. For men, each point increase in the balance score, while keeping other factors constant, results in an increase of 0.1349 units in MQI. This observation supports earlier studies, which highlight the role of muscle quality in supporting balance (Balogun et al., 2018; Gadelha, Neri, Nóbrega, et al., 2018), improving the complexity of postural control, which is indicative of better balance and lower risks of falls and fear of falling (Gadelha, Neri, Bottaro, et al., 2018; Gadelha, Neri, Nóbrega, et al., 2018; Michel et al., 2024; Nogueira Paranhos Amorim et al., 2021). The connection between muscle quality and balance can be partly explained through neuromuscular processes. A decline in muscle quality, indicated by a decrease in strength relative to muscle mass, is associated with the loss of motor neurons, remodeling of motor units, and decreased cortical excitability and nerve conduction velocity, all of which are vital for maintaining postural control (M. Fragala et al., 2015; Walsh et al., 2022). Effective postural control depends on precise neuromuscular outputs, meaning that deteriorating muscle quality can disrupt balance and elevate fall risks. On the other hand, preserving muscle quality may support the integrity of motor neurons and neuromuscular function, thus helping to maintain balance in older individuals (Gadelha, Neri, Nóbrega, et al., 2018; Walsh et al., 2022).

The findings suggest that measuring walking speed, specifically through the 4-metre walking test, results in a more consistent and meaningful relationship with MQI than using the total time taken to cover the same distance. In particular, each increase of 1 metre per second in gait speed is associated with a rise of 0.1320 units in MQI. This is consistent with other research highlighting muscle quality as an important factor influencing gait speed, which is a crucial indicator of both functionality and mobility in people with varying health statuses (Hirano et al., 2022; Lin et al., 2021; Volpato et al., 2012; Yoshiko et al., 2019). Nonetheless, it is essential to recognize that not all studies confirm this link. Some have found no substantial connection between muscle quality and gait velocity (Martinikorena et al., 2016; Millor et al., 2020), maybe as a result of self-selected gait velocity, which is more impacted by personal habits and coping mechanisms than by inherent muscle strength (Martinikorena et al., 2016). Additionally, it's important to consider that different approaches to measuring muscle quality yield different correlations with gait performance. For instance, morphological assessments, which examine muscle structure and composition, tend to give a clearer picture of muscle health and show stronger correlations with gait speed, possibly because they directly reflect the muscles engaged in walking. On the other hand, strength-to-mass ratios offer a broader measure of neuromuscular health but may not align as closely with walking performance (Rech et al., 2014). Moreover, the specific location of muscle quality measurement plays a critical role, with studies focusing on the rectus femoris, an essential muscle for walking mechanics, tending to show stronger links with walking ability (Guadagnin et al., 2019; Martinikorena et al., 2016).

There is a significant relationship between MQI and the variable ID2, which is divided into two categories. When all other factors are held constant, women in the lower socioeconomic group (ID2 level 2) have an estimated MQI value that is 0.0425 units lower than those in the more prosperous socioeconomic group (ID2 level 1). This outcome aligns with previous research, which indicates that higher income and education levels are linked to better health and functional outcomes (Malkowski et al., 2023; Noppert et al., 2018; Shankar et al., 2010; Stringhini et al., 2018; Wang & Wei, 2024). Additionally, individuals facing socioeconomic disadvantage are often at a higher risk for chronic diseases and experience a quicker decline in physical function (Shankar et al., 2010; Stringhini et al., 2018).

The muscle variable has a significant impact for women but not for men. MQI is predicted to rise by 0.0236 units for every kilogram of muscle. There is a complicated interaction between muscle size and muscle quality. Although more muscle mass has historically been linked to stronger muscles and, thus, better muscular quality, scientific research shows varying outcomes. The connection between muscle mass and strength is a well-known physiological principle (Naimo et al., 2021), but research suggests that the ability to generate force depends more on the quality of skeletal muscle than on its volume alone (Fukumoto et al., 2012; Goodpaster et al., 2006). Some studies, in line with our findings, highlight a link between muscle mass and muscle quality (Akazawa et al., 2022; Stotz et al., 2024; Streb et al., 2023). Moreover, other researches emphasize that muscle reduction due to aging can negatively impact strength in older adults (Rech et al., 2014).

Muscle quality is commonly understood as the force or power generated per unit of muscle mass (de Lucena Alves et al., 2023). In some cases, individuals with less muscle mass may exert less force compared to those with greater muscle volume, due to the non-linear relationship between muscle size and strength (Barbat-Artigas et al., 2012). Significant muscular hypertrophy is not always necessary for strength gains to occur (Dankel et al., 2018, 2019), and increases in muscle size can also happen without corresponding increases in force production (Reggiani & Schiaffino, 2020). Indeed, some studies suggest that larger muscle mass might be negatively correlated with muscle quality, emphasizing that muscle mass alone is not a reliable predictor of functional improvements (Barbat-Artigas et al., 2012, 2013). Thus, while muscle mass remains a significant element, the relationship is influenced by various other aspects, such as architecture, composition, metabolism, and neural activation, all of which contribute to the total strength production ability (McGregor et al., 2014; Michel et al., 2024). According to our findings, the correlation between muscle mass and quality appears to show that gains in strength occur along with mass growth in our group, indicating that the hypertrophy is functional rather than merely a mechanically insignificant increase in muscle volume. Otherwise, according to the method used to evaluate muscle quality, muscle quality should decline if the gain in mass is not accompanied by an increase in strength (Barbat-Artigas et al., 2012, 2013).

Given the substantial collinearity across anthropometric variables, BMI was incorporated into the model because it was more appropriate than height and weight. The impact of BMI on MQI is marginally higher for women (about -0.050) than for males (approximately -0.042). With all other factors held constant, MQI is predicted to drop by 0.050 units for every unit increase in BMI. nevertheless is a complicated link between older persons' BMI and muscle quality. A higher BMI is commonly associated with an increase in fat accumulation within muscle tissue, especially when this index rises due to an excessive amount of fat and a reduction in muscle mass (Salmón-Gómez et al., 2023; Volpato et al., 2012). Although individuals with a higher BMI tend to have a smaller chance of experiencing a decline in appendicular lean mass, this condition also correlates with a heightened risk of impaired muscle quality. Therefore, a larger BMI might suggest greater muscle mass, but it does not necessarily result in improved muscle function or quality in older adults (Cooper et al., 2014). In addition, BMI does not distinguish between the types of mass, fat or muscle, and focuses solely on total body weight, making it an inadequate metric for assessing older populations (Liu, Cheng, et al., 2023; Liu, Wong, et al., 2023; Salmón-Gómez et al., 2023; Volpato et al., 2012). The loss of muscle mass and strength that comes with aging does not always

lead to weight reduction. Instead, muscle tissue is frequently replaced by fat, particularly visceral fat, which can keep body weight stable while worsening the decline in muscle function (Y. Chen et al., 2023).

Our results indicate that muscle quality is significantly impacted by fat mass in women but not in males. Given that men have larger levels of visceral fat, which has a more detrimental metabolic effect, and women tend to collect more subcutaneous fat, these disparities in body composition and fat distribution among both sexes may help to explain this (Almeida et al., 2018; Straight et al., 2015b). Subcutaneous fat may act as a beneficial "metabolic sink" for the preservation of extra energy, particularly in the lower body (Lumish et al., 2020). Additionally, there may be an acceptable level of adiposity where fat accumulation starts to impair muscle performance, rather than a strictly linear connection between fat mass and muscle quality (Abidin, 2023; Koster et al., 2011). We might be in a range where fat mass does not have a negative impact or even serves as an energy reserve for maintaining muscular function, since none of the women in our group are morbidly obese or have extremely high levels of adiposity (Abidin, 2023; Straight et al., 2015a). However, extremely elevated fat content may cause muscle quality to deteriorate and favor myosteatosis, or the migration of ectopic fat into the muscle (Streb et al., 2023).

Various strategies were investigated for integrating squat test data, all demonstrating a non-linear correlation with MQI\_max, likely due to saturation effects. To mitigate this, the test results were categorized into three distinct intervals: [0;11.2), [11.2;13.7), and [13.7;  $\infty$ ), in accordance with established frailty thresholds, such as those used in the SPPB. It's interesting to note that these cut-points matched our sample's natural dispersion quite well, confirming their ability to accurately identify notable variations in muscle quality. This alignment made it easier to linearize the model and guaranteed that the SPPB assessment battery's levels accurately represented the functional performance differences in the sample we used (Guralnik et al., 1994). The model's final predictions showed that transitioning to a lower time category was associated with an increase of 0.0511 units in the estimated MQI value. In addition, as the 5STS is a commonly utilized functional evaluation of lower body strength, power, and total functional capacity, power—despite not being explicitly incorporated in the model—is indirectly captured via squat test results. Numerous investigations support our findings, showing a correlation between muscle power and squat tests and muscle quality (Lopez et al., 2017; Millor et al., 2020; Wilhelm et al., 2014; Yuan & Kim, 2023). As people age, their physical strength and power both drastically decrease, with power suffering the most. Since relative power is a crucial component of MQI, indicating the functional importance of muscular architecture and impacting force output and physical function, this makes the loss of muscle quality worse (Jerez-Mayorga et al., 2020; Millor et al., 2020; Riviati & Indra, 2023). For instance, engaging in physical activity or exercise may reduce or even reverse these declines (Izquierdo et al., 2021; Izquierdo & Cadore, 2024; Lizama-Pérez et al., 2023).

Based on distinct models for men and women, this study raises the possibility of sex-specific variations in the factors impacting MQI in older persons. While age, BMI, squat time, and balance were the only factors linked to MQI in males, muscle mass, fat mass, and functional capacity (gait speed, squat time, and balance) were revealed to be important predictors in women. The reduced sample size and males' superior overall health may have contributed to the model's lower predictive value for them by lowering performance measure variability. Care must be taken if these results are to be interpreted together due to the significant variation in sample size between the sexes. The statistical power to identify relationships may have been restricted by the significantly fewer male sample, and the observed patterns may have been influenced by the lower variability in their indicators of performance. Consequently, further study with balanced numbers of participants is required to confirm these disparities and improve the generalizability of the findings, even though the results suggest that the assessment of muscle quality should take gender-specific features into account, particularly given the greater impact of body composition and functional capacity in women.

#### **5.4 Case Study IV: Article V: Gait speed in older adults: exploring the impact of functional, physical and social factors.**

Finally, we conclude this research by examining the factors that influence walking speed in older adults, a key marker of functionality. To do so, we build on the knowledge gained from previous studies on muscle quality and physical functioning, focusing on a key indicator of health and autonomy in this population.

Throughout the thesis, we have highlighted that sarcopenia and muscle quality are two critical aspects that need to be monitored during ageing. We have identified the determinants, their impact on muscle quality and sarcopenia, and the key characteristics that need to be addressed to prevent physical disability and maintain optimal health in old age. As EWGSOP points out, it is not only essential to detect and treat loss of muscle mass, strength and quality, but also to assess and preserve muscle function (Cruz-Jentoft et al., 2019).

The muscles of the lower limbs are the first to be affected by age-related changes, making gait speed a particularly relevant marker of function in this region (Cruz-Jentoft et al., 2019; Zhai et al., 2023). Moreover, as has been pointed out throughout the thesis, muscle quality deteriorates before strength and muscle mass, which makes it a more sensitive marker of age-related changes and an early sign of functional decline in the context of sarcopenia and other musculoskeletal disorders. Therefore, its assessment, together with the analysis of gait speed, allows a more accurate approximation of the state of health and functionality of the musculoskeletal system in older adults.

If we combine this information and, in addition to monitoring muscle quality, monitor gait speed as a reflection of regional changes that first affect the lower limbs, we could establish markers that allow us to anticipate and address musculoskeletal complications before they manifest clinically, facilitating more effective preventive and therapeutic strategies. Therefore, this latest study aims to assess the determinants that influence gait speed in older adults.

A total of 1,253 older adults (89.5% female) with a mean age of  $78.1 \pm 5.8$  years voluntarily participated in this descriptive cross-sectional study, which examines functional capacity test scores and socioeconomic data in older adults. The final regression model showed that gait speed was partially significantly explained ( $R^2=0.35$ ;  $p<0.01$ ) by socioeconomic background, age, balance and relative power. At the same time, belonging to a higher socioeconomic background was associated with lower relative power ( $p<0.01$ ;  $\eta^2=0.07$ ). These results provide information on clinical markers that influence the design of effective personalised interventions that promote healthy ageing.

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## Gait speed in older adults: exploring the impact of functional, physical and social factors Velocidad de la marcha en adultos mayores: explorando el impacto de factores funcionales, físicos y sociales

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**Abstract.** Purpose: With age there is a neuromuscular and cognitive decline that impacts on functional ability. One of the most characteristic and easily recognisable signs of this decline is a decrease in usual gait speed. For older adults, gait speed is a non-invasive indicator of health and functional status and is regarded as a vital sign. As it predicts various conditions later in life, measuring usual walking speed is crucial in the clinical setting. Therefore, analysing and determining the association between walking speed and the impact of functional and socio-economic variables may facilitate the prevention of associated health problems and the maintenance of physical function in older adults. This study aims to identify the key factors that influence walking speed in older adults, as well as to examine the influence of socio-economic status on walking speed. Methods: A total of 1253 older adults (89.5% women) with a mean age of  $78.1 \pm 5.8$  voluntarily participated in this descriptive cross-sectional study, which examines the results of functional capacity tests and socioeconomic data in older adults. To assess physical function, SPPB tests (chair stand test, balance tests, gait speed test), manual grip strength, muscle quality index, and power were conducted, in addition to measuring body composition and socioeconomic status. Results: The final regression model showed that gait speed was significantly partially explained ( $R^2=0.35$ ;  $p<0.01$ ) by the socioeconomic environment, age, balance, and relative power. At the same time, belonging to a higher socio-economic environment is linked to lower relative power ( $p<0.01$ ;  $\eta^2=0.07$ ). Conclusions: Exploring the factors that affect walking speed in older adults, this study highlights that age, relative power and balance are significant determinants. These clinical markers provide crucial information for designing personalized and effective interventions to promote healthy aging.

**Keywords:** Frailty, gait speed, elderly, relative power, socioeconomic status.

**Resumen.** Objetivo: Con la edad, se produce un deterioro neuromuscular y cognitivo que afecta la capacidad funcional. Uno de los signos más característicos y fácilmente reconocibles de este deterioro es la disminución de la velocidad de marcha habitual. En los adultos mayores, la velocidad de la marcha es un indicador no invasivo del estado de salud y funcional, y se considera un signo vital. Dado que predice diversas condiciones en etapas posteriores de la vida, medir la velocidad de marcha habitual es crucial en el ámbito clínico. Por lo tanto, analizar y determinar la asociación entre la velocidad de la marcha y el impacto de las variables funcionales y socioeconómicas puede facilitar la prevención de problemas de salud asociados y el mantenimiento de la función física en los adultos mayores. Este estudio tiene como objetivo identificar los factores clave que influyen en la velocidad de marcha en adultos mayores, así como examinar la influencia del estado socioeconómico sobre la velocidad de marcha. Métodos: Un total de 1,253 adultos mayores (89.5% mujeres) con una edad media de  $78.1 \pm 5.8$  años participaron voluntariamente en este estudio transversal descriptivo, que examina los resultados de pruebas de capacidad funcional y datos socioeconómicos en adultos mayores. Para evaluar la función física, se realizaron pruebas SPPB (prueba de levantarse de la silla, pruebas de equilibrio, prueba de velocidad de la marcha), fuerza manual, índice de calidad muscular y potencia, además de medir la composición corporal y el estado socioeconómico. Resultados: El modelo de regresión final mostró que la velocidad de la marcha fue explicada significativamente de forma parcial ( $R^2=0.35$ ;  $p<0.01$ ) por el entorno socioeconómico, la edad, el equilibrio y la potencia relativa. Al mismo tiempo, pertenecer a un entorno socioeconómico más alto se asocia con una menor potencia relativa ( $p<0.01$ ;  $\eta^2=0.07$ ). Conclusiones: Este estudio destaca que la edad, la potencia relativa y el equilibrio son determinantes significativos de la velocidad de la marcha en los adultos mayores. Estos marcadores clínicos proporcionan información crucial para diseñar intervenciones personalizadas y efectivas que promuevan un envejecimiento saludable.

**Palabras clave:** Fragilidad, velocidad de la marcha, adulto mayor, potencia relativa, estatus socioeconómico.

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### Introduction

The hallmark of aging is the gradual loss of physiological and physical abilities, which results in diminished function and increased mortality risk (López-Otín et al., 2023). Aging, even in healthy individuals, is associated with a progressive decline in muscular, neuronal, and cognitive function leading to deficits in functionality (Hortobágyi et al., 2015). Functional disability is a growing global problem that becomes more pronounced as we age (Hu et al., 2022; Navarrete-Villanueva et al., 2021). While the average trend shows declining health and function with age, individual experiences vary greatly (Rothermund et al., 2023). One of the most characteristic and easily recognizable signs of this decline is a decrease in usual walking speed (Abellan Van

Kan et al., 2009; Andrews et al., 2023; Bohannon & Williams Andrews, 2011). This slowing of usual walking pace stands out as a significant indicator, potentially declining up to 16% per decade beginning at the age of 60 years (Hortobágyi et al., 2015).

Gait speed is considered a vital sign which serves as a non-invasive predictor of health and functional status in older adults (Middleton et al., 2015). Walking speed tests have become widely used in clinical and research contexts because of their sensitivity, validity, and reliability (Middleton et al., 2015). There are several walking speed tests with different distance ranges, one of the commonly employed tests for measuring gait speed is the 4m gait speed test (Hirabayashi et al., 2020; Lin et al., 2021). It has been demonstrated that the 4m gait speed is an important component of

physical function related to sarcopenia and functional independence, serving as a significant predictor of frailty in older adults (Middleton et al., 2015; Navarrete-Villanueva et al., 2021).

Predicting various conditions later in life, measuring usual walking speed is crucial. A walking speed that exceeds 1 m/s is typically considered normal among the elderly population without disabilities (Hainline et al., s. f.). Speeds below 0.6 m/s are predictive of adverse events, while a threshold below 0.8 to 1 m/s is commonly recognised as a reliable indicator of frailty (Castell et al., 2013; Cawthon et al., 2021). However, the walking speed generally used and associated with adverse health outcomes is less than 0.8 m/s (Abellan Van Kan et al., 2009; Studenski et al., 2011). Having a gait speed lower than 0.8m/s represents a risk factor for functional dependence, frailty, cognitive decline, falls, hospitalization, cardiovascular events, and all-cause mortality (Abellan Van Kan et al., 2009; M<sup>a</sup> Lourdes et al., 2024; Middleton et al., 2015; Studenski et al., 2011). Furthermore, it is essential to recognize that these implications extend beyond individual health; slow walking also increases the financial cost of care, due to the greater need for long-term nursing home assistance (Lyons et al., 2016). While additionally contributing to the overall burden of morbidity, specific diseases, and geriatric deficits (Piotrowicz et al., 2023).

Consequently, there is a significant interest in identifying elements that influence reduced walking speed, aiming to enhance primary prevention and maintain functionality (Lara et al., 2024). Several factors that can affect gait speed can be categorized into four aspects: socio-cultural, gender and age, medical and psychological factors (Franz, 2016; Manjavong et al., 2023). Socio-cultural factors, such as economic status, industrialization level, population size, climate, cultural values, education, and feelings of loneliness, can influence gait speed, with more industrialized countries often exhibiting faster walking speeds (De Bartolo & Iosa, 2018). Furthermore, health and socioeconomic position take the form of a gradient, where more advantaged individuals show better health indicators and a higher walking speed (Malkowski et al., 2023; Radford, 2021). Second, there are gender differences, with men exhibiting swifter gait, while walking speed generally diminishes with age (Aboutorabi et al., 2016; Bohannon & Williams Andrews, 2011; Córdova-León et al., 2024; Frutos et al., 2022; Sialino et al., 2021). Additionally, individuals with elevated disease burdens, higher body mass indices (BMI), and increased levels of pain are more prone to experience slower gait speeds (Duan-Porter et al., 2019; Sialino et al., 2021). Beyond clinical aspects, psychological factors, like purpose in life or depression, might play a role in determining walking speed and its alterations over time (Sialino et al., 2021; Sutin et al., 2024).

Given the nature of walking speed as a clinical outcome influenced by numerous factors, understanding how each determinant impacts walking speed in older adults can aid

in developing effective intervention programs. Despite previous research highlighting the roles of socioeconomic status, personal characteristics and functional factors, physical activity, and health conditions, the specific contributions of these factors to different walking speed profiles in a cohort of healthy older Spanish adults remain unclear. Our objective is to identify key factors that effectively differentiate between different walking speed profiles. Additionally, we seek to evaluate the influence of socioeconomic status on walking speed to provide comprehensive insights into the determinants of mobility among older adults.

However, the proportion in which each factor contributes to gait speed performance is not well established. Thus, this study aims to investigate the impact, separate and combined, of functional and strength variables, anthropometric and socioeconomic factors on gait speed of older adults using a multivariable regression models to determine which factors most significantly explain variations in walking speed. We hypothesize that functional and strength variables will have a more significant impact on gait speed compared to socioeconomic factors, and that socioeconomic status will also play a notable role in gait speed variations. To achieve this, we will use multivariable regression models to identify which factors most significantly explain variations in walking speed. This analysis will involve validating the model through k-fold cross-validation and evaluating performance with metrics such as root mean square error (RMSE) and R<sup>2</sup>. Additionally, we will assess the influence of socioeconomic status on gait speed using one-way ANOVA, with significance set at  $p < 0.05$ . This approach will help identify key determinants and inform targeted intervention strategies for improving mobility in older adults.

## Methods

### *Participants and Procedure*

This descriptive cross-sectional study investigates dynamometric, anthropometric, and Short Physical Performance Battery (SPPB) test outcomes, including balance, gait speed test and chair stand test alongside socioeconomic index data. A group of 1253 participants (89.5% women), with more than 60 years old with a mean age of  $78.1 \pm 5.8$  voluntarily participated in this descriptive cross-sectional study. Participants were selected through non-probabilistic convenience sampling from the "Health for the Elderly" program sponsored by the Bilbao City Council. Inclusion criteria for participants encompassed being aged 60 or older, currently enrolled in the "Health for the Elderly" program, and voluntarily participating, with the inability to walk independently serving as the exclusion criteria.

The subjects were examined by evaluators who went to the centres at the times specified by the programme. As this was a study with a large number of participants, auxiliary personnel were required for data collection. To avoid bias and ensure the quality of the data, personnel from the Higher Level Training Cycle in Teaching and Socio-sports

Animation received specialized training from physical exercise professionals. This training covered the tests to be conducted as well as subsequent data collection procedures.

### **Measures and Material**

#### *Functional assessment: SPPB and Manual Grip Strength*

The Short Physical Performance Battery (SPPB) is a widely utilized clinical functional assessment test known for its high reliability and validity (Santamaría-Peláez et al., 2023). The SPPB comprises three parts: balance assessment (in the standing, semi-tandem, and tandem positions), a 4-meter gait assessment (time taken to walk 4 meters at normal pace), and the five-repetition chair stand test (5STS) performed as quickly as possible (Guralnik et al., 1994). Scores range from zero to four for each component, with zero indicating the lowest score. Additionally, a composite score, ranging from zero to 12 points, is derived by summing the scores from the three components (Guralnik et al., 1994).

This test provides knowledge of the relationship between balance, strength and power of the lower body and is of vital importance to identify individuals at risk in old age, since deficits in these neuromuscular components are associated with an increased risk of injury and falls (Baltasar-Fernandez, Alcazar, Mañas, et al., 2021), closely related to gait speed (Kirk et al., 2023). Due to this, the following balance test results are collected. In the first position, the individual must stand with their feet together, side by side, for 10 seconds. The second position involves standing in a semi-tandem stance, with the side of the heel of one foot touching the big toe of the other foot for 10 seconds. Finally, the full tandem position is performed, standing with the heel of one foot in front and touching the toes of the other foot for 10 seconds, using the more comfortable foot in front.

For the 4m gait speed test, the protocol established by the SPPB battery was followed. The test was explained along with instructions to perform it as they normally walk. Subsequently, in the prepared space, measured and marked with a 4-meter tape (Softex tape), the test was timed with a stopwatch.

Lastly, the 5STS test was performed. This test has demonstrated excellent intra- and inter-rater reliability, as well as consistency across successive repetitions, making it a reliable measurement tool for both experienced and novice raters (Bohannon & Williams Andrews, 2011; Teo et al., 2013). This test was chosen over the minimum chair height standing test because of its greater efficacy in patients with osteoarthritis (Reider & Gaul, 2016), a condition with a significant prevalence (70%) in individuals over the age of 65 years (Wilson et al., 1990). For the 5STS, a chair with a height of 49 cm and a stopwatch were used (Alcazar et al., 2018). First, the test and the procedure were explained to the participants, mentioning that the test measures leg strength and that they should perform the chair poses as quickly as possible, five times without stopping between repetitions. To begin, they should cross their arms over

their chest and sit down so that their feet are on the floor; they should then stand up with their arms crossed over their chest and repeat until they have completed all five repetitions.

MGs was conducted utilizing a Camry EH101 electronic handheld dynamometer from Sensun Weighing Apparatus Group Ltd., located in Guandong, China. This dynamometer is recognized as medical equipment approved by the Spanish Agency of Medicines and Health Products. The testing protocol involved maintaining a standing position with the shoulder slightly abducted (approximately 10°), the elbow fully extended, and the forearm and hand positioned neutrally (*Fitness für Health: The ALPHA-FIT Test Battery for Adults Aged 18–69. Tester's Manual – ScienceOpen*, s. f.). Each participant underwent the test twice, and the higher of the two recorded values was considered for analysis.

#### *Relative Power and Absolute Power*

The mechanical power, the result of strength and speed, experiences a more pronounced decline compared to other muscle attributes such as muscle mass and strength (Siglinsky et al., 2015). Above the age of 70, relative power (normalized to body mass) decreases due to the loss of absolute power (both specific power and lean mass in the legs) (Alcazar et al., 2020). The 5STS test, explained in the previous section, is utilized to assess lower extremity muscle power in clinical or field environments (Ferrari et al., 2022). Based on the 5STS, both the absolute and relative power of the lower limbs were calculated (Baltasar-Fernandez, Alcazar, Losa-Reyna, et al., 2021). To calculate the mean absolute value, the equation developed by Alcazar et al., 2018 was applied, which considers performance in the 5STS (measured in time to complete five STS repetitions), body mass, body height, and chair height (Alcazar et al., 2018). To relativize the data, the result was divided by body weight.

#### *Muscle Quality Index*

Muscle Quality Index (MQI) is a useful indicator for assessing total muscle integrity (Mayrink Ivo et al., 2023). There is a remarkable diversity in the definitions and methods used to assess muscle quality in older adults (de Lucena Alves et al., 2023). In this study, muscle quality index was defined as handgrip strength (kg) divided by relative skeletal muscle mass (Barbat-Artigas et al., 2012; Chang et al., 2021).

#### *Anthropometry*

Currently, there are new perspectives on the association between anthropometry, functionality and mortality (Ceolin et al., 2024). Body composition variables were analyzed using segmental bioimpedance with the Tanita BC-601 Segment analyzer (Tanita Corp., Tokyo, Japan). This method provides information on weight (W), body fat percentage (fat %), and kilograms of muscle (Kg\_Muscle). The Tanita BC-601 Segment is considered a reliable and non-invasive

method that yields accurate measurements ( $R^2 = 0.98$ ) (Yamada et al., 2021). Additionally, the Tanita HR 001 Leicester portable stadiometer was employed for height measurements.

### **Socioeconomic Environment**

The socioeconomic and built environment of an area is interrelated with health data and directly influences the quality of life of the elderly (Ding & Gebel, 2012; Molero Jurado & Pérez Fuentes, 2011). There is a significant association between social frailty and functional limitations, cognitive impairment and depressive symptoms in older adults (Huang et al., 2024). This frailty can impact both intrinsic and functional capacity, key aspects for healthy aging.

The Euskadi 2021 socioeconomic deprivation index was constructed following the methodology used in the ME-DEA project described in Domínguez-Berjon et al. (2008) (Domínguez-Berjón et al., 2008). This variable has been defined on the basis of the average personal income of the municipality of Bilbao by city neighborhoods, according to type of income (in euros) for the year 2021. Thus, 3 socioeconomic indexes have been extracted, defined as SI1 (low rent  $< 20.000$  euros), SI2 (medium rent  $20.000-30.000$  euros) and SI3 (high rent  $> 30.000$  euros). (Eustat, s. f.)

### **Statistical Analysis**

The data homogeneity of variance test was performed using Levene's test, and Kolmogorov–Smirnov, Cramer-von Mises, and Anderson-Darling tests were used to analyze the normal distribution of all continuous variables.

First,  $\chi^2$  Pearson test was performed to check possible dependencies between variables. If the previous analysis showed a significant association, Cramér's V was set to establish the effect size (ES); thresholds or effects were:  $< 0.2$  "small",  $0.2 \leq 0.6$  "medium", and  $> 0.6$  "large". A subsequent correspondence analysis was performed to determine the proximity relationship between the variables.

A correlation analysis was carried out with two objectives. First, we analysed whether there was a relationship between the quantitative variables and then determined the magnitude and action of this relationship ( $R^2$ ). Secondly, possible multicollinearity between independent quantitative variables was checked to avoid biases in the interpretation of future regression coefficients. Consequently, before performing the regression analyses, a correlation matrix between the independent variables was established. The probability of collinearity was correlated with a Pearson correlation coefficient  $> 0.8$  (Shrestha, 2020; Vatcheva et al., 2016). Therefore, one of the variables was eliminated if a high correlation coefficient ( $R^2 > 0.8$ ) was observed between them.

Following this initial test, the regression model took into account nearly all independent variables. The explanatory variables: MGS, MQI vs. right MGS, weight vs. BMI, relative vs. mean power, squat vs. mean power, squat vs.

relative power, SPPB vs four meters walking, and SPPB vs. squat showed a high correlation ( $R^2 > 0.8$ ). Thus, left MGS, MQI, weight, mean power, squat and four meters walking variables were removed. For the final regression model the best explanatory independent variables were selected using a stepwise regression approach based on the Ordinary Least Squares (OLS), for performing this analyzes R's package `olsrr` (Hebbali, 2024) was used.

After completing these preliminary tests, we set up a multiple regression model with gait speed as the dependent variable. Simultaneously, the interaction between categorical (socioeconomic environment) and other quantitative variables was considered for the regression model. The interaction is a combination of variables, creating a new one that has a significantly larger effect on the dependent variable than the sum of individual independent variables alone.

For internal validation, a k-fold cross-validation (10 folds and five repetitions) was performed. Internal validation was performed to reduce possible overfitting of the model (Bullock et al., 2021).

The R package `dplyr` was used to identify possible outliers and improve the fitting of the regression model (Wickham et al., 2022). Outlier data in the multiple regression model were identified and removed when the absolute value of the studentized residual (SRE) was  $\geq 3$ . After this analysis, a final sample of 1209 participants was considered for the final regression model.

The Shapiro-Wilk test was used to check the normal distribution of the residuals in the regression model. In turn, the homoscedasticity of the regression model was checked using the Breusch-Pagan test.

The model performance was assessed using the root mean square error (RMSE) and  $R^2$ . The RMSE is the error of the model reported in the outcome units (i.e., min:s).

After the regression analysis, whether the categorical variable (Socioeconomic environment) was taken into account as a predictive variable, a subsequent one-way ANOVA was set to determine different significations of gait speed and socioeconomic belonging group. When the ANOVA test showed significant differences between factors, partial eta squared ( $\eta^2$ ) was used as a measure of ES, using the reference values of small ( $\eta^2 = .01$ ), medium ( $\eta^2 = .06$ ), and large ( $\eta^2 = .14$ ). A subsequent post-hoc Holm's test was performed to compare potential differences between the factors. For significant differences, Cohen's d was used as a measure of ES, using the reference values of small ( $d = .2$ ), medium ( $d = .5$ ) and large ( $d = .8$ ) for interpreting them, as suggested by Cohen (Ellis, 2010).

In all statistical analyses, the significance level was set at  $p < 0.05$ . Statistical analysis was conducted using R software 4.2.2 (Team, R. C., 2022) and RStudio version 2022.12.0.353 (Rstudio Team, 2022) (Rstudio Team, 2022).

After previous statistical analyses, 1209 participants were included in the power analysis. To establish the ES and power in the future linear multiple regression, post-hoc

power analysis was performed using the G\*Power software. The power analysis was performed based on  $R^2=0.35$  and considering seven predictors (see the Results section, Table 2). Statistical analyses established a medium ES ( $f^2=0.54$ ) at a power of 99% and an  $\alpha$  of 0.05.

## Results

The descriptive characteristics of the participants are

presented in Table 1. First, the total number of participants (n:1253) in the study is shown. The participants are then divided by gender, indicating the number of females (n:1121) and males (n:132). Additionally, the participants are segmented based on their socioeconomic index, with segment 1 representing the highest values. Finally, the remaining results are presented according to the established segmentation.

Table 1. Mean values by sex and socioeconomic index of the physical and functional parameters analyzed (n = 1,253).

Total	Sex	Soc_Index	BMI	Muscle	Fat	MGS	gait speed m/s	gait speed 4m	M_Pow	Rel_Pow	MQI	5STS	SPPB	Balance
N= 1,253 Aged: 78.1 (5.78)	Women (N=1121)	1 (N=65) Aged: 80.0 (5.9)	28.3 (5.1)	39.4 (5.0)	38.0 (5.3)	19.7 (5.3)	0.92 (0.2)	4.53 (1.0)	109 (37.2)	1.62 (0.5)	1.21 (0.3)	17.0 (5.8)	9.26 (1.5)	3.69 (0.6)
		2 (N=373) Aged: 78.0 (5.85)	27.7 (3.8)	37.9 (3.9)	38.0 (5.3)	19.6 (5.3)	0.99 (0.2)	4.31 (1.2)	111 (41.7)	1.69 (0.5)	1.22 (0.3)	15.7 (4.9)	9.51 (1.7)	3.63 (0.7)
		3 (N=683) Aged: 77.4 (5.6)	28.9 (4.1)	38.2 (4.0)	39.3 (5.4)	19.2 (4.8)	0.98 (0.2)	4.37 (1.2)	120 (37.6)	1.79 (0.4)	1.17 (0.3)	14.1 (3.8)	9.87 (1.6)	3.71 (0.6)
	Men (N=132) Aged: 78.9 (5.18)	1 (N=1) Aged: 79.0 (-)	31.0 (-)	53.0 (-)	30.0 (-)	20.0 (-)	1.01 (-)	3.97 (-)	102 (-)	1.28 (-)	1.01 (-)	22.1 (-)	8.00 (-)	3.00 (-)
		2 (N=55) Aged: 78.9 (5.18)	27.9 (3.6)	49.3 (6.5)	31.3 (7.9)	31.4 (6.5)	1.07 (0.2)	4.03 (1.2)	161 (56.6)	2.14 (0.6)	1.72 (0.3)	14.5 (3.5)	9.87 (1.5)	3.71 (0.7)
		3 (N=76) Aged: 78.1 (5.1)	28.3 (3.0)	49.8 (5.6)	31.5 (4.6)	32.8 (6.9)	1.04 (0.2)	4.09 (1.1)	176 (56.0)	2.28 (0.5)	1.79 (0.3)	13.6 (3.3)	10.30 (1.4)	3.82 (0.5)

Data presented as mean (SD). BMI (Body Mass Index\_weight (kg)/ [height (m)]<sup>2</sup>; Muscle (kg); Fat (%); MGS (kg); gait speed m/s; gait speed 4m (s); M\_Pow (Mean Power\_(weight\*0,9\*9,81\*(height\*0,5-0,49))/(5STS\*0,1); Rel\_Pow (Relative Power\_Mean Power/weight); MQI (Musque Quality Index\_MGS (kg)/relative skeletal muscle mass; 5STS (five-repetition chair stand test in second); SPPB (Short Physical Performance Battery in points 0-12); Balance (In points 0-4).

Pearson's  $\chi^2$  test showed a significant association between SPPB and Socioeconomic Environment ( $\chi^2(16) = 33.4, p = 0.007$ ; Cramer's  $V = 0.115$ ). The subsequent correspondence analysis revealed a tendency to achieve higher SPPB scores in low socioeconomic environments (Figure 1). Nevertheless, this relationship must be interpreted cautiously because of the small effect size.

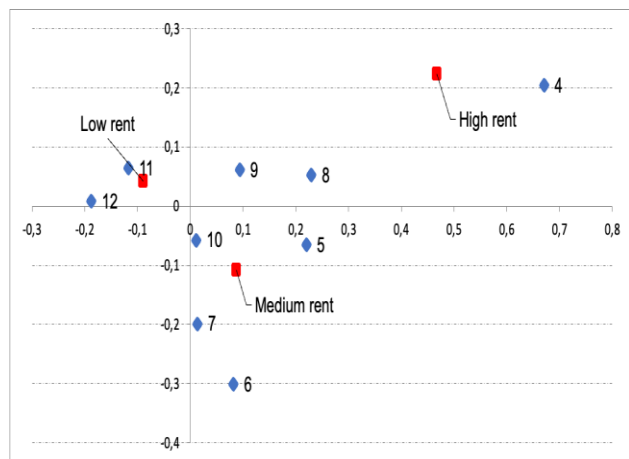


Figure 1. Correspondence analysis between SPPB scores and socioeconomic environments.

Correlation analysis revealed several significant relationships between the quantitative variables (Figure 2). As expected, certain variables displayed very high relationships ( $R^2 > 0.8$ ) (i.e., MGS, MQI vs. right MGS, weight vs. BMI, relative vs. mean power, squat vs. mean power, squat vs. relative power, SPPB vs four meters walking, and SPPB vs. squat) (Figure 2). Therefore, the regression analysis only considered the following independent variables: MGS, BMI, relative power, socioeconomic environment, fat %, kilograms of muscle, SPPB, and the interaction between socioeconomic environment and all anterior quantitative independent variables.

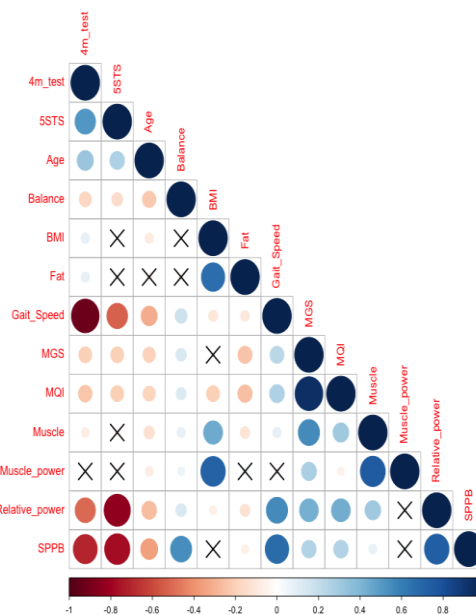


Figure 2. Correlation analysis between the quantitative variables. Note. For better understanding, the non-significant correlations were not provided on the figure (they were shown as "X"). The magnitude of the circle was in accordance with  $R^2$ , as explained in the legend.

After OLS regression, five independent variables (socioeconomic environment, age, balance, relative power, and socioeconomic environment\*relative power) were used to predict gait speed. The final regression model showed in Table 2 ( $R^2 = 0.35, 95\%CI 0.31-0.39, RMSE = 0.18 \text{ m}\cdot\text{s}^{-1}; p < 0.001$ ). Although some independent variables that constructed the model were not significant, the recommended

stepwise regression was included in the final model to improve prediction and decrease the RMSE.

Table 2.  
Regression results using gait speed as the criterion.

Predictor	b	STD. Error	t- value	p-value
Intercept	0.98	0.12	8.35	<0.001
Soc_Index (middle)	0.02	0.08	0.29	0.77
Soc_Index (low)	0.09	0.08	1.14	0.25
Age	-0.01	0.00	-7.07	<0.001
Relative_Power	0.23	0.05	5.17	<0.001
Balance	0.03	0.01	3.25	0.001
Soc_Index (middle)*Rel_Pow	0.01	0.05	0.23	0.82
Soc_Index (low)*Rel_Pow	-0.05	0.05	-1.08	0.28

Note. A significant b-weight indicates the beta-weight and semi-partial correlation are also significant. b represents unstandardized regression weights. beta indicates the standardized regression weights.  $sr^2$  represents the semi-partial correlation squared. r represents the zero-order correlation. LL and UL indicate the lower and upper limits of a confidence interval, respectively.

The proposed model met the criteria for homoscedasticity and showed no multicollinearity; however, the residuals were not normally distributed. Therefore, transformation and standardization of the independent variables

were performed to achieve a normal distribution. However, the resulting regression did not meet the normality criterion. For this reason, the final model was based on a generalized linear model (GLM).

After the generalized regression model was established, its internal validation was verified using a cross-validation model. The results were nearly identical to those of the proposed model ( $R^2=0.37$ ,  $RMSE=0.18 \text{ m}\cdot\text{s}^{-1}$ ). Thus, there is a lack of evidence for the possible overfitting of the proposed generalized linear model.

Subsequently, and based on previous regression analysis, a one-factor ANOVA was conducted to establish possible differences in relative power based on the Socioeconomic Environment of belonging. There was a significant difference between these two variables ( $p < 0.001$ ;  $\eta^2=0.07$ ). Post-hoc analysis showed that the higher income group was related to lower relative power than the lower income group ( $p=0.03$ ;  $d=-0.37$ ), and the lower-income group displayed a significantly higher power than the middle-income group ( $p=0.03$ ;  $d=-0.17$ ) (Figure 3).

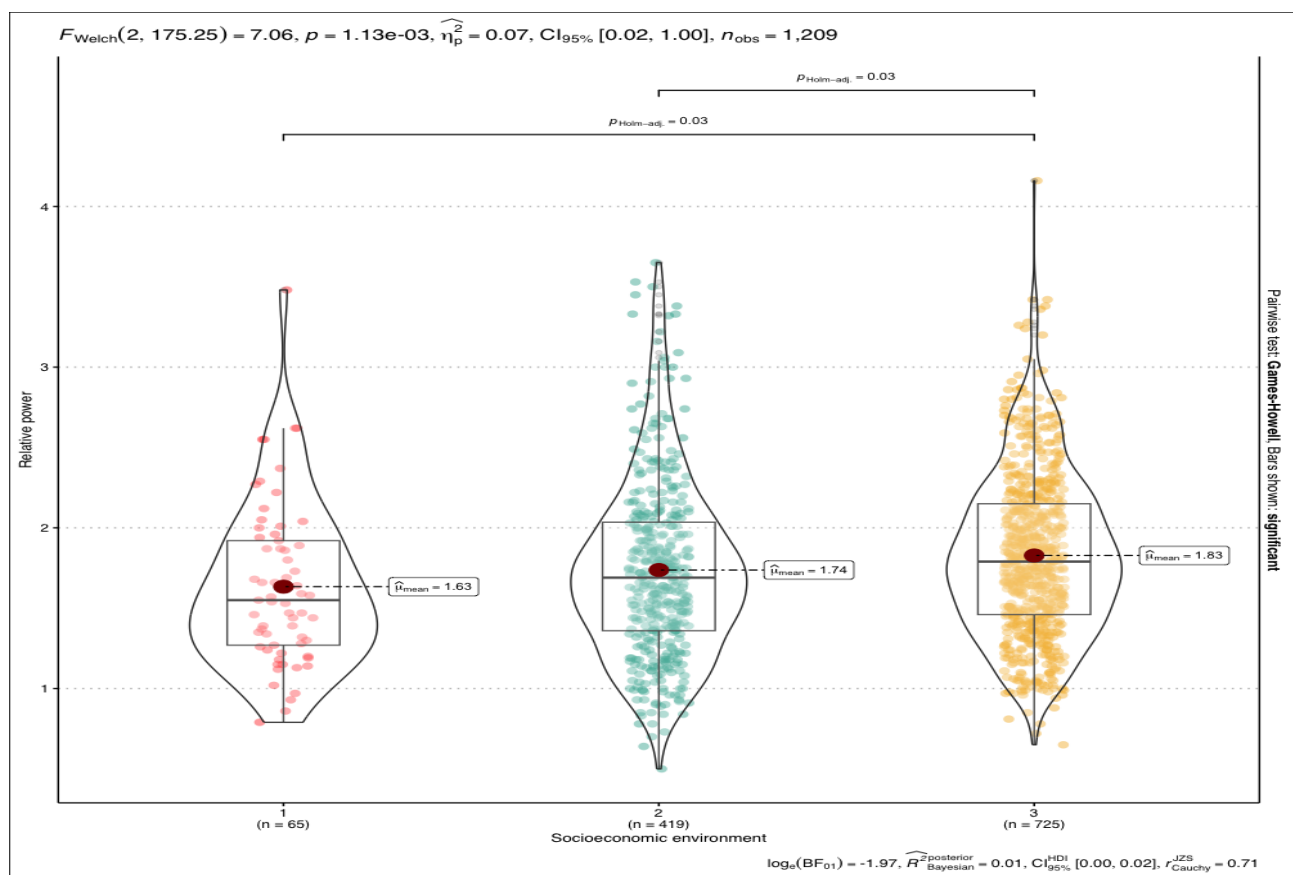


Figure 3. One-factor ANOVA to establish possible differences in relative power as a function of the socioeconomic environment to which they belong.

## Discussion

This study examined the determinants of gait speed in a population of older adults from the Spanish locality of Bilbao, focusing not only on the predictive capacity of the regression model but also on exploring the interactions among variables related to gait speed. It is important to note that, while the predictive capacity of the regression model

was limited, our main objective was to better understand the underlying mechanisms influencing this health marker, aiming to identify relationships among the different variables.

The impact of age on gait speed is noteworthy. In the presented regression model, a significant negative association is evident between the coefficient of age and gait speed, highlighting the impact of aging on gait speed. Specifically,

there is an average decrease of 0.01 m/s for each additional year of age in older adults. These findings are consistent with the existing literature on the progressive decline in muscular, neuronal, and cognitive functions impacting the reduction of gait speed with age (Abellan Van Kan et al., 2009; Andrews et al., 2023; Bohannon & Williams Andrews, 2011). In line with the results obtained, a previous study has identified the reduction in gait speed as a significant indicator of these age-related changes, suggesting a potential reduction of 16% per decade from the age of 60 (Hortobágyi et al., 2015).

On the other hand, as for power, regression analysis highlighted it as a significant predictor of gait speed in our sample. We found that a one unit increase in relative power was associated with a 0.23 m/s increase in walking speed on average. Power, especially in the legs, plays an important role in gait speed and overall mobility in older people (Baltasar-Fernandez, Alcazar, Mañas, et al., 2021; Cuoco et al., 2004). As gait speed increases, an increase in both power and mechanical work of the lower limb joints is required (da Silva et al., 2020).

In this sense, and in relation to power and age, a decrease in the power of the plantar flexors has been observed, which is linked to a significant functional limitation in the gait of older adults as these muscles are critical for forward propulsion and the initiation of foot swing (Aboutorabi et al., 2016; DeVita & Hortobágyi, 2000; Franz, 2016; Gill et al., 2022). This results in a decrease in ankle power (Aboutorabi et al., 2016; DeVita & Hortobágyi, 2000; Morfis & Gkaraveli, 2021). Additionally, decreases in knee power are observed in older subjects (Aboutorabi et al., 2016; DeVita & Hortobágyi, 2000). These reductions in plantar flexor power lead to a redistribution of power generation towards more proximal leg muscles, increasing hip extensor and/or flexor strength. This effect may represent a neuromuscular compensation that counteracts distal weakness and allows for slower gait production (Aboutorabi et al., 2016; Franz, 2016; Kerrigan et al., 1998). Similar patterns have also been identified in populations with pathologies, such as traumatic brain injuries, which compensate for decreased ankle power by relying more on hip muscles (Gill et al., 2022). This suggests that a portion of age-related gait speed reduction may be biomechanically mediated, through increases in proximal muscle recruitment compensating for reductions in plantar flexor power generation during push-off.

The role of balance in gait speed in older adults is essential, as evidenced by the results of our regression model. Notably, the positive coefficient associated with balance in the model suggests that better balance is related to higher walking speeds. This underscores the importance of addressing balance deficits in interventions aimed at improving mobility in older adults (Alizadehsaravi et al., 2022; WEI et al., 2023). Balance is essential for the majority of activities of daily living and stability during ambulation. It has a multicomponent nature

in which it integrates information from the sensory and musculoskeletal systems. Balance control in older adults involves a combination of factors, such as muscle strength, proprioception, vestibular function and tactile sensitivity, which contribute to maintaining stability and preventing falls (Osoba et al., 2019; Wang & Fu, 2022). During the aging process the systems that contribute to stabilization tend to deteriorate (Halvarsson et al., 2015; Osoba et al., 2019; Wang & Fu, 2022), leading to a decline in balance and an increased risk of falling. This loss of balance and fear of falling can lead to a reduction in step length and increased time spent in the support phase of the gait cycle, resulting in a slower walking speed. This compensatory strategy is adopted in order to maintain a more stable state during gait (Aboutorabi et al., 2016; Halvarsson et al., 2015; Osoba et al., 2019).

In exploring the relationship between socioeconomic status and health indicators, particularly walking speed, the results offer an intriguing insight. The results reveal that socioeconomic status does not show a significant direct association with walking speed. However, the association between physical functionality, measured by the SPPB, and socioeconomic environment suggests a tendency towards better performance in lower-income settings, albeit with a small effect size. Additionally, ANOVA revealed significant differences in relative power based on socioeconomic environment, indicating a trend towards better values in lower-income groups. These findings present a contrast to the broader literature, where higher income and education levels are commonly associated with better functional and health outcomes (Malkowski et al., 2023; Noppert et al., 2018; Shankar et al., 2010; Stringhini et al., 2018). Socioeconomic disadvantages are typically linked to earlier declines in physical functionality and greater risk of non-communicable diseases (Shankar et al., 2010; Stringhini et al., 2018). However, the observed variation in this Bilbao-based sample suggests that local factors, such as urban design and resource distribution, may play a pivotal role in shaping these outcomes.

One hypothesis is that the city's topography contributes to these differences. For instance, neighborhoods with lower socioeconomic status, often situated at higher altitudes or with hilly terrain, may present greater mobility challenges (topographic map, 2024). However, these environmental obstacles might paradoxically promote the maintenance of functional capacities over time due to increased physical activity levels associated with navigating such environments (Maharana & Nsoesie, 2018). This urban design factor could explain why lower-income participants in Bilbao exhibit relatively better functional performance than might be expected based on their socioeconomic status alone. Moreover, various studies suggest that prevention strategies aimed at addressing unfavorable socioeconomic circumstances, along with common risk factors for non-communicable diseases, could be crucial for promoting healthy aging (Caballero-Mora et al., 2020; De la Cámara et al., 2020; Stringhini et al., 2018). For example,

participation in community programs could mitigate the disparities observed in physical functionality among different socioeconomic groups, and it is noteworthy that these participants are part of a specific program, such as the "Health for the Elderly" program sponsored by the Bilbao City Council (Shankar et al., 2010; Stringhini et al., 2018).

Upon further analysis, we observed that MGS and MQI were not included in the final regression model. These two variables showed a high correlation with each other but ultimately did not reveal clinical significance within the model. This could be attributed to the fact that, while grip strength is a widely used indicator of overall muscle strength (Bohannon et al., 2012; Cruz-Jentoft et al., 2010; Delinocente et al., 2021), its ability to reflect specific lower limb muscle strength is debatable (Ogawa et al., 2022; Tatangelo et al., 2022; Yeung et al., 2018). In the literature, MGS has been highlighted as a relevant indicator for detecting slow gait speeds ( $<0.8\text{m/s}$ ) (Alley et al., 2014; Duchowny et al., 2017; Lin et al., 2021); however, this relationship is attenuated in populations with faster gaits (Busch et al., 2015; Fragala et al., 2016), such as ours. The connection between MGS and gait speed may vary depending on various factors, such as the level of physical activity and the general health of the population studied (Yeung et al., 2018). For example, the presence of severe MGS weakness affects gait speed, although the relationship between MGS and gait speed is less evident in stronger individuals (Buchner et al., 1996; Fragala et al., 2016). Additionally, studies have shown that a higher level of daily physical activity was significantly associated with higher knee extension strength (KES), but not with MGS, in community-dwelling older adults (Ikenaga et al., 2014; Samuel & Rowe, 2012). Lastly, it is important to note that the effect of decreased limb mobility and reduced physical activity associated with aging, coupled with the predominant role of the upper limb in daily activities, results in a more pronounced deterioration of lower limb strength compared to the upper limb (Nogueira et al., 2013; Tatangelo et al., 2022). This difference in decline rates could also be a hypothesis to explain the contradictory results. Therefore, since lower limbs are particularly crucial for gait speed, the importance of considering strength measures that may be more related to this specific motor function such as the KNE test or power test is emphasized (Tatangelo et al., 2022; Yeung et al., 2018).

As with the MGS, when calculating the MQI using the MGS indicator, no relationships were found in this context either. In this research, MQI was assessed indirectly by employing the approach suggested by Barbat-Artigas et al. (2012) and Chang et al. (2021) (Barbat-Artigas et al., 2012; Chang et al., 2021), MGS/ skeletal muscle mass. The optimal method for quantifying MQI is unclear and varies in cost, complexity and availability and this formula provides an accessible one (Heysmsfield et al., 2015). Results from other research suggest that assessing MQI through MGS could serve as a reliable indicator of upper body functional abilities among older individuals but may

not be an ideal indicator for the lower extremity (Felicio et al., 2014; Nascimento et al., 2020; Yeung et al., 2018). The inclusion of a muscle quality indicator more tailored to the specific characteristics of the legs or the general body could provide a more complete and accurate understanding of the relationship between gait speed and muscle quality.

The findings of this study provide valuable insights into the factors influencing gait speed in older adults. A key contribution of this research is its potential application in clinical practice, specifically addressing these influential factors. The most important consideration for exercise prescription is that it must be individualized, taking into account not only functional capacity and tolerance but also risk factors and medical history (Izquierdo et al., 2021; Izquierdo & Cadore, 2024). By focusing on the most significant variables identified and aligning with recent studies, the optimal training approach would involve a multicomponent program (generally including various combinations of strength, power, gait, balance, and functional training) (Izquierdo & Cadore, 2024). In this case, the program should include power and balance exercises as key components to effectively enhance gait speed.

Power training is a type of muscle training that combines force production with speed. It is considered a subcategory of strength training. While strength training focuses on the ability to overcome resistance, power training emphasizes overcoming that resistance as quickly as possible (Izquierdo et al., 2021). Age-related power loss occurs before strength and muscle mass decline, primarily due to a reduction in the size of type II fibers, atrophy of remaining fibers, or changes in neural recruitment (Chodzko-Zajko et al., 2009; Izquierdo et al., 2021). These findings justify the inclusion of power training as a key component of concurrent training approaches. For optimal power training, concentric contractions should be performed rapidly, followed by a slower eccentric phase, always avoiding reaching concentric failure. Power is optimized using loads that represent 30-45% of the one-repetition maximum (1RM) for upper limbs and 60-70% 1RM for lower limbs. Heavy loads during resistance training can simultaneously improve muscle strength and power in older adults. However, for frail individuals or those with reduced force production capacity, moderate loads (40-60% 1RM) have also been shown to provide benefits (Izquierdo et al., 2021; Izquierdo & Cadore, 2024).

As for the balance and gait training, progressions should involve increasing difficulty of the exercise as they tolerate it, just as with strength and power training, when a load is no longer challenging enough they adapt. To achieve this there are different strategies such as narrowing or disruption of the base of support, proprioceptive or visual decrease, dual tasking... (Izquierdo & Cadore, 2024).

For the strengths of this study, it benefits from a large sample size, which enhances its representativeness and provides valuable insights into improving gait interventions for older adults. The results fill a gap in the literature, offering guidance for more effective public health strategies. As for

the limitations, the study's reliance on convenience sampling and the non-representative gender distribution may affect the generalizability of the findings. Additionally, the use of postal codes alone for socioeconomic status limits our understanding of the reasons behind variations in gait speed compared to other current studies. Furthermore, including a more tailored muscle quality indicator could yield a more comprehensive understanding of the relationship between gait speed and muscle quality. Another limitation of the study is the absence of a specific measure for lower limb strength, such as the KNE test, which could have provided a more precise assessment of this particular motor function.

## Conclusion

This study explored factors influencing gait speed in older adults. Age was a significant predictor of gait speed decline, in line with age-related declines in neuromuscular and cognitive function. Lower limb power emerged as an important marker, hypothesising that declines in plantar flexor power affect gait propulsion. In addition, better balance was associated with higher walking speeds, highlighting the importance of balance interventions for mobility.

Although socioeconomic status did not directly impact gait speed, low-income settings showed better physical functioning, possibly due to greater physical activity in challenging environments. Further studies on the involvement of MGS and indirect muscle quality are needed to validate their usefulness as reliable indicators of lower limb specific muscle strength and quality in older adults and determinants of gait speed. In general, understanding the determinants of gait speed is essential to promote healthy aging to maintain individual functional capacity. These determinants, such as power and balance, provide valuable information on the functionality of older adults, which will enable more effective and personalised interventions to be designed to promote healthy aging in clinical practice.

## Conflicts of interest

The authors declare that they have no conflicts of interest.

## Ethics approval

The data collection of the study was approved by the University of Deusto Ethics Committee (reference # ETK-32/18–19) and written informed consent was obtained from each participant prior to study.

## Consent for publication

All authors have seen and approved the final manuscript, and agree to its submission to the Journal of Frailty & Aging.

## Availability of data

Data available from corresponding author on reasonable

request with approval from data custodian at University of Deusto.

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## Author contributions

Study concepts: N.V. and X.R. Data acquisition: X.R. Quality control of data and algorithms: I.M. Data analysis and interpretation: N.V., X.R. and I.M. Statistical analysis: I.M. Manuscript preparation: N.V., X.R and I.M. Manuscript editing: N.V, X.R., I.M., A.M-Z and B.G-Z. Manuscript review: N.V, X.R., I.M., A.M-Z and B.G-Z. All authors read and approved the final manuscript.

### List of abbreviations:

*Manual Grip Strength (MGS), Short Physical Performance Battery (SPPB), Five-repetition Chair Stand Test (5STS), Muscle Quality Index (MQI), Body Mass Indices (BMI), Ordinary Least Squares (OLS), Studentized Residual (SRE), Root Mean Square Error (RMSE), Generalized Linear Model (GLM), Analysis of Variance (ANOVA).*

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## 5.5 Results discussion:

Musculoskeletal disorders, especially those that can aggravate common pathologies in ageing, such as sarcopenia and frailty, have become a public health priority due to their close association with multiple adverse health outcomes (Alkhodary et al., 2020; Cruz-Jentoft et al., 2019; Cruz-Jentoft & Sayer, 2019). Despite the knowledge about the negative consequences of these musculoskeletal pathologies, there are still barriers and knowledge gaps around this topic, as stated in the research questions of this thesis. For this reason, this thesis project aims to align with global and national strategies that seek to make a significant contribution to public health by addressing sarcopenia and muscle quality in older adults.

To achieve this, research questions have been formulated in line with international and national guidelines, ensuring alignment with current public health priorities. One of the key objectives of the European Working Group on Sarcopenia in Older People (EWGSOP) is to improve the understanding and treatment of sarcopenia through comprehensive assessment of muscle quality and function (Cruz-Jentoft et al., 2019). The updated EWGSOP2 guidelines underline the fundamental role of muscle quality, recognising it as an essential component in the assessment of sarcopenia. In this context, the diagnosis of sarcopenia is now primarily characterised by the assessment of muscle strength, while muscle quality and quantity are considered as confirmatory factors. This paradigm shifts from focusing solely on muscle mass to a more qualified analysis of muscle strength, quality and function underlines the need for more accurate and meaningful indicators of muscle health. Accordingly, the guidelines emphasise the importance of advancing non-invasive tools and methodologies to improve the assessment of muscle quality parameters, determining optimal muscle quality indicators and developing accurate and affordable tools that will ultimately improve clinical outcomes. This approach effectively bridges individual research initiatives, such as this thesis, with broader collective and organisational strategies, which ultimately enhance the understanding of aging and promote well-being in later life.

Furthermore, these international bodies also note that, at present, these muscle quality parameters are predominantly used in research settings rather than routinely in clinical and community practice, primarily due to the technical challenges associated with their measurement (Buckinx et al., 2018; Masanés et al., 2017; McGregor et al., 2014; Treviño-Aguirre et al., 2014). For this reason, the aim is not only to determine the most effective non-invasive tools for muscle quality assessment but also to bring the opportunity for muscle quality quantification closer to the community by using tools that are more accessible, affordable, and easier to implement.

As for non-invasive tools for the detection of muscle quality, these have been classified into two distinct domains depending on the areas of muscle quality they assess. On the one hand, there are tools that measure morphological muscle quality, which focus on direct assessments of muscle architecture and muscle composition (de Lucena Alves et al., 2023; M. Fragala et al., 2015). Among them, CT and MRI are essential for analysing muscle composition, providing measures of intramuscular fat infiltration and cross-sectional area (Correa-de-Araujo et al., 2017; Cruz-Jentoft et al., 2019; Faron et al., 2020; Niklasson et al., 2022; Oba et al., 2021). CT offers a quick and cost-effective analysis of muscle quality; however, it generates radiation exposure. In contrast, MRI provides a radiation-free alternative at a higher cost (Niklasson et al., 2022; Oba et al., 2021). On the other hand, ultrasound has emerged as a rapid, non-invasive and accessible imaging modality for musculoskeletal assessment, allowing detailed analysis of muscle architecture (Correa-de-Araujo et al., 2017; Sconfienza et al., 2018). Furthermore, it has demonstrated significant correlation with other imaging modalities, as reported in previous studies (Casey et al., 2022; Nijholt et al., 2020; Price & Earthman, 2019). Although major international guidelines recognise its potential as a promising tool, challenges remain due to the lack of standardised protocols. Operator experience remains a determining factor, limiting its ability to provide definitive results in the early detection of muscle quality loss (Cruz-Jentoft et al., 2019; Lopez-Lopez et al., 2021; Perikisas et al., 2018). Another emerging tool is BIA,

specifically through the analysis of PhA, which has been identified as an effective non-imaging-based method for characterising muscle quality components (Correa-de-Araujo et al., 2017; Di Vincenzo et al., 2021). Recent studies have recognised PhA as a significant predictor of muscle quality in older adults, with strong associations with adverse clinical outcomes, including increased risk of mortality (Duarte Martins et al., 2023; Norman et al., 2023). However, its use still requires standardisation and validation, as PhA measurements are sensitive to external factors such as hydration status and temperature (Duarte Martins et al., 2023; Norman et al., 2023). Finally, Tensiomyography (TMG) and Myotonometry are non-invasive tools used to assess the contractile and mechanical properties of muscles. TMG measures parameters such as contraction time and maximal radial displacement, being sensitive to changes in muscle composition, architecture, and pre-atrophy phases of skeletal muscles. Despite its reproducibility and portability, this technique requires specialized equipment and operator expertise, as well as facing challenges related to standardization (Čular et al., 2023; Lohr et al., 2019; McGowen et al., 2022). On the other hand, Myotonometry evaluates muscle stiffness, elasticity, and compliance, presenting a faster, more portable, and cost-effective option compared to TMG, with higher reliability and validity for differentiating muscle stiffness levels. However, its routine clinical application remains uncertain due to the need for further validation and limitations in depth measurement and adipose tissue interference (Brazier et al., 2014; Čular et al., 2023; Ilahi et al., 2020; Lohr et al., 2019; McGowen et al., 2022; Morgan et al., 2019; White et al., 2018; Wilson et al., 2023).

Among the methods identified in the literature review, ultrasound emerges as the most appropriate technique, given its alignment with the characteristics of the study and the requirements of the subsequent analysis. Although more accurate modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI), offer a detailed assessment, their application is currently restricted to research settings or as complementary examinations in specific primary indications, due to their high cost and potential associated complications for the patient. Furthermore, ultrasound has demonstrated a significant correlation with these imaging modalities, as documented in previous studies (Casey et al., 2022; Nijholt et al., 2020; Price & Earthman, 2019; Yoshiko et al., 2018, 2021; Zubac et al., 2019), which reinforces its validity as an assessment tool. In this context, a growing interest in the use of ultrasound techniques to quantify muscle quality and assess musculoskeletal pathologies has been observed, consolidating as a promising approach in clinical practice and research (Bartley & Studenski, 2017; Dubois et al., 2018; Patil & Dasgupta, 2012; Ruby et al., 2021; Sconfienza et al., 2018).

Nevertheless, in resource-limited settings, the assessment of muscle quality using ultrasound techniques presents accessibility challenges. For this reason, although one of the studies in this dissertation employs ultrasound due to its advantages in accuracy and correlation with other imaging modalities, we have also explored the integration of this morphological quantification tool with more accessible methods. In particular, we have considered indirect muscle quantification tools that assess muscle quality from a functional perspective (Barbat-Artigas et al., 2012). Through this initial study (Pilot Study I), a correlation has been established between the geometric variables obtained via ultrasound and functional variables, providing a potentially more accessible technique for community-based muscle quality assessment. Notably, the analysis of functional muscle quality presents considerable potential for daily application, as the technical challenges associated with its measurement are significantly lower. This makes it a viable tool for implementation in clinical and community settings with limited resources, and several studies have already adopted these tools (Baek et al., 2022; Chiles Shaffer et al., 2017; Emerson et al., 2014; Nunes et al., 2019; Yoda et al., 2012; You et al., 2023). This is particularly relevant, as the ability to perform accurate assessments across diverse contexts, adapting tools to the specific needs of each setting, is crucial for optimizing therapeutic interventions. Without precise evaluation, the effective implementation of improvement and treatment strategies remains unattainable.

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As for the functional domain, it offers greater accessibility for the assessment of muscle quality, as it is commonly quantified by the ratio of strength per muscle mass. Assessment methods within this domain vary considerably in terms of complexity and technical requirements. Some procedures require specialised equipment and operator expertise to ensure accurate measurements, which may limit their applicability in resource-limited settings. Among these specialised methods, we would find; force assessment tools which may include isokinetic dynamometers or power assessment devices. These tools tend to require specialised equipment and trained personnel, making them less suitable for widespread application outside of clinical or research settings (Bassey & Short, 1990; Chamorro et al., 2017; Hurst et al., 2018; Jenner et al., 2024; Luna-Heredia et al., 2005; Martin et al., 2006; Reid & Fielding, 2012). In addition, for muscle mass assessment, reference tools such as MRI, DXA and CT offer exceptional accuracy and validity. However, while they allow for a comprehensive analysis of body composition, their high cost and operational complexity often limit their use to specialised settings, making them difficult to apply in community or resource-limited settings (Albano et al., 2020; Blake & Fogelman, 2007; Correa-de-Araujo et al., 2017; Cruz-Jentoft et al., 2019; Faron et al., 2020; Jain & Vokes, 2017; Niklasson et al., 2022; Oba et al., 2021).

Nonetheless, many of these methods are simple, time-efficient and accessible, requiring minimal equipment, which facilitates their implementation in a variety of clinical and community settings without compromising the reliability of the results. In this study, we will focus on one of these easily accessible indices, given its feasibility for use in resource-limited settings and its potential for widespread application in daily practice. Among these more accessible methods, we find the different force measurement tools where hand-held dynamometers and 1RM tests stand out as the simplest and most practical options, especially for community applications (Abe et al., 2016; American College of Sports Medicine et al., 2009; Baechle et al., 2000; Cruz-Jentoft et al., 2019; Grgic et al., 2020; Jenner et al., 2024; Medicine et al., 2018). For determining muscle mass, more accessible alternatives, such as BIA and US, offer scalable and cost-effective solutions, making them suitable for use in community settings (Correa-de-Araujo et al., 2017; Cruz-Jentoft et al., 2019; Niklasson et al., 2022; Sconfienza et al., 2018).

As we have seen throughout the thesis, all muscle quality measurement tools have been carefully selected. Through this figure we illustrate the decision-making process for choosing the appropriate muscle quality assessment tools depending on the context. It takes into account key parameters such as accessibility, measurement accuracy, budget level, training requirements and the need to assess morphological or functional outcomes. The diagram provides a structured approach to selecting appropriate tools for various research contexts and practical applications, including advanced and community settings.

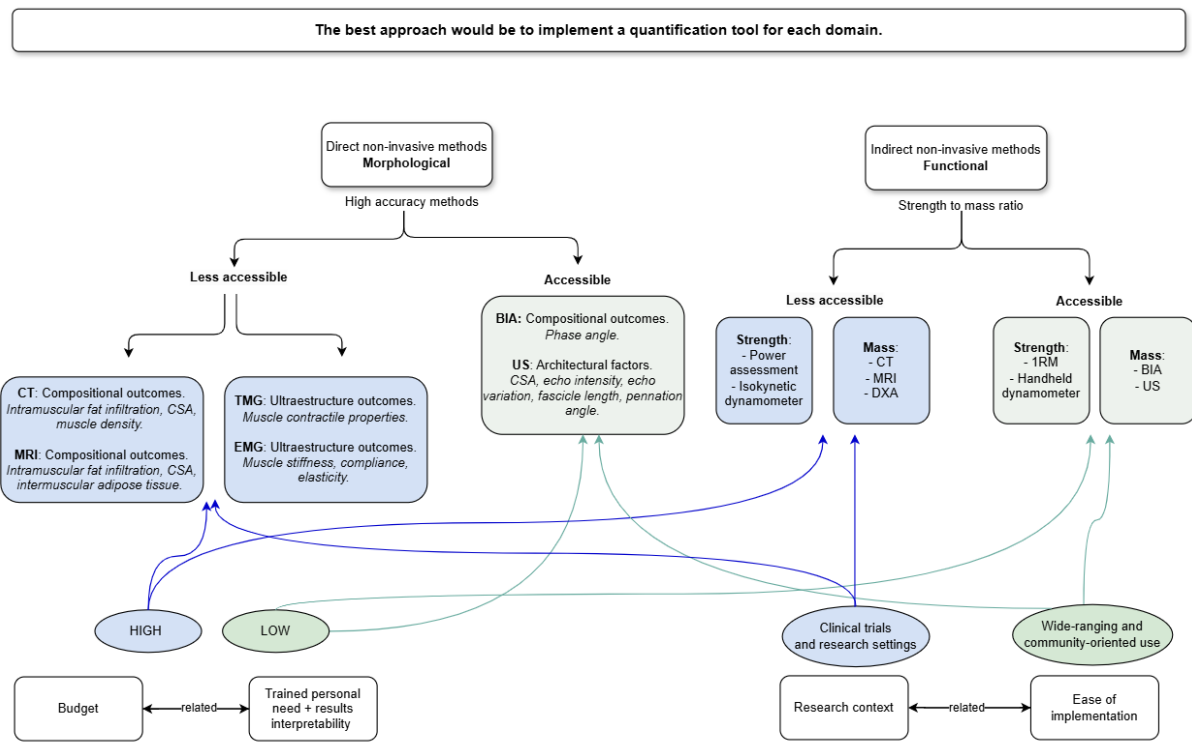


Figure 10. Key parameters for the election of muscle quality assessment methods

After evaluating various measurement methods, we selected the most appropriate ones for the following studies, aiming to identify the specific factors that significantly influence sarcopenia, muscle quality, and functionality. We employed the index proposed by Barbat and Artigas, which has gained considerable recognition in recent years. This index is calculated by dividing handgrip strength by relative skeletal muscle mass, providing a valuable indicator of muscle quality. Handgrip strength was measured in a community setting using a Camry EH101 electronic hand dynamometer, certified as medical equipment by the Spanish Agency for Medicines and Health Products. To assess body composition, we used segmental bioimpedance analysis. Although BIA may slightly overestimate or underestimate skeletal muscle mass compared to gold-standard methods like DXA and CT, it consistently shows strong correlations with these reference techniques (Achamrah et al., 2018; Cruz-Jentoft et al., 2019; Ribeiro et al., 2016; Zuo et al., 2024).

Through the completion of the final studies, this dissertation thoroughly investigates the multifactorial nature of sarcopenia, muscle quality, and functionality in older adults, emphasizing the complex interactions among the various contributing factors. The findings reveal that the key determinants of sarcopenia include declining muscle power, advanced age, strength, body mass index (BMI), and sex, while balance, muscle and fat mass, and socioeconomic status also significantly influence its development and severity. Muscle quality, particularly in women, is affected by age, BMI, muscle mass, fat mass, gait speed, squat test time (which encompasses both lower limb strength and power), balance, and socioeconomic level. Regarding functionality, which is closely related to gait speed and analyzed in relation to neuromuscular and cognitive decline associated with aging, lower limb power and balance play crucial roles.

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Although certain factors, such as age and gender, are not modifiable, this thesis strategically focuses on enhancing those variables that can be influenced by physical exercise intervention. In addition, the lower adherence rates observed among men will be addressed through the implementation of specific recruitment strategies supported by the literature. Gender has been identified as a significant factor in the representation of men in health promotion programmes, with participation rates remaining worryingly low at around 20% or even lower, as evidenced in this study (Anderson et al., 2016; Howell et al., 2023; Ory et al., 2014; Smith et al., 2014; Smith & Ory, 2014). Key barriers include rigid gender roles, the perception of programmes as predominantly female and the overrepresentation of female participants and instructors (Anderson et al., 2016; Howell et al., 2023). With this in mind, in order to increase male recruitment, it would be interesting to employ different strategies proposed by different scientific studies. These include support from male community leaders, advertisements tailored to male audiences, and tailoring programme content to resonate more effectively with this demographic (Anderson et al., 2016; Howell et al., 2023).

Before starting any exercise programme, it is essential to identify the presence of risk factors and to perform a preliminary assessment of the individual's health status. This process allows personalisation of the intervention, considering not only functional capacity and exercise tolerance, but also specific risk factors and relevant medical history (Medicine, 2013; Ozemek et al., 2025). As most physiological and anatomical systems undergo functional and structural deterioration during ageing, health status and functional capacity often provide more information than mere chronological age. In this context, a comprehensive screening will be carried out, in line with the recommendations of organisations such as the ACSM (Campbell et al., 2019; Medicine, 2013; Ozemek et al., 2025). Such screening will focus on assessing the current level of physical activity, the presence or absence of known diseases (both symptomatic and asymptomatic) and the existence of previous injuries. In addition, given the focus of this thesis on musculoskeletal pathologies, a targeted functional analysis for the detection of sarcopenia and frailty will be included. To enhance this approach, an assessment of muscle quality will also be conducted, guided by the decision-making process illustrated in the figure above, which outlines the key parameters for the selection of muscle quality assessment methods.

From this comprehensive assessment and having previously identified, from previous studies, the most relevant variables on which intervention is desired, a training approach will be designed that considers the relevant factors. By focusing on the significant variables identified and aligning with the most recent research, the optimal training approach will consist of a multicomponent programme, typically incorporating a combination of strength, power, gait, balance and functional training (Izquierdo & Cadore, 2024). Furthermore, to ensure the success of interventions and promote positive physiological adaptations through training, it is essential to assess and take into account key factors such as frequency, intensity, duration and type of exercise, which is in line with the FITT (Frequency, Intensity, Time and Type) principle (Campbell et al., 2019; Medicine, 2013; Medicine et al., 2018; Ozemek et al., 2025).

Table 16. FITT principle for exercise prescription.

Frequency	Intensity	Time	Type	Special considerations
3-5 days per week if the intensity mix is moderate to vigorous. If it is moderate closer to 5 and vigorous it could be reduced to 3 days a week.	Moderate intensity (5-6 borg scale) to vigorous (7-8)	20-60 minutes per session (varies depending on intensity).	Multicomponent programme.	Exercise should be stopped immediately and followed by medical evaluation if any of the following occur: dizziness, chest pain, unexplained shortness of breath, retinal hemorrhage, lower extremity edema, vasovagal response, blood glucose <70 mL·dL <sup>-1</sup> , systolic BP >220 mm Hg, diastolic BP >105 mm Hg, syncope, or orthostasis.
*Gradually exceed the minimum recommended levels of physical activity to improve or maintain physical fitness and better manage chronic diseases and health conditions, as tolerated.				

Adapted from: American College of Sports Medicine. (2013). ACSM's guidelines for exercise testing and prescription. Lippincott williams & wilkins.

Taking into account the established FITT principles, exercise prescription should be individualised, having carried out the relevant assessment of risk factors, function, etc... Ideally, prior to beginning aerobic training, deficiencies in strength, power, gait, or balance should ideally be addressed. Progressive increases in exercise volume, intensity, and complexity should be a part of multi-component programs.

Within a multicomponent training approach, resistance training should be a core component of exercise prescription for all older adults, unless contraindicated, as muscular strength is essential for aging successfully and maintaining independence. To address muscular strength in healthy older adults, exercises involving one or multiple joints (one to three sets) should be included. These exercises can be performed using free weights, machines, bodyweight exercises, or a combination of these modalities. When performing unilateral exercises, it is important to note that they increase exercise intensity. It is recommended to perform between 1 to 3 sets per exercise to avoid fatigue, while refraining from training to muscular failure. The exercise load should be moderate to moderately high (60%-75% of 1-RM), with a rep range of 8-12 repetitions performed at a high velocity. However, decisions regarding resistance training should be tailored to the current strength and load stability of older adults, their prior experience with resistance training, and the potential for injury. Nevertheless, muscular strength can be optimized by progressively increasing the load from low-moderate (20-50% 1-RM) to higher loads (70-80% 1-RM), adapting the intensity to the individual's condition (Campbell et al., 2019; Medicine, 2013; Medicine et al., 2018; Ozemek et al., 2025).

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Power training, a subset of strength training, focuses on the rapid application of force. While traditional strength training emphasizes the capacity to overcome resistance, power training prioritizes the speed at which this resistance is executed (Izquierdo et al., 2021). In the aging population, declines in power precede reductions in strength and muscle mass. This early decline is mainly attributed to a decrease in the size of type II muscle fibers, atrophy of the remaining fibers, or alterations in neural activation patterns (Chodzko-Zajko et al., 2009; Izquierdo et al., 2021). These insights support incorporating power training as a vital element in combined training strategies. For effective power development, it's recommended to perform concentric muscle actions swiftly, followed by a controlled, slower eccentric phase, ensuring that concentric failure is avoided. Optimal power outputs are achieved with loads approximating 30-45% of one-repetition maximum (1RM) for upper body exercises and 60-70% 1RM for lower body movements. Utilizing heavier loads in resistance training can enhance both muscle strength and power in older adults. However, for those who are frail or have diminished force production capabilities, moderate loads (40-60% 1RM) have also demonstrated benefits (Chodzko-Zajko et al., 2009; Izquierdo et al., 2021; Izquierdo & Cadore, 2024).

In terms of training for balance and gait, progressions must involve boosting the workout's complexity as they can handle it; similarly, with strength and power training, they adjust when a load becomes too easy. Many techniques, including proprioceptive or visual decline, dual tasking, restricting or disrupting the base of support, etc., can be used to accomplish this (Izquierdo & Cadore, 2024). In terms of aerobic training in the older adult, it is essential to first establish a basic level of strength before starting with more intense aerobic exercise. Once this level has been reached, it is recommended to start with 5-10 minute sessions, progressively increasing to 15-30 minutes. Suggested activities include walking, cycling, stair climbing or dancing, always adapting the modality according to the person's walking ability and functional status. In addition, it is important to monitor intensity to ensure safe and effective progression (Chodzko-Zajko et al., 2009; Izquierdo et al., 2021; Izquierdo & Cadore, 2024).

While total body weight, muscle mass and muscle cross-sectional area may decrease with age, strength and power training can maintain strength relative to muscle mass (eventually increasing muscle mass) and limit fat infiltration, potentially improving overall physical function in older adults (M. S. Fragala et al., 2019; Goodpaster et al., 2008; Marzuca-Nassr et al., 2024; Orssatto et al., 2020). In this context, the proposed exercise protocol not only seeks to improve the specific parameters it targets but also aims to mitigate these adverse effects by significantly optimising key metabolic parameters, such as fat mass, muscle mass and BMI, which have been shown to directly influence sarcopenia and muscle quality.

## 6 International stay:

During the third year of the doctoral program, an international research stay was conducted to enhance research activities and foster collaboration. This stay took place at Ruhr University Bochum, under the supervision of Dr. Markus Reichert. Over the course of three months (September 2024 to December 2024), the primary objectives were to engage with international experts, exchange knowledge, and advance the research agenda. The stay provided key opportunities for networking, learning, and enriching the research focus. A particular emphasis was placed on examining how physical activity and exercise can promote psychological well-being, especially in the context of major depressive disorders that are related with sarcopenia. This broadened the scope of the dissertation, integrating the psychological dimension into the analysis, which had not been previously explored during this work plan.

It is essential to emphasize that this dissertation has thoroughly examined the physical aspects of musculoskeletal pathologies and the role of muscle quality. However, aging and the geriatric conditions that may arise from this process are closely linked to depressive disorders, a critical component that transcends the purely physical realm. In this regard, the international stay aimed to broaden this physical perspective by integrating a new analysis of the psychological dimension, seeking a more holistic understanding that had not been addressed during the dissertation. This approach, which will be explored further during the international stay, will enable us to investigate how factors related to physical activity and exercise can serve as essential promoters of psychological well-being. This is crucial for a comprehensive approach to healthy aging, sarcopenia prevention, and the maintenance of independence. As a result of the research stay, a comprehensive exploration of major depressive disorders, along with the impact of just-in-time interventions and physical activity, culminated in the publication of a journal article.

The relationship between sarcopenia and common mental disorders, such as depression and anxiety, has gained recognition in recent years. While the influence of body composition on metabolic and cardiovascular diseases has been extensively studied, the implications of body composition for the development of psychological disorders are now under investigation (K.-V. Chang et al., 2017; Pasco et al., 2015; Zhong et al., 2023). In this regard, pathophysiological pathways have been found to be shared between sarcopenia and psychiatric diseases, including neurotrophins, oxidative stress and inflammation, all modulated by lifestyle-related behaviours (Z. Li et al., 2022; Pasco et al., 2015; Zhong et al., 2023). Focusing on the role of skeletal muscle, skeletal muscle contraction plays a key role in releasing neurotrophic factors, which have been shown to be crucial in the regulation of mood and mental health (Pasco et al., 2015). Additionally, muscle activity influences the immune and inflammatory system, contributing to the reduction of muscle catabolism and improves emotional well-being (Zhong et al., 2023). Evidence suggests that sarcopenia, especially in terms of loss of muscle strength, is strongly associated with depression, and this association persists even when adjusting for factors such as gender, age and other comorbidities (K.-V. Chang et al., 2017; Fukumori et al., 2015; Hayashi et al., 2019; Z. Li et al., 2022; Sanders et al., 2012; Szejf et al., 2019; Zhong et al., 2023). Recent meta-analyses and studies show a significant association of low grip strength and slow gait with an increased risk of depressive symptoms in older people (K.-V. Chang et al., 2017; Fukumori et al., 2015; Hayashi et al., 2019; Z. Li et al., 2022; Sanders et al., 2012; Szejf et al., 2019; Zhong et al., 2023).

Major depressive disorder (MDD) is a prevalent mental illness that stands as the leading cause of disability, affecting approximately 185 million people worldwide (GBD, 2019; WHO, 2017). Treatment guidelines for depression generally advise the use of medication, psychotherapy, or a combination of both approaches (Marx et al., 2023). One of the most prominent psychotherapeutic approaches is behavioral activation, which aims to modify how individuals engage with their environment by encouraging participation in activities that provide positive reinforcement (Janssen et al., 2020). This approach helps alleviate depressive symptoms by

improving mood and overall well-being (Janssen et al., 2020). Recent studies emphasize the interactions between physical activity and perceived energy levels in daily life as a potential intervention target for major depressive disorder (Timm et al., 2024). While structured exercise is already well-established as an effective treatment for MDD (Heissel et al., 2023; Schuch et al., 2016), non-exercise activities, such as brief, informal actions like taking the stairs, plays a significant role (Packheiser et al., 2024). Within this framework, the MASE project aims to develop individually tailored BA interventions that focus on increasing physical activity and, consequently, subjective energy levels to reduce depressive symptoms and prevent relapse. Moreover, real-time dynamic interventions, such as just-in-time adaptive interventions, are proposed as a promising alternative to static interventions.

## 7 Conclusions:

*Have no fear of perfection; you'll never reach it. – Marie Curie.*

This chapter introduces the most relevant conclusions drawn after the development of this work. These findings will be introduced following the completion of the different research questions outlined in the introduction chapter.

Aging is a global phenomenon that reflects the extraordinary adaptability of human beings. This process has led to significant demographic changes, resulting in a population transition that has increased life expectancy. While this achievement represents a remarkable social success, it also poses a crucial challenge: the need to reform social and healthcare systems to meet the demands of this new population paradigm (Preston & Biddell, 2021). Projections indicate that this demographic trend will continue, bringing multiple challenges for public health (Crimmins, 2021). Among them, musculoskeletal diseases stand out due to their impact on functionality and quality of life in older adults, highlighting the importance of addressing them effectively (Cruz-Jentoft et al., 2019).

In this context, it is crucial to have effective tools to assess muscle quality not only in clinical settings, but also in the community, allowing early and accessible detection (Cruz-Jentoft et al., 2019). In response to this need, this thesis has investigated the tools available for muscle quality assessment, identifying their key parameters and analysing which are best suited to different settings and needs. It has also explored the factors that influence muscle quality, highlighting the need for solutions that facilitate more effective diagnosis and treatment in clinical and community settings. Finally, an exercise protocol has been proposed based on non-invasive muscle quality measurement tools, selected for their accessibility and efficacy in the community, and aimed at improving muscle quality through evidence-supported interventions that address the key characteristics identified in the analysis conducted throughout the thesis.

The conclusions derived from this work will be presented throughout this section. Firstly, the hypothesis stated in Chapter 1, Introduction, is as follows: “It is hypothesized that non-invasive diagnostic methods, encompassing both morphological and functional approaches, are effective for assessing muscle quality in older adults, enabling their routine application in community settings and the identification of essential factors for the design of exercise protocols to enhance muscle quality and functionality”.

Based on the findings of this thesis, it can be affirmed that the proposed hypothesis is largely supported. The results indicate that, among the morphological measures for quantifying muscle quality in older adults, US and MRI are the most used for direct assessment after an exercise intervention. Other methods include CT, EMG, myotonometry, and BIA. Additionally, US stands out as an emerging tool for direct muscle quality assessment, driven by ongoing technological advancements.

Current research frequently integrates direct assessments of muscle quality with indirect methods and functional capacity tests. Within this framework, the heterogeneity in defining muscle quality in the functional domain arises from methodological variability in strength and muscle mass assessment, despite a common conceptual foundation linking strength to the muscle mass-to-strength ratio (Cruz-Jentoft et al., 2019; de Lucena Alves et al., 2023; Virto, Río, Méndez-Zorrilla, et al., 2024). The findings of this thesis work indicate that while hand-held dynamometry and 1RM testing are feasible for community-based applications, isokinetic dynamometry and power assessments, despite their superior precision, remain specialized tools. Regarding muscle mass evaluation, reference techniques such as MRI and DXA offer high

accuracy but are constrained by cost, whereas alternative methods like BIA and ultrasound provide more accessible and cost-efficient options for broader implementation (Albano et al., 2020; Blake & Fogelman, 2007; Correa-de-Araujo et al., 2017; Cruz-Jentoft et al., 2019; Faron et al., 2020; Jain & Vokes, 2017; Niklasson et al., 2022; Oba et al., 2021; Sconfienza et al., 2018).

In relation to the determinants of muscle quality, this study has identified that, in older women, muscle mass, fat mass and functional performance (gait speed, squat time, including the importance of power and balance) are significant predictors of muscle quality. On the other hand, in men, factors such as age, BMI, squat time and balance were relevant, although the hypothesis in men could not be fully clarified due to the smaller male sample and lower variability in their performance measures, which may have influenced the predictive power of the model.

The following is a summary of the contributions made in this doctoral thesis within the field of muscle quality in older adults. These contributions provide insights into the research questions posed in chapter 1 of the introduction and are structured accordingly:

*- How can muscle quality be best assessed non-invasively in older adults? What are the most effective indicators of muscle quality predicting outcomes and analyzing the effects of exercise interventions? What factors, such as cost, accessibility, required training, and the distinctions between direct (morphological) and indirect (functional) non-invasive tools, influence the adoption and implementation of muscle quality assessments?.*

In this thesis, the non-invasive assessment of muscle quality in older adults has been thoroughly investigated, establishing a crucial differentiation between the morphological (direct non-invasive measurement) and functional (indirect non-invasive measurement) domains of muscle quality. This distinction has allowed a more precise analysis of the available tools, highlighting that the choice of methodology depends not only on the domain assessed, but also on practical factors such as cost, accessibility and the training required for its correct application. In addition, the most appropriate tools for measuring each key variable and indicator of muscle quality have been identified, helping to fill the knowledge gaps identified as priorities by EWGSOP (Cruz-Jentoft et al., 2019).

As for the morphological domain, it is characterised by a focus on direct assessments of muscle architecture, considering both microscopic and macroscopic characteristics of the muscle structure, as well as its composition (e.g., amount of muscle tissue, fat infiltration, water content) (Coronado-Zarco & de León, 2023; de Lucena Alves et al., 2023; M. Fragala et al., 2015). The following table presents the most effective tools for assessing morphological muscle quality, along with the key indicators associated with each tool for predicting muscle quality and robustly analysing the effects of exercise interventions. On the other hand, ultrasound is presented as a rapid, non-invasive and accessible modality to assess muscle architecture, with good correlation with other imaging techniques (Correa-de-Araujo et al., 2017; Price & Earthman, 2019; Sconfienza et al., 2018). Although international guidelines acknowledge its potential, the lack of standardization and reliance on operator expertise constrain its use for the early detection of muscle quality loss (Cruz-Jentoft & Sayer, 2019; Lopez-Lopez et al., 2021; Perkisas et al., 2018).

Table 17. Specific outcomes measured to assess morphological muscle quality using non-invasive tools.

Tool	Outcomes Measured	Advantages	Disadvantages
Magnetic Resonance Imaging (Correa-de-Araujo et al., 2017; Faron et al., 2020; Niklasson et al., 2022; Oba et al., 2021)	Intramuscular fat infiltration, cross-sectional area, intermuscular adipose tissue.	<ul style="list-style-type: none"> <li>- The most accurate tool for measuring composition (muscle volume and quality).</li> <li>- No radiation exposure.</li> <li>- Very high validity.</li> <li>- Quantitative and qualitative assessment.</li> </ul>	<ul style="list-style-type: none"> <li>- Very costly and not accessible for most community studies.</li> <li>- Operational complexity, non portable equipment and training requirements.</li> </ul>
Computed Tomography (Correa-de-Araujo et al., 2017; Faron et al., 2020; Niklasson et al., 2022; Oba et al., 2021)	Intramuscular fat infiltration, cross-sectional area, muscle density.	<ul style="list-style-type: none"> <li>- High validity and accuracy in the assessment of muscle quality.</li> <li>- Quantitative and qualitative assessment.</li> </ul>	<ul style="list-style-type: none"> <li>- High cost and radiation exposure.</li> <li>- Not routinely applicable in community studies.</li> <li>- Non portable</li> </ul>
Ultrasonography (Bartley & Studenski, 2017; Correa-de-Araujo et al., 2017; Dubois et al., 2018; Lopez-Lopez et al., 2021; Patil & Dasgupta, 2012; Perkisas et al., 2018; Ruby et al., 2021; Sconfienza et al., 2018)	Cross-sectional area, echo intensity, echo variation, fascicle length, pennation angle.	<ul style="list-style-type: none"> <li>- It measures muscle architecture as an accurate marker of muscle quality.</li> <li>- Good precision.</li> <li>- It is non-invasive, no radiation, fast and can be portable.</li> </ul>	<ul style="list-style-type: none"> <li>- Measurements highly dependent on operator expertise.</li> <li>- Intermachine and interoperator variability.</li> <li>- Intermediate cost and technical training requirement.</li> </ul>
Bioelectrical Impedance Analysis (Cruz-Jentoft et al., 2019; Di Vincenzo et al., 2021; Sergi et al., 2016)	Phase Angle (PhA)	<ul style="list-style-type: none"> <li>- Recently recognized as a key predictor of muscle quality.</li> <li>- Non-invasive, quick, and accessible technique.</li> </ul>	<ul style="list-style-type: none"> <li>- Lower accuracy compared to tools such as MRI or CT.</li> <li>- Sensitive to external variables (hydration, temperature).</li> </ul>
Tensiomyography (Brazier et al., 2014; Ćular et al., 2023; Ilahi et al., 2020; Lohr et al., 2019; McGowen et al., 2022; Morgan et al., 2019; White et al., 2018; Wilson et al., 2023).	Muscle contractile properties (contraction time and maximal radial displacement), muscle tone.	<ul style="list-style-type: none"> <li>-Non-invasive, measures muscles mechanical properties.</li> <li>- Sensitive to changes in muscle composition, architecture, and pre-atrophy of skeletal muscles</li> <li>-Reproducible and relatively portable</li> </ul>	<ul style="list-style-type: none"> <li>- Specialized equipment and need of operator expertise.</li> <li>- Standardization issues.</li> <li>- Not widely available due to their cost</li> </ul>
Myotonometry (Brazier et al., 2014; Ćular et al., 2023; Ilahi et al., 2020; Lohr et al., 2019; McGowen et al., 2022; Morgan et al., 2019; White et al., 2018; Wilson et al., 2023).	Muscle stiffness, compliance, elasticity.	<ul style="list-style-type: none"> <li>- Compared to TMG, fast, portable and cost-effective, displaying higher reliability and validity for differentiating muscle stiffness levels.</li> </ul>	<ul style="list-style-type: none"> <li>- Need of validation for its routine clinical application.</li> <li>- Limited depth and adipose tissue interference.</li> </ul>

The literature shows a remarkable diversity in approaches for the direct assessment of muscle quality, two of the tools mainly used in the quantification of muscle quality are ultrasound and MRI. In particular, ultrasound emerges as a promising method for skeletal muscle assessment, as it offers a more accessible and cost-effective alternative to MRI. However, it emphasises the need for further research into its clinical application to ensure consistent and validated measurements in various population contexts.

In the functional assessment of muscle quality in older adults, various non-invasive techniques are available, with accessible technologies gaining popularity in both clinical and community settings. Hand-held dynamometry and 1RM testing are among the most practical and widely applicable strength assessment tools, particularly for community-based use. In contrast, power assessments and isokinetic dynamometry, while offering greater precision, are more specialized and less feasible for routine application outside clinical or research environments. Regarding muscle mass evaluation, reference methods such as MRI, DXA, and CT provide high validity and accuracy; however, their cost and complexity often limit their widespread implementation. More accessible alternatives, such as BIA and US, offer scalable and cost-effective solutions, making them well-suited for community-based applications (Albano et al., 2020; Blake & Fogelman, 2007; Correa-de-Araujo et al., 2017; Cruz-Jentoft et al., 2019; Faron et al., 2020; Jain & Vokes, 2017; Niklasson et al., 2022; Oba et al., 2021; Sconfienza et al., 2018).

In conclusion, a comprehensive assessment of muscle quality should integrate both morphological and functional measurements, as each provides complementary and essential information. However, when considering the resources required for each type of assessment, indirect methods for quantifying functional muscle quality emerge as the most accessible and feasible option in settings with budgetary and personnel constraints. These methods not only require less infrastructure but also demand minimal specialized training, facilitating their implementation in both community and clinical environments with limited resources. Conversely, in settings with greater financial capacity and trained personnel, the combination of morphological and functional assessments represents the optimal approach, offering a more thorough evaluation of muscle quality. This approach is summarised in Figure 10, which provides a visual representation of the proposed framework for assessing muscle quality across different contexts.

*- Can novel methods using advanced non-invasive tools and machine learning techniques improve our understanding and application of key muscle quality determinants in older adults in clinical practice?.*

New optimisation methods using advanced non-invasive tools may represent a significant advance towards a more efficient and effective approach to muscle quality assessment. As highlighted in chapter 2, sarcopenia and muscle quality measurements are under-diagnosed (Cruz-Jentoft & Sayer, 2019; Sánchez Tocino et al., 2024) due to the lack of consolidated diagnostic criteria and heterogeneity in measurement tools. However, the emerging consolidation of advanced methods, such as ultrasound, offers a promising solution.

The use of portable and non-invasive technologies, such as ultrasound, facilitates the implementation of clinical protocols in hospital and primary care settings, improving access and applicability of muscle quality assessments. In addition, the correlation between ultrasound-derived geometric parameters and functional variables allows optimisation of muscle quality assessment strategies in community practice. This not only enables more accurate and accessible assessments, but also promotes early intervention and ongoing monitoring of muscle health in older adults, directly addressing current limitations in the diagnosis and management of sarcopenia.

*- What specific factors significantly influence sarcopenia, muscle quality, and functionality?*

This thesis has comprehensively assessed the factors influencing sarcopenia, muscle quality and functionality in older adults, highlighting its multifactorial profile, which involves complex interactions between biological, functional and social factors. Our analyses indicate that the most important variables in the diagnosis of sarcopenia are influenced by key factors such as loss of muscle power, advanced age, strength, body mass index (BMI), and gender. Additionally, balance, muscle and fat mass, as well as socioeconomic status, significantly affect the development and severity of the condition. Regarding muscle quality, our detailed analysis revealed that, for women, the final regression model included age, BMI, muscle mass, fat mass, performance in the 4-meter walk test, time in the squat test, balance, and socioeconomic background (classified into two groups).

Functionality, on the other hand, was assessed primarily by gait speed, which is recognised as a vital sign and non-invasive predictor of health status and functionality in older adults (Middleton et al., 2015). Age was found to significantly predict gait speed decline, in line with age-related declines in neuromuscular and cognitive function. In addition, lower limb power was highlighted as a key marker. Better balance was also associated with higher walking speeds, highlighting the importance of balance-focused interventions to improve mobility.

These determinants provide valuable information on muscle quality and functionality in older adults, allowing the design of specific and effective interventions that address these markers, contributing to a more accurate and personalised approach to the assessment and management of musculoskeletal pathologies and functionality in clinical and community practice.

*- How can an evidence-based exercise protocol be developed and implemented to effectively assess and improve muscle quality in older adults, integrating non-invasive measurement tools and tailored physical activity interventions in both clinical and community settings?.*

To develop and implement an evidence-based exercise protocol that effectively assesses and improves muscle quality in older adults, it is crucial to integrate non-invasive measurement tools and tailor physical activity interventions to the most relevant determinants of muscle quality. As demonstrated in this work, muscle quality encompasses multiple domains, so it is essential to use a multidimensional approach that combines various non-invasive measurement tools.

Different measurement strategies are proposed based on a decision-making process, which is detailed in the results chapter (Figure 10. Key parameters for the election of muscle quality assessment methods). This process takes into account key factors such as tool accessibility, measurement accuracy, available budget, training requirements, and the need to assess both morphological and functional outcomes. To bring these measurements closer to community practice, tools such as ultrasound for analyzing muscle architecture, bioimpedance analysis (BIA) to assess phase angle and body composition, and functional tests to measure strength and generate the muscle quality index (strength relative to mass) are recommended. These tools, in addition to being accessible and cost-effective, allow for a comprehensive and effective assessment of muscle quality in various settings, both clinical and community-based.

On the other hand, regarding the exercise intervention, by understanding the specific factors that most significantly influence muscle quality, such as muscle power, balance, body composition, and socioeconomic context, the exercise protocol has been adapted to address these determinants. While some of these specific elements are non-modifiable, such as sex or age, the focus of the study is on intervening in variables that are susceptible to improvement through multicomponent physical exercise programs. These programs should integrate strength, power, walking, and balance training, following principles such as FITT. Additionally, specific challenges, such as low adherence to health programs among men, are addressed by proposing potential strategies to improve the low participation rates of men in these programs (Campbell et al., 2019; Medicine, 2013; Medicine et al., 2018; Ozemek et al., 2025).

A multicomponent training approach for older adults should include resistance training as a core component, as it is essential for maintaining independence and aging successfully. Exercises involving one or more joints, performed with free weights, machines, or bodyweight, should focus on moderate to moderately high loads (60%-75% 1-RM) with 8-12 repetitions per set, avoiding fatigue and muscular failure. Power training, which emphasizes the rapid application of force, is equally important, as declines in muscle power precede reductions in strength and muscle mass in older adults. To optimize power, concentric actions should be performed swiftly with a controlled eccentric phase, using loads of 30-45% 1-RM for upper body exercises and 60-70% 1-RM for lower body movements. For frail individuals, loads can be reduced to 40-60% 1-RM to better match their initial capabilities, as moderate loads have also shown benefits. Additionally, balance and gait training should progressively increase in complexity, incorporating techniques such as dual-tasking and altering the base of support. Aerobic exercise should start with basic strength development and progressively increase in intensity. The exercise protocol aims to improve muscle strength and power, mitigate age-related muscle mass decline, and optimize key metabolic parameters like fat mass, muscle mass, and BMI to counteract sarcopenia and improve overall physical function (Campbell et al., 2019; Medicine, 2013; Medicine et al., 2018; Ozemek et al., 2025).

## 7.1 Limitations and Future research:

While the present study provides valuable insights into the evaluation of muscle quality in older adults, several limitations must be acknowledged. This section will identify these limitations and provide suggestions for future research to address these.

Firstly, although a comprehensive assessment of non-invasive tools was conducted, the absence of a standardized gold standard for muscle quality evaluation represents a significant limitation. This lack of consensus and the diversity in the evaluation methods leads to variability in the parameters measured across studies, complicating direct comparisons with other studies that use similar methodologies but assess different key indicators of muscle quality. Also, studies that did not explicitly mention muscle quality in their title or abstract, or those that defined muscle quality differently from pre-established definitions, may have been excluded.

On the other hand, in the first case study, although ultrasound was identified as a promising method for assessing skeletal muscle, its use may be influenced by the lack of standardised protocols and operator dependence, which could introduce variability in measurements. Similarly, in the following investigations, the use of an MQI based on the strength-to-mass ratio primarily focuses on one aspect of muscle quality, leaving room to explore other relevant dimensions that could provide a more nuanced understanding. Nevertheless, these results serve as a fundamental basis to implement further research aimed at expanding the current knowledge. So, the crucial aspect for this line of future research would be the validation of a single functional muscle quality index that can be used in a standardized manner across community studies. This would enable more robust comparisons between different studies using non-invasive tools to measure muscle quality and, in turn, facilitate the implementation of interventions in communities with limited infrastructure.

Moreover, in the 4,5 and 6 analysis the relatively small number of male participants limits the ability to generalize the results to a broader male population. Additionally, the sample lacks sufficient diversity, with most participants being Basque, which introduces a potential bias due to shared demographic, racial, and physiological characteristics. This homogeneity may not reflect the variability found in more diverse populations. Furthermore, a limitation of this study is the reliance on a muscle quality index based solely on the strength-to-mass ratio, which does not consider other key aspects of muscle quality, such as muscle composition, architecture, and ultrastructure. Incorporating these additional dimensions could provide a more comprehensive and accurate understanding of muscle quality, potentially offering new avenues for improving diagnostic accuracy and treatment strategies. In the context of future research, it is suggested to apply the findings of this study to a cohort of older adults in order to evaluate the effectiveness of an exercise program based on the recommendations presented in this work, with particular emphasis on the key features identified as determinants for improving muscle quality. The goal would be to replicate this study in a community setting, which would allow for testing the feasibility and effectiveness of interventions designed to promote musculoskeletal health in this population. Additionally, the simultaneous evaluation of muscle quality from both morphological and functional approaches should be considered, aiming to compare which of these methods is more sensitive to exercise-induced changes. The comparison of both domains could provide a deeper understanding of the dynamics between muscle quality and functionality in older adults, as well as identify the most suitable method for monitoring them in community contexts.

Future studies could build on the findings of this research by incorporating the knowledge gained about muscle quality assessment into the development of more comprehensive assessment tools and methodologies. Expanding the scope of the study to include a wider range of dimensions of muscle quality, such as muscle composition, architecture and ultrastructure, could provide a more nuanced understanding of muscle function.

## 8 Contributions

In addition to the scientific publications that underpin this research, this section presents additional work derived from the knowledge acquired in the area throughout this doctoral thesis. These collaborative publications, developed with other researchers, are listed below.

### 8.1 Scientific contributions.

Table 18. Publication I - International Journal with Impact Factor

<b>Title</b>	Effects of a 12-week exercise intervention on glycated hemoglobin (HbA1c) levels in cancer patients.		
<b>Authors</b>	Virto, N., Etayo-Urtasun, P., Isla, J. R. S., Arietanzbeaskoa, M. S., Gallastegui, N. M., Grandes, G., ... & Río, X.		
<b>Journal</b>	Retos		
<b>IF</b>	Quartile	SJR: Q2	
<b>Date</b>	30 Jan 2023		
<b>DOI</b>	<a href="https://doi.org/10.47197/retos.v48.96221">https://doi.org/10.47197/retos.v48.96221</a>		

Table 19. Publication II - International Journal with Impact Factor

<b>Title</b>	Development of Continuous Assessment of Muscle Quality and Frailty in Older Patients Using Multiparametric Combinations of Ultrasound and Blood Biomarkers: Protocol for the ECOFRAIL Study.		
<b>Authors</b>	Virto N, Río X, Angulo-Garay G, García Molina R, Avendaño Céspedes A, Cortés Zamora E, Gómez Jiménez E, Alcantud Córcoles R, Rodríguez Mañas L, Costa-Grille A, Matheu A, Marcos-Pérez D, Lazcano U, Vergara I, Arjona L, Saeteros M, Lopez-de-Ipiña D, Coca A, Abizanda Soler P, Sanabria S.		
<b>Journal</b>	JMIR Research Protocols		
<b>IF</b>	Quartile	SJR: Q3	
<b>Date</b>	23 Feb 2024		
<b>DOI</b>	<a href="https://doi.org/10.47197/retos.v48.96221">https://doi.org/10.47197/retos.v48.96221</a>		

Table 20. Publication III - International Journal with Impact Factor

<b>Title</b>	Ultrasound quantitative monitoring of muscle quality changes in sarcopenia patients after supervised exercise intervention	
<b>Authors</b>	Morelva Saeteros, Naiara Virto, Ignacio Oyarzábal, Xabier Río de Frutos, Rafael García, Almudena Avendaño, Elisa Belén Cortés, Elena Gómez, Pedro Abizanda, Leocadio Rodríguez-Mañas, Ander Matheu, Uxue Lazcano, Itziar Vergara, Laura Arjona, Aitor Coca, Sergio J Sanabria	
<b>Journal</b>	IEEE International Ultrasonics Symposium	
<b>IF</b>	Quartile	
<b>Date</b>	3 Sept 2023	
<b>DOI</b>	10.1109/IUS51837.2023.10307573	

Table 21. Thesis Publication I - International Journal with Impact Factor

<b>Title</b>	Non invasive techniques for direct muscle quality assessment after exercise intervention in older adults: a systematic review.	
<b>Authors</b>	Virto, N., Río, X., Méndez-Zorrilla, A., & García-Zapirain, B.	
<b>Journal</b>	BMC Geriatrics	
<b>IF</b>	Quartile	SJR: Q1
<b>Date</b>	31 July 2024	
<b>DOI</b>	10.1186/s12877-024-05243-3	

Table 22. Thesis Publication III - International Journal with Impact Factor

<b>Title</b>	Gait speed in older adults: exploring the impact of functional, physical and social factors.	
<b>Authors</b>	Virto, N., Río, X. ., Muñoz-Pérez, I., Méndez-Zorrilla, A. ., & García-Zapirain, B.	
<b>Journal</b>	Retos	
<b>IF</b>	Quartile	SJR: Q2
<b>Date</b>	31 July 2024	
<b>DOI</b>	<a href="https://doi.org/10.47197/retos.v61.109902">https://doi.org/10.47197/retos.v61.109902</a>	

Table 23. Publication VI - International Journal with Impact Factor

<b>Title</b>	Effects of 12 weeks of short-duration isometric strength training in university students	
<b>Authors</b>	Leguina, A. S., Mojas, E., Virto, N., Fernández, J. R., Gómez, R., & Río, X.	
<b>Journal</b>	European Journal of Human Movement	
<b>IF</b>	Quartile	SJR: Q3
<b>Date</b>	30 June 2024	
<b>DOI</b>	<a href="https://doi.org/10.21134/eurjhm.2024.52.8">https://doi.org/10.21134/eurjhm.2024.52.8</a>	

Table 24. Publication VII - Deusto Engineering Journal

<b>Title</b>	Evaluación continua de fragilidad muscular en sujetos mayores mediante inteligencia artificial aplicada a ecografía y biomarcadores	
<b>Authors</b>	Saeteros Ortiz, Celida Morelva; Virto Castro, Naiara; Río De Frutos, Xabier; Arjona Aguilera, Laura; Sanabria Martín, Sergio José; Lopez De Ipiña Gonzalez De Artaza, Diego	
<b>Journal</b>	European Journal of Human Movement	
<b>Date</b>	2024	

Table 25. Thesis Publication III - International Journal with Impact Factor

<b>Title</b>	Exploring determinant factors influencing muscle quality and sarcopenia in Bilbao's older adult population through machine learning: A comprehensive analysis approach.		
<b>Authors</b>	Naiara Virto, Danielle Marie Dequin, Xabier Río, Amaia Méndez-Zorrilla, Begoña García-Zapirain		
<b>Journal</b>	Plos One		
<b>IF</b>		Quartile	SJR: Q1
<b>Date</b>	31 Dec 2024		
<b>DOI</b>	10.1371/journal.pone.0316174		

## 8.2 Communication contributions:

Table 26. Publication I - Conference

<b>Title</b>	Ultrasound quantitative evaluation of morphometric changes in rectus femoris after a 16-week supervised exercise programme in elderly frail subjects.
<b>Authors</b>	Presented by Naiara Virto. Naiara Virto, Xabier R��o, Garazi Angulo, Rafael Garc��a Molina, Almudena Avenda��o C��spedes, Elisa Belen Cort��s Zamora, Elena G��mez Jimenez, Pedro Abizanda Soler, Leocadio Rodriguez Ma��nas, Ander Matheu, Uxue Lazcano, Itziar Vergara, Laura Arjona, Morelva Saeteros, Aitor Coca, Sergio J Sanabria.
<b>Conference</b>	International Conference on Frailty & Sarcopenia Research
<b>Date and Place</b>	22-24 March 2023, Toulouse.

Table 27. Publication II - Conference

<b>Title</b>	Point-of-care automatic assessment of muscle morphometry for sarcopenia monitoring in community care based on automatic U-Net segmentation of rectus femoris.
<b>Authors</b>	Morelva Saeteros, Laura Arjona, Naiara Virto, Xabier R��o, Rafael Garc��a,, Almudena Avenda��o, Elisa Bel��n Cort��s, Elena G��mez, Esther L��pez, Marta Neira, Raquel Ram��rez, Cristina Alonso, Concha Grau, Patricia P��rez, Mar��a Alcantara, Mar��a Alcantud, Carmen Rosa Hern��ndez, Diego L��pez-de-Ipi��a, Pedro Abizanda, Leocadio Rodr��guez, Ander Matheu, Itziar Vergara, Aitor Coca, Sergio J Sanabria.
<b>Conference</b>	International Conference on Frailty & Sarcopenia Research
<b>Date and Place</b>	22-24 March 2023, Toulouse.

Table 28. Publication III – Conference

<b>Title</b>	Evaluación Ecográfica De Cambios Morfométricos Del Recto Femoral Tras Intervención De Programa De Ejercicio Supervisado En Adultos Mayores Frágiles.
<b>Authors</b>	Virto, Naiara; Río De Frutos, Xabier; García, Rafael; Gómez, Elena; Abizanda, Pedro; Sanabria, Sergio.
<b>Conference</b>	Sociedad Castellano Manchega de Geriatria y Gerontología
<b>Date and Place</b>	3-4 March 2023, Toledo.

Table 29. Publication IV - Conference

<b>Title</b>	Efectos de 12 semanas de entrenamiento de fuerza isométrica de corta duración en la Hemoglobina glicada (HbA1c) en estudiantes universitarios.
<b>Authors</b>	Virto, N, Mojas, E, Fernández, R, Roberto Gómez, R, Santisteban, A , Río, X.
<b>Conference</b>	Congreso Internacional de la Asociación Española del Deporte
<b>Date and Place</b>	21-24 June 2023, Madrid.

Table 30. Publication V - Conference

<b>Title</b>	Efectos de 12 semanas de entrenamiento de fuerza isométrica de corta duración en el ángulo de fase.
<b>Authors</b>	Moja, E , Virto, V, Fernández, R, Roberto Gómez, R, Santisteban, A , Río, X.
<b>Conference</b>	Congreso Internacional de la Asociación Española del Deporte
<b>Date and Place</b>	21-24 June 2023, Madrid.

Table 31. Publication VI - Conference

<b>Title</b>	Physical exercise, physical function and geometric muscle ultrasound. ecofrail study.
<b>Authors</b>	López Jiménez, Esther; Morelva Saeteros Ortiz, Celida; Marcos Pérez, Diego; Costa Grille, Alba; Martínez Sánchez, Esther; Paterna Mellinas, Gema; García Molina, Rafael; Alcantud Córcoles, Rubén; Virto Castro, Naiara; Cruces Salguero, Sara; Rodríguez Mañas, Leocadio; Matheu Fernández, Ander; Sanabria Martín, Sergio José; Abizanda, Pedro.
<b>Conference</b>	European Geriatric Medicine Society Congress,
<b>Date and Place</b>	18-20 September 2024, Valencia.

Table 32. Publication VIII - Conference

<b>Title</b>	Muscle ultrasound and physical function. ecofrail study.
<b>Authors</b>	López Jiménez, Esther; Morelva Saeteros Ortiz, Celida; Marcos Pérez, Diego; Costa Grille, Alba; Martínez Sánchez, Esther; Paterna Mellinas, Gema; García Molina, Rafael; Alcantud Córcoles, Rubén; Virto Castro, Naiara; Cruces Salguero, Sara; Rodríguez Mañas, Leocadio; Matheu Fernández, Ander; Sanabria Martín, Sergio José; Abizanda, Pedro.
<b>Conference</b>	European Geriatric Medicine Society Congress,
<b>Date and Place</b>	18-20 September 2024, Valencia.

Table 33. Publication VII - Conference

<b>Title</b>	Ultrasound quantitative monitoring of muscle quality changes in sarcopenia patients after supervised exercise intervention
<b>Authors</b>	Morelva Saeteros, Naiara Virto, Ignacio Oyarzábal, Xabier Río de Frutos, Rafael García, Almudena Avendaño, Elisa Belén Cortés, Elena Gómez, Pedro Abizanda, Leocadio Rodríguez-Mañas, Ander Matheu, Uxue Lazcano, Itziar Vergara, Laura Arjona, Aitor Coca, Sergio J Sanabria
<b>Conference</b>	IEEE International Ultrasonics Symposium
<b>Date and Place</b>	3 Sept, 2023, Canada.

### 8.3 Other scientific activities:

Table 34. Other scientific activities

Other scientific activities (reviews...)	
2023	Summer School Liège (September 17-23, 2023) Certificate of membership in the AFDySalud research team Certificate of membership in the eVida research team
2024	Review activity for "The Journal of Frailty & Aging"
2024	Review activity for "Retos"
2025	Review activity for "The Journal of Frailty & Aging"
2024	International stay, Ruhr University Bochum (Germany)

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## 10 Annex

### 10.1 Annex 1

 <p>GERENCIA DE ATENCIÓN INTEGRADA DE ALBACETE</p>	<b>COMITÉ DE ÉTICA DE LA INVESTIGACIÓN CON MEDICAMENTOS</b>	Informe Conformidad del CEIm
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D<sup>ña</sup>. Karen Nieto Rodríguez, Vicepresidenta del Comité de Ética de la Investigación con Medicamentos de la Gerencia de Atención Integrada de Albacete

#### INFORMA

Que este Comité en su reunión de fecha 21 de diciembre de 2021, Acta 11/2021, evaluó el proyecto con código interno N<sup>o</sup> 2021-151.

**TITULADO: DESARROLLO DE EVALUACIÓN CONTINUA DE LA FRAGILIDAD Y LA CALIDAD MUSCULAR EN SUJETOS MAYORES MEDIANTE ÓMICAS MULTI-PARAMÉTRICAS BASADAS EN ECOGRAFÍA Y ANALÍTICA DE SANGRE. ESTUDIO ECOFRAIL.**

Investigador Principal: **D. Pedro Abizanda Soler.**

Considera que: Se cumplen los requisitos necesarios de idoneidad del proyecto en relación con los objetivos del estudio.

La capacidad del investigador y los medios disponibles son apropiados para llevar a cabo el estudio. Es adecuado el procedimiento para obtener el consentimiento informado.

Revisadas las aclaraciones por la Comisión Permanente del CEIm, esta emite: **INFORME FAVORABLE.**

Este Comité en sus funciones, composición y en los PNT's cumple con las normas de BPC-CPMP/ICH/135/95 y el Real Decreto 1090/2015 y que su composición actual es la siguiente:

En el caso de que algún miembro participe en un estudio bien como investigador, colaborador o tenga algún conflicto de interés, no habrá participado ni en la evaluación ni en el dictamen de autorización del mismo, en cumplimiento de la normativa legal.

**D. Pedro Abizanda Soler**  
**D<sup>ña</sup> Karen Nieto Rodríguez**  
**D<sup>ña</sup>. M<sup>ra</sup> Ángeles Lloret Callejo**  
**D. Juan José Nuñez Tintero**  
**D. Fernando Andrés Pretel**  
**D<sup>ña</sup>. Dolores Jativa Gascó**  
**D<sup>ña</sup>. Pilar Córcoles Jiménez**  
**D<sup>ña</sup>. Syonghyun Nam Cha**  
**D<sup>ña</sup>. María Soledad Fernández de Córdoba**  
**D<sup>ña</sup>. Carmen Díaz Delgado**  
**D. Alberto Sánchez Romero**  
**D. Ignacio Parraga Martínez**  
**D<sup>ña</sup>. M<sup>ra</sup>. del Carmen Carrascosa Romero**  
**D. Manuel Gerónimo Pardo**  
**D<sup>ña</sup>. Luisa María Charco Roca**  
**D. Jesús López-Torres Hidalgo**  
**D. Sebastián Sabater Martí**  
**D. Raúl Godoy Mayoral**  
**D. Francisco Javier Callejas González**  
**D<sup>ña</sup>. María Rosa Ortiz Navarro**  
**D<sup>ña</sup>. Belén Serna Serrano**  
**D<sup>ña</sup>. Cristina del Pozo Carlavilla**

**PRESIDENTE.** Dr. en Medicina. S. Geriátría.  
**VICEPRESIDENTA.** Dra. en Psiquiatría. S. Psiquiatría  
**SECRETARÍA TÉCNICA.** Licenciada en Farmacia. S. Farmacia Atención Primaria  
Licenciado en Derecho. Ajeno a la profesión sanitaria  
Ingeniero Técnico Informático de Gestión.  
Vocal representante de los pacientes. Ajeno a la profesión sanitaria  
Diplomada en Enfermería. Supervisora de Investigación y Docencia  
Licenciada en Medicina. S. Anatomía Patológica.  
Dra. en Medicina. S. Cirugía Pedlátrica  
Dra. en Biología. Profesora Titular de Histología UCLM  
Dr. en Medicina. S. Farmacología Clínica  
Dr. en Medicina. Centro de Salud La Roda  
Licenciada en Medicina. S. Pediatría  
Dr. en Medicina. S. Anestesiología  
Licenciada en Medicina. S. Anestesiología y Reanimación  
Dr. en Medicina. Centro de Salud Zona VIII  
Dr. en Medicina. S. Oncología Radioterápica  
Dr. en Medicina. S. Neumología  
Dr. en Medicina. S. Neumología  
Licenciada en Farmacia. Farmacia Hospitalaria  
Residente de Farmacia Hospitalaria  
Residente de Farmacia Hospitalaria

Albacete, 17 de enero de 2022

Fdo.: Karen Nieto Rodríguez



## 10.2 Annex 2



**DICTAMEN DEL COMITÉ DE ÉTICA EN LA INVESTIGACIÓN DE LA  
UNIVERSIDAD DE DEUSTO**  
Ref: ETK-32/18-19

Tras la evaluación del proyecto de tesis Funcionalidad y prevalencia de la fragilidad en el programa de salud del Ayuntamiento de Bilbao, realizada por D. Xabier Rio de Frutos, y que el Dr. D. Aitor Coca Nuñez presenta para su evaluación, en calidad de Investigador Principal y Responsable de Investigación del Equipo de Ciencias de la Actividad Física y del Deporte de la Facultad de Psicología y Educación, el Comité de Ética en Investigación de la Universidad de Deusto, tal y como se hace constar en el acta de la reunión del 4 de abril de 2019 en la que se tomó el acuerdo, emite un **INFORME FAVORABLE**.

El Comité de Ética en Investigación considera que desde el punto de vista ético el proyecto es adecuado en todo lo referente a la protección y evitación de riesgos a los participantes y el respeto a la autonomía. Asimismo, se ajusta a los principios metodológicos, éticos y jurídicos que debe tener este tipo de investigación. No se observan riesgos de ningún tipo para los participantes y se establecen medidas adecuadas que ofrecen suficientes garantías éticas durante su desarrollo.

El proyecto tiene en cuenta la regulación sobre de protección de datos personales (UE 2016/679) aprobada por la Comisión y el Consejo de la UE en abril de 2016 en relación al i) procedimiento de consentimiento informado; ii) acceso a datos personales; iii) el uso de datos para el interés público; y iv) las responsabilidades de los investigadores responsables del proyecto.

El Comité de Ética ha examinado toda la documentación para recabar el consentimiento, en el que se facilita de manera adecuada toda la información necesaria para la participación, garantizando el cumplimiento de todas las exigencias éticas de consentimiento y confidencialidad.

Y para que así conste,

Dra. Dña. Cristina de la Cruz Ayuso  
Coordinadora de la Comisión de Ética en Investigación  
Universidad de Deusto

En Bilbao a 5 de Abril de 2019