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The impact of obesity on muscle function in older adults: from clinical evaluation to lifestyle management

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Coordinator: Prof. Giovanni Targher

Tutor: Prof. Mauro Zamboni
Co-tutor: Prof. Andrea P. Rossi

Doctoral Student: Valentina Muollo

The impact of obesity on muscle function in older adults: from clinical evaluation to lifestyle management
– Valentina Muollo

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Author's address

Valentina Muollo
Department of Medicine
University of Verona, Italy
valentina.muollo@univr.it

Supervisor

Prof. Mauro Zamboni
Department of Medicine
University of Verona, Italy
mauro.zamboni@univr.it

Co-supervisor

Prof. Andrea P. Rossi
Department of Medicine
University of Treviso, Italy
andrea.rossi@aulss 2.veneto.it

Reviewers

Prof. Per Aagard
Department of Sports Science and Clinical Biomechanics
University of Southern Denmark, Odense, Denmark
paagaard@health.sdu.dk

Prof. Massimo Pellegrini
Department of Biomedical, Metabolical and Neural Sciences
University of Modena and Reggio Emilia
massimo.pellegrini@unimore.it

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SOMMARIO

Nella popolazione geriatrica l'obesità e la sarcopenia rappresentano due problematiche rilevanti per la sanità pubblica a causa della loro associazione con la probabilità di incorrere nella sindrome di fragilità, perdita di mobilità o indipendenza e l'alto rischio di mortalità. Negli studi precedenti, poca attenzione è stata rivolta all'impatto dell'obesità sulla forza muscolare, sulla potenza e sulla funzione fisica degli arti inferiori nella popolazione anziana. Ciò è sorprendente dato che il maggior declino fisiologico colpisce la parte inferiore del corpo con conseguenze negative soprattutto nella capacità di svolgere diverse attività della vita quotidiana. Inoltre, per la valutazione della debolezza muscolare, il possible contributo dei muscoli degli arti inferiori è stato scarsamente studiato. Infine, anche se esistono vari studi sui possibili approcci per curare e migliorare la condizione di obesità e sarcopenia, vi sono attualmente delle discrepanze sugli effetti aggiuntivi dati dalla supplementazione rispetto al solo esercizio fisico. Questo lascia aperto il dibattito sui migliori trattamenti da adottare in questa popolazione. Pertanto, gli obiettivi di questa tesi stanno nel cercare di colmare tali lacune e nello specifico: *i)* determinare l'impatto dell'obesità sulla forza e sulla funzione muscolare degli arti inferiori in anziani di entrambi i sessi; *ii)* indagare le loro associazioni con l'handgrip ed il possibile contributo nel predirre la massa muscolare appendicolare; *iii)* proporre un protocollo di intervento volto a migliorare o contrastare la condizione di obesità sarcopenica nella popolazione geriatrica.

Nel primo capitolo, particolare enfasi viene posta sull'importante ruolo del mantenimento e della valutazione della forza muscolare, della massa muscolare e della performance fisica. Inoltre, viene fornita una panoramica generale sulle diverse strategie per trattare o contrastare l'obesità e la sarcopenia attraverso l'esercizio fisico e la nutrizione. Il secondo capitolo presenta le conseguenze dell' obesità sui muscoli degli arti inferiori, aggiungendo nuovi dati di riferimento sulla forza e la potenza degli estensori e dei flessori di ginocchio nella popolazione geriatrica di entrambi i sessi. Il terzo capitolo si concentra sugli strumenti utilizzati per valutare la debolezza muscolare. Qui, il ruolo dell'handgrip come surrogato della forza muscolare viene discusso attraverso una revisione critica della letteratura precedente e uno studio sperimentale. In quest'ultimo, vengono discusse

le associazioni tra forza muscolare degli arti superiori ed inferiori, osservando le possibili differenze in base al sesso. Il quarto capitolo descrive i risultati preliminari sul ruolo di cinque mesi di dieta controllata combinato all’allenamento della forza muscolare da solo o con integrazione di aminoacidici in anziani con obesità, dinapenia e sarcopenia. Dopo l’intervento, vengono descritti i cambiamenti su svariati outcomes (ad esempio la composizione corporea, la forza e la potenza muscolare degli arti superiori ed inferiori, la performance fisica) confrontando i diversi gruppi di intervento. Infine, il quinto capitolo delinea i principali risultati di ogni studio presentato, seguito da una conclusione generale con le indicazioni necessarie da sviluppare in futuro su questi argomenti di ricerca.

ABSTRACT

In the geriatric population, obesity and sarcopenia constitute two important public concerns due to their association with disability, loss of independence, comorbidity, and mortality. Only few studies previously evaluated the impact of obesity on the *in vivo* muscle strength, power, and physical function in the older population, particularly on the lower extremities. This is surprising, since particularly the decline of lower body physical function negatively affects important daily activities. In older adults the role of obesity and adipose tissue on muscle function decline is complex and not completely understood. Furthermore, the possible contribution of lower limb muscles in the evaluation of muscle weakness has been poorly investigated. Finally, various studies exist on the possible approaches using exercise and nutrition to treat and to ameliorate obesity, dynapenia and sarcopenia; discrepancies are instead presented on the potential beneficial effects associated with the supplementations compared to exercise alone, leaving open questions about the best treatments to adopt in this population. Therefore, the goals of this thesis are: *i)* to determine the impact of obesity on the *in vivo* lower limbs muscle strength and function in older adults of both sexes; *ii)* to investigate the associations between lower limbs muscle strength and function and the handgrip dynamometer and the possible contribution to predict the appendicular muscle mass; *iii)* to propose an intervention protocol aimed at improving or reversing obesity and sarcopenia condition.

Chapter one explored the literature around the effects of obesity in the geriatric population. A particular emphasis is made on the important role of maintaining and assessing muscle strength, muscle mass and function. Additionally, an overview of different strategies for treating or reversing obesity and sarcopenia through exercise and nutrition are provided. Chapter two presents the consequences of obesity on the lower limbs' muscles, adding new reference data of knee extensors and knee flexors strength and power in geriatric population of both sexes. Chapter three focuses on the tools used for evaluating muscle weakness. In this context, the role of handgrip dynamometer as a proxy of muscle strength is argued with a comprehensive narrative review and an experimental study. In the latter, the associations between

upper *vs* lower limbs muscle strength and physical function are discussed looking at the possible sex differences in geriatric population. Chapter four describes the preliminary results on the role of a 5-month controlled diet plus strength training alone or amino acids supplementation in older adults with obesity, dynapenia and sarcopenia. After the intervention, the changes in several outcomes (i.e., on body composition, upper and lower limbs muscle strength and power, physical performance) are described, by comparing the different interventional groups. Lastly, chapter five outlines the main results of each study and presents a general conclusion with proposals for future directions needed on these research topics.

INTRODUCTION

In recent years, the term “pandemic” has become a commonality in people’s lives due to the coronavirus disease 2019 (Covid-19), which has spread worldwide and infected almost 500 million people by the end of 2019, that included over 6 million deaths globally. However, it should be kept in mind that the global spread of obesity has also been labelled a pandemic, albeit with a slower occurrence of cases and less harmful effects than the Covid-19 or other previous pandemic.

In recent decades, the demographic age of the world has continued to rise and with it, problems related to aging such as greater risk of falling, loss of independence and institutionalization, which substantially place a burden on the costs associated with the national health system. Due to aging, sarcopenia constitutes one of the main conditions involved in the physiological deterioration, characterised by a generalised loss of muscle mass, strength, and physical function. With aging, body composition can dramatically change, favouring the increase of fat deposit (particularly of the visceral region) instead of lean muscle mass. Sarcopenia with obesity (also known as sarcopenic obesity) can coexist, leading to older adults having an accelerated risk in developing several disabilities and mortality.

Research interest has grown around this topic over the last few decades. Clinicians and researchers have focused on the diagnostic criteria as well as on strategies for the earlier identification, prevention, and treatment of this condition. Despite the considerable number of studies, the best approach to define sarcopenic obesity with appropriate tools and cut-offs needs to be investigated further. Lifestyle factors have a fundamental role in the prevention and management of this condition. Indeed, exercise alone or combined with an appropriate caloric restriction can limit the negative effects of sarcopenia, counteracting the loss of muscle mass with overall benefits on body composition and reducing the cardio-metabolic risks related to obesity. Other nutritional strategies (e.g., supplementation of amino acids or proteins) might be essential to increase or preserve muscle mass during weight loss and might be helpful for improving muscle strength, muscle function and performance. Several gaps remain in the literature about these important aspects.

CHAPTER 1: INTERRELATIONSHIP BETWEEN OBESITY AND AGING: A COMPREHENSIVE VIEW

Obesity in adults and in geriatric population: an overview

Overweight and obesity are defined by the World Health Organization (WHO) as an abnormal or excessive accumulation of adiposity that is a risk for health (World Health Organization, 2019). The body mass index (BMI) calculated by dividing the body weight (in kilograms) by the height (in meters squared) is the simplest and most convenient metric used to indicate overall body adiposity. The WHO defines a normal BMI range of 18.5 to 24.9 kg/m^2, while a BMI ≥ 25 kg/m^2 is considered overweight and a BMI ≥ 30 kg/m^2 is classified as obesity (World Health Organization, 2019). Despite this simplistic definition, obesity is a multifactorial disease resulting from a chronically positive energy balance, i.e., dietary energy intake outweighing energy expenditure. The accumulation of the energy intake is transformed into triglycerides which are stored in fat depots that expand in volume, increasing body fat and causing weight gain. The latter can be a consequence of complex environmental factors, including energy-dense food being more readily available. Indeed, the globalization of food systems (e.g., the rise in more ultra-processed as well as affordable food) have encouraged nutrient-poor foods or beverages, representing the main drivers of obesity. However, the decline in physical activity and increase in sedentary behaviour are also involved (Swinburn et al., 2011). The complex interactions between these factors have led to an alarming increase of adults with excess body weight over the past few decades across the world, particularly in western countries. Indeed, the global prevalence of overweight and obesity has doubled since 1980 to such an extent that nearly a third of the world’s population is now classified as living with overweight or obesity (Chooi et al., 2019).

As described in **Figure 1. 1**, compared to 1980, in the last 35 years the proportion of adults with overweight increased from 26.5 to 39%, whereas those with obesity increased from 7 to 12.5%. The two countries with the highest prevalence of overweight and obesity were the Americas and Europe. In the Americas, from the 1980, the rate of overweight and obesity increased around 20% and 15.4%. Similarly, European countries showed a similar trend; from 1980 to 2015 the rate of overweight and obesity increase of 11.6% and 8.4%, respectively as illustrated in **Figure 1. 2**.

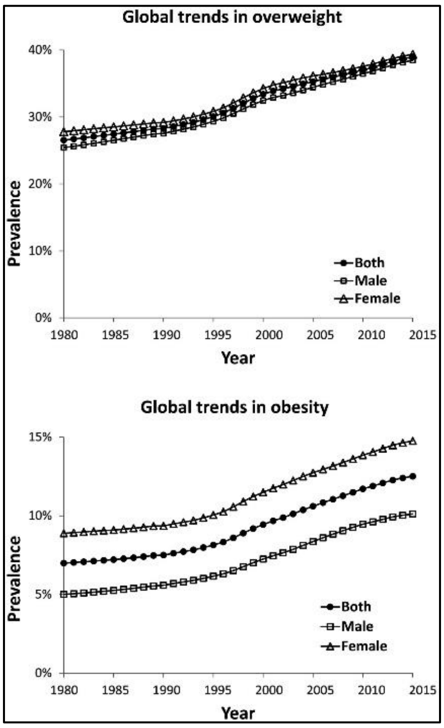


Figure 1. 1: Prevalence of overweight (top) and obesity (bottom) in adults of both sexes (> 20 years) from 1980 to 2015. (Taken from Y.C. Choi et al., 2019)

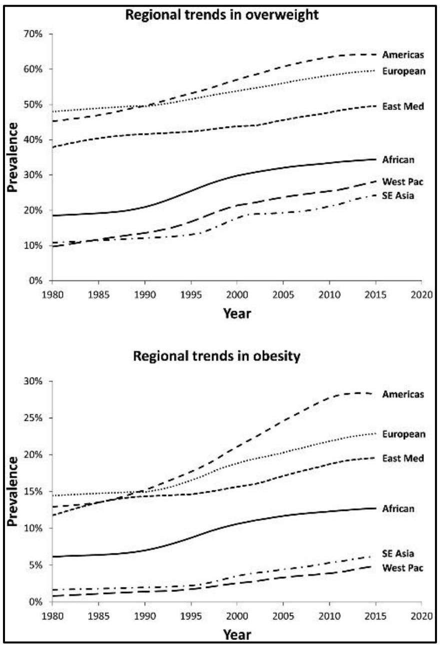


Figure 1. 2: Prevalence of overweight (top) and obesity (bottom) in adults of both sexes (> 20 years) from 1980 to 2015 in different countries. (Taken from Y.C. Choi et al., 2019)

If the current trends continue, by 2030 it is estimated that universally around 60% of the adults will have overweight or obesity (Kelly et al., 2008). In Italy a survey data from 2006 to 2010 (Gallus et al., 2013) conducted on 14,135 Italian adults, estimated that 31.8% and 8.9% of adults were overweight or in an obesity category. This situation is getting worse; a recent retrospective observational study (DiBonaventura et al., 2018) which involved a sample of 9.433 Italian adults, showed a rate of overweight and obesity equal to 34.85% and 12.89% respectively. Due to the global spread of obesity, this disease has been associated with high societal costs which constitutes a universal concern. For instance, in the USA the rate of absenteeism among workers with obesity is largely presented with an indirect cost estimated approximately to $8.65 billion every year (Andreyeva et al., 2014). A recent study (d'Errico et al., 2022) conducted in Italy reported that in 2020 the costs due to obesity were €13.34 billion.

Obesity affects all physiological functions of the body and is considered a serious public health threat. It can increase the risk of developing multiple diseases conditions: metabolic (diabetes mellitus, non-alcoholic fatty acid diseases), respiratory (asthma, obstructive sleep apnea, chronic obstructive pulmonary disease) and cardiovascular diseases (stroke, ischaemic heart diseases, heart failure, hypertension), different forms of cancer (which include endometrial, breast, ovarian, prostate, liver, kidney, and colon), musculoskeletal disorders (osteoarthritis) and mental health (Samper-Ternent and Al Snih, 2012). The consequence is the poor quality of life contributing to a shorter life expectancy and increasing the healthcare costs. For example, in 2020 the direct costs in Italy were €7.89 billion, with cardiovascular diseases representing the highest impact on public costs (€0.65 billion), followed by cancer (€0.33 billion) and bariatric surgery (€0.24 billion) (d'Errico et al., 2022). However, higher BMI showed an association with indirect costs which can reach €7.89 billion (d'Errico et al., 2022) including presenteeism and absenteeism (d'Errico et al., 2022), loss of productivity and health care provider visits (DiBonaventura et al., 2018).

Obesity can present at any age and its prevalence continues to increase from childhood to older age (Chooi et al., 2019). With obesity, also the rate of the older adults is growing worldwide and is projected to increase in the next 40 years. As described in **Figure 1. 3** (left panel), by 2030, more than 20% of the population in the United States will be over 65 years old, up from 15% of the current population

(Batsis and Zagaria, 2018). This rapid increase will particularly involve those individuals above 85 years old; according to current data the new average life expectancy is 82.8 years and 85.3 years in men and women respectively (Batsis and Zagaria, 2018). Recent estimates from the National Health and Nutrition Examination Survey show that the prevalence of older men and women (>60 years) affected by obesity constitute 37.5% and 39.4% respectively (**Figure 1. 3**, right panel).

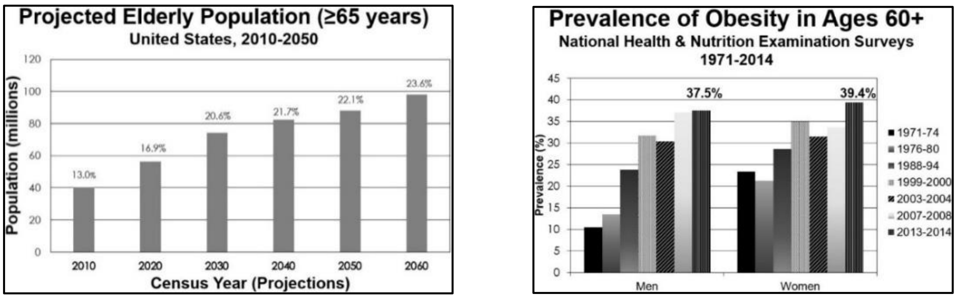


Figure 1. 3: Percentage of increasing in older population (>65 year and older) in the United States up to 2060 (on the left) and changes in the prevalence of obesity in older men and women (>60 years and older) over the past 4 decades (on the right). (Taken from Batsis and Zagaria 2018).

In Europe, a recent study (Peralta et al., 2018) investigated the current data available from 2005 to 2013 on the percentage of overweight and obesity in middle-aged and older adults in 10 European countries. The overall prevalence of obesity significantly increased from 17.5% in 2005 to 19.2% in 2013. These authors showed a high prevalence of obesity in the older European population (mainly in the age groups 60-69 years and 70-79 years), concluding that this condition among the older population has already reached epidemic proportions (Peralta et al., 2018). Interestingly, among the European countries, Italy comprises the largest proportion of the older population which is projected to increase in both sexes by 2065 based on data available from the Italian National Institute of Statistics (**Figure 1. 4**).

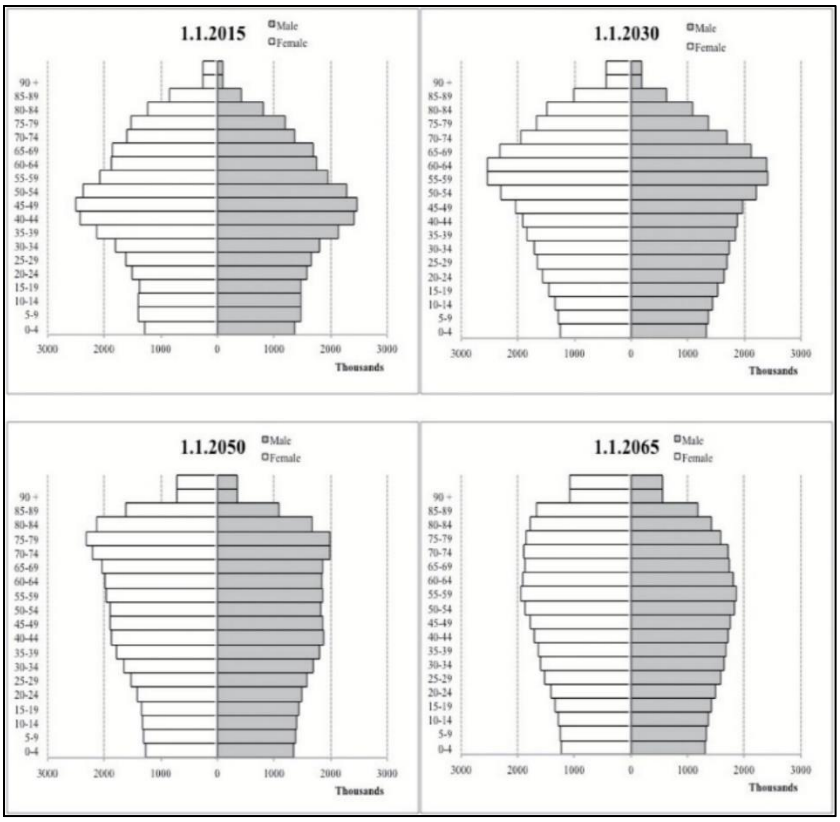


Figure 1. 4: Projection of population by sex and age in 2015, 2030, 2050, 2065 based on the data from the National Institute of Statistics (Taken from Mazzola et al., 2016).

The epidemic wave of obesity amongst the geriatric population will continue to impact the primary care system. Therefore, different strategies to delay the onset of disability and the consequent impairments of the health-related quality of life cannot be overstated. Effective lifestyle changes for weight loss are simple and inexpensive areas of focus for implementation furthermore, they constitute an important way to delay disability and improve physical functioning.

The negative consequences of aging and obesity on skeletal muscle

The reserve capacity of the majority of the body's organs is progressively reduced with aging (McLeod et al., 2016a). In particular, the reduction in cardiac output and lung function lead to a loss in skeletal muscle oxidative capacity and changes in body composition, which reduce the maximum oxygen consumption approximately by 1% per year after the age of 25. Skeletal muscles contributes approximately to 40% of total body weight and cover important functions: *i)* they are the most important regulator of glucose homeostasis; *ii)* storage and release of protein and amino acids important when other sources are depleted; *iii)* they are involved in vital activities which include breathing, strength transmission to the bones, maintenance of posture and global locomotion (Riuzzi et al., 2018). Furthermore, skeletal muscle is remarkably a plastic tissue, able to constantly change in response to calorie and nutrient intake, illness, injury, disuse, or physical stress. Even with healthy aging, skeletal muscle decline primarily because of a loss in fibers number, and in the cross-sectional area (i.e., atrophy), which affects mainly the type II fibers (**Figure 1. 5**).

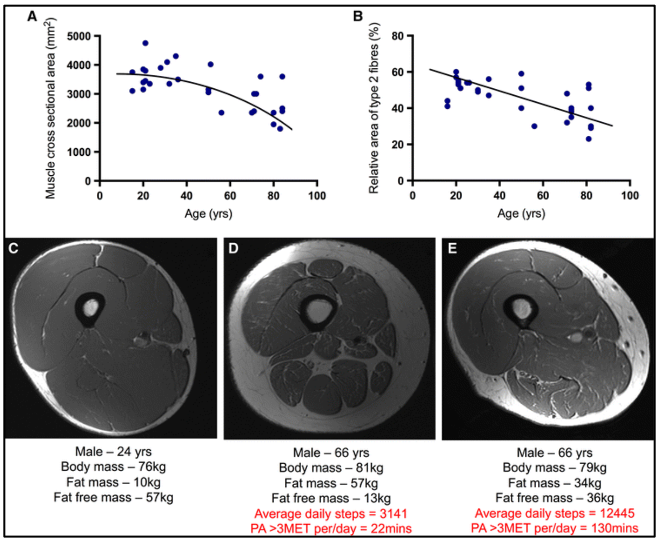


Figure 1. 5: Decline in the muscle cross-sectional area (Panel A) and percentage area of type II fibres (Panel B). In the bottom the MRI images of the skeletal muscle architecture in three different conditions: young (C) vs old active (D) vs inactive (E) men. (Taken from McLeod et al., 2016).

In addition, inside the skeletal muscle can occur a shift from the type II to the type I fibers (the slow myosin forms); the latter are characterized by a lower ability to quickly mobilize the adenosine triphosphate needed to perform daily tasks and those actions that require to express the strength in a short period of time. This condition is known as sarcopenia and has been formally established as a real muscle disease in 2016 through a specific International Classification of Disease code (Vellas et al., 2018).

During aging, together with the reduction in generating strength, the total muscle mass can change both in volume and quality. The peak reduction of muscle mass is close to 5% in men and 4% in women (Mitchell et al., 2012). An example is described in **Figure 1. 5** from the magnetic resonance imaging (MRI) scan in three different participants: the young men (panel C) have greater muscle mass and lower fat infiltration around the muscle bundles compared to the two older adults (panel D and E). However, in the two older adults with a similar daily protein intake, we can observe that the old inactive men with a low average of daily physical activity (and steps) (Panel D) presented a high content of fat infiltration through the fibres and around the muscle compared to an active age-matched men with a high average of physical activity level (Panel E). In the latter, the muscle mass is preserved, indicating that the progressive onset of sarcopenia can be accelerated by an insufficient level of physical activity and reduced protein dietary intake.

Obesity can further negatively affect the muscle structure with different mechanisms which include: a reduction of capacity in expressing contractile and non-contractile sarcomeric proteins, a change in the expression of myosin heavy chain isoform and the lipid deposition between and inside the muscle fibres (Bollinger, 2017a). The amount of intramuscular fat can constitute a driver for the decline in muscle mass and strength. Indeed, with aging the adipose tissue increases and releases proinflammatory cytokines which can accelerate muscle catabolism with a dangerous, vicious cycle of muscle loss and fat accumulation. Age associated muscle loss combined with increasing fat mass has been called sarcopenic obesity (Zamboni et al., 2008) and the very first definition was coined by Heber in 1996: "*reduced lean mass with excess fat as a percentage of body weight*" (Heber et al., 1996). In the future, from the confluence of two epidemics, aging and obesity, the number of people affected by sarcopenic obesity will increase with substantial higher risks of developing other comorbidities, disability, institutionalisation, psychological health issues (e.g., depression and poor mental health) and mortality (Roh and Choi, 2020). Therefore, not only the cardiorespiratory fitness, but also the muscle strength, muscle mass and function constitute important determinants to care about during aging, particularly in older adults with obesity.

Muscle strength is mainly assessed using an isometric and/or an isokinetic modality. The isometric strength is defined as the maximal force that can be exerted against an immovable object and it mainly depends on the number of sarcomeres which can act in parallel (i.e., the cross-sectional area) and the length at which the sarcomere (i.e., the muscle) works (Macaluso and De Vito, 2004; Narici and

Maffulli, 2010). The isokinetic strength is defined as the maximal force that can be exerted against a load that moves through a pre-set angular velocity and depends on the number of sarcomeres placed in series (i.e., fibre length) together with the speed of shortening in each sarcomere. Muscle power is the product between the speed and force of contraction which are important features to preserve during aging. Recent works have investigated how aging can impact skeletal muscle strength and function (Raj et al., 2010) and how obesity might potentially exacerbate these impairments especially for the aging population (Bollinger, 2017a; Tallis et al., 2018). As an example, a literature review (Tallis et al., 2018) explored the role of *in vivo* contractile function of skeletal muscle in human, which concluded that people with obesity might develop premature fatigue, a decrease in the strength and power expression particularly when these variables are normalised to the body mass or lean mass. This can lead to several impairments in mobility, exercise capacity and lipid oxidation (**Figure 1. 6**). However, these authors found limited and conflicting findings in previous studies which involved the older population and suggested future directions about the need to determine the synergistic effect between ageing and obesity on skeletal muscle contractile function.

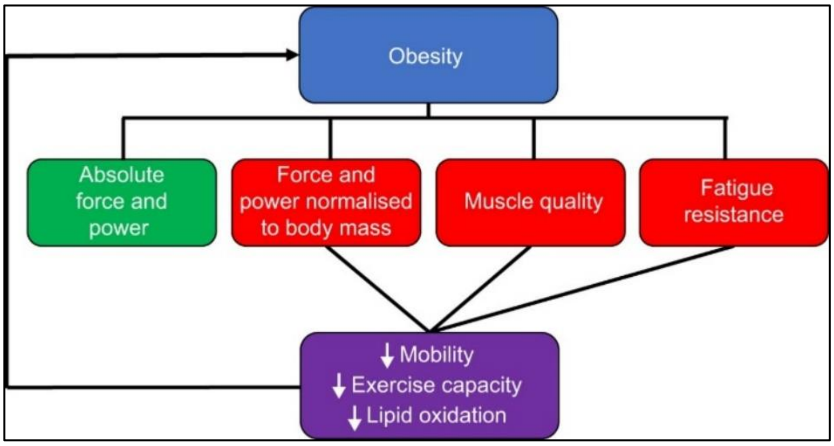


Figure 1. 6: A schematic summary of the effects of obesity on skeletal muscle function. Individuals with obesity typically presents high absolute muscle strength and power even though they showed lower ability when these values are normalised by body mass or lean mass, thus increasing muscle fatigue. These factors lead to a decline in mobility, exercise capacity and lipid oxidation. (Taken from Tallis et al., 2018).

The force-velocity and power-velocity profile: a tool for monitoring the aging-trajectory

In skeletal muscles, the structural and physiological changes which occur with aging affect the individual ability to express strength and power, especially at high speeds of contraction. The force-velocity profile has been largely used to quantify the dynamic muscle contraction both in young and in the older population. A literature review (Raj et al., 2010) has summarised the findings of previous studies regarding the force-velocity profile in different muscle groups using an isokinetic dynamometer. The authors reported that compared to the young, the older adults presented a greater loss of strength at all speeds, but this decline was found markedly reduced in concentric rather than eccentric actions, suggesting that with aging an effort should be made in monitoring and preventing the decline of concentric muscles.

As displayed in the **Figure 1. 7**, the force-velocity curve has a downward and leftward shift in older compared to the young adults, with a low estimated maximal velocity (Vmax) of contraction by the muscles. Using the force-velocity profile, it is possible to further determine the maximal power (Pmax) from derivatives of the Hill's equation (Hill, 1938). The power-velocity profile can also change with aging, showing lower values in Pmax as well as in force and velocity at maximum power (i.e., Topt and Vopt, respectively). The few studies that investigated the effects of aging on all these variables found a major decline between the 7th and 8th decades of life with a considerable loss in Pmax between 30-80%, maximal strength and Vmax both around 20-40%. As stated earlier, these changes can be explained by several factors which include a reduction in the cross-sectional area and in the ability to produce a force per unit of cross-sectional area, pennation angle, fascicle length and the atrophy of type II fibres.

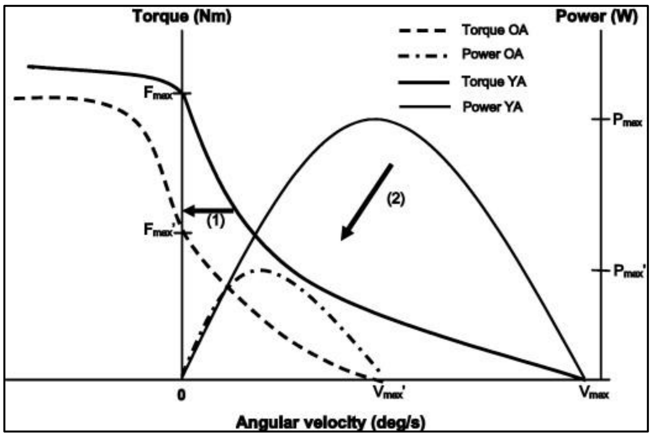


Figure 1. 7: Different torque-velocity and power-velocity profile between young (YA, solid line) and old (OA, dashed) adults. The maximal force (Fmax) and velocity (Vmax) of contraction are reduced in the old compared to the young adults (Taken from Raj et al., 2010).

In both men and women, the changes in muscle contractility are more pronounced in the lower compared to the upper limbs, with negative consequences when it is required to move the body in space. The functional implications mainly concern a decline in tasks like chair rising and stair-climbing, therefore in all those activities that required the development of muscle power. In this regard, a growing body of evidence has shown a strong link between functional tasks and muscle power compared to muscle strength. As an example, in a group of older healthy women, an association was found between Pmax and Vopt with functional tasks; indeed, the 5-chair rise time was inversely associated with Pmax and Vopt ($r=-0.596$; $r=-0.414$, all $p<0.01$) but not with Topt (Clémençon et al., 2008). In another study, walking speed showed a positive association with the leg extensor muscle power ($r= 0.412$-0.939) in older men and women aged between 80-85 years of age (Rantanen and Avela, 1997).

More recently, Alcazar et al showed that Pmax can negatively influence physical function with an increased risk to develop frail and a poor quality of life (Alcazar et al., 2018b). However, it seems that Pmax impairments can be attributed to deficits that can affect the older individuals differently. Some older adults may exhibit deficits on the force of contraction, while others on the velocity of contraction (Alcazar et al., 2018b). These findings highlight that aging affects muscle contraction with different mechanisms that can lead to a decline in force or velocity of contraction; the force-power-velocity profile appears a useful way to monitor these deficits, leading the experts to design interventions targeted to individual's needs.

Different exercise modalities (e.g., progressive resistance training or power training) might help to improve the force-velocity profile with an upward and rightward shift of the curve. This means that due to the positive muscle adaptations usually observed with strength exercises, our muscles might increase the ability to produce force across all speeds of contraction with possible improvements in Vmax (Raj et al., 2010) and thus in functional capacity. However, other features associated with the exercise prescription (e.g., intensity, number of repetitions, velocity of movement) influence the changes in muscle's architecture, favouring for example, a gain in the pennation angle instead of the fascicle length after a high-intensity resistance training (Raj et al., 2010).

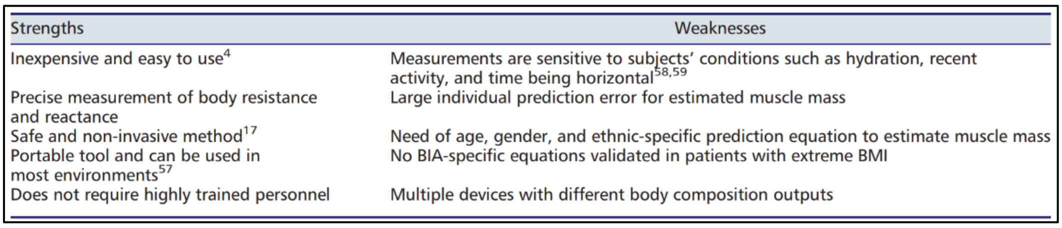
To summarise, existing data has been collected in a healthy older population and several research gaps are evident: *i)* a paucity of cross-sectional studies have characterised the force-velocity profile in older individuals with obesity and therefore, it is not known if obesity can exacerbate this relationship; *ii)* the link between the variables related to the force-velocity (and power-velocity) profile and physical functional tests has not been investigated yet; *iii)* no studies have elucidated if exercise can ameliorate the effects of muscle deterioration and/or have explored the changing variables about the force-velocity profile in older people with obesity. Due to a combination of aging and disuse, the changes in skeletal muscle involve the lower extremities; therefore, new investigations should particularly focus on those muscle groups generally used during locomotion or activities of daily living, looking at the possible functional implications.

Assessing body composition: the common techniques in clinical and research settings

The aging process influences body composition and in particular, muscle mass (Janssen et al., 2000). Several techniques have been proposed for the assessment of body composition in different clinical settings and in research field where the most common are the following: computed tomography (CT), magnetic resonance imaging (MRI), bioimpedance analysis (BIA) and dual-energy X-ray absorptiometry (DEXA).

The CT scan, considered with MRI the gold standard for body composition, is a 3D imaging technique firstly introduced to quantify the regional skeletal muscle mass. Body composition is evaluated through manual segmentation or semiautomatic segmentation software using a single slice. In addition, the composition of muscle tissue can also be quantified by separate segmentation of muscle and adipose tissue or with the analysis of muscle density. Even though it is a painless technique, the high dose of radiation to which the individual is exposed, the low accessibility in terms of costs, need for qualified personnel, or difficulties to perform in individuals with high grades of obesity, make this tool an unpopular choice for clinical practice. However, to assess muscle quantity and quality, the CT scan together with MRI are considered the reference standard imaging modalities (Buckinx et al., 2018). To date, the MRI analysis is recognized as a promising technique for monitoring muscle mass (and therefore sarcopenia) due to several advantages: low radiation exposure, high resolution, and no barriers for people with a severe obesity condition. On the other hand, to assess the whole-body composition protocols composed by numerous images to acquire and analyze, hence qualified personnel are required; in addition, the high costs, low availability, and the lack of specific cutoff for sarcopenia make it hard to access in clinical and research practice.

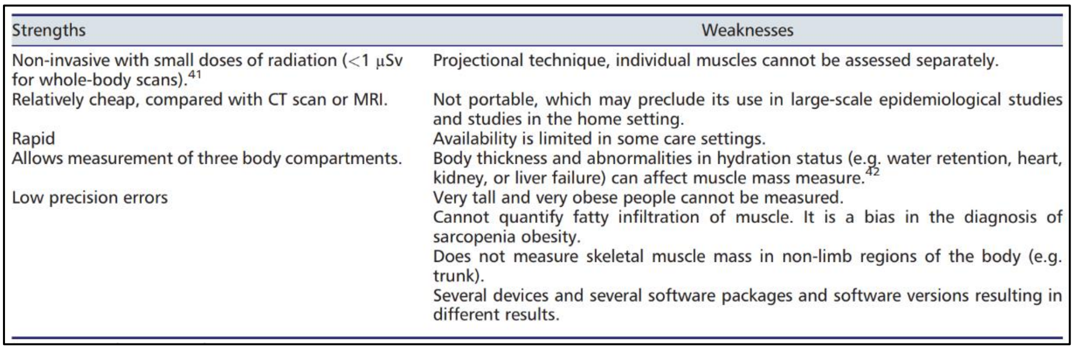
Another tool extensively used in different environments (research, daily clinical practice, public facilities) is the BIA. Compared to the previous measurements, it is widely available, inexpensive, portable, less expensive and entails lower periods of training for the operator and for collecting body composition outcomes. By contrast, the BIA has been established as unideal in the evaluation of lean body mass. For instance, one study (Buckinx et al., 2015) observed a different reliability if one or two operators used the appendicular lean mass (ALM) (Intraclass Correlation (ICC)= 0.89 and 0.77, respectively); in addition the authors reported a low agreement between DEXA scan and BIA in predicting the ALM (ICC= 0.37). **Figure 1. 8** briefly shows advantages and disadvantages in assessing muscle mass via BIA. In general, it is reported an underestimation in assessing lean body mass with the BIA; however, due to the several advantages, it is widely used when other instruments are not desirable.



Strengths	Weaknesses
Inexpensive and easy to use[4]	Measurements are sensitive to subjects' conditions such as hydration, recent activity, and time being horizontal[58,59]
Precise measurement of body resistance and reactance	Large individual prediction error for estimated muscle mass
Safe and non-invasive method[17]	Need of age, gender, and ethnic-specific prediction equation to estimate muscle mass
Portable tool and can be used in most environments[57]	No BIA-specific equations validated in patients with extreme BMI
Does not require highly trained personnel	Multiple devices with different body composition outputs

Figure 1. 8: A summary with strengths and limitations for muscle mass estimation via BIA. Abbreviations: BIA: Bioelectrical Impedance Analysis; BMI: Body Mass Index (Taken from Buckinx et al., 2018).

The DEXA scan is the widely used tool in clinical and research settings to assess body composition and it can assess three body compartments: lean mass, bone and fat mass of the whole body and regional sections (legs, arms, and trunk), based on their density. The strengths and weaknesses about DEXA are summarized in **Figure 1. 9**. Briefly, DEXA has a good precision, low exposure to radiation and allows a relatively quick evaluation for the individuals. Furthermore, it can assess the total body lean soft tissue mass (i.e., skeletal muscle mass and the mass of all the other organs) and the ALM. The latter is defined as the muscle mass of the upper and lower limbs where is found the major distribution (~75%) of the skeletal muscle mass of the whole body (Buckinx et al., 2018), proportional to the height squared (ALM/h^2 (ALMI)).



Strengths	Weaknesses
Non-invasive with small doses of radiation (<1 μSv for whole-body scans).[41]	Projectional technique, individual muscles cannot be assessed separately.
Relatively cheap, compared with CT scan or MRI.	Not portable, which may preclude its use in large-scale epidemiological studies and studies in the home setting.
Rapid	Availability is limited in some care settings.
Allows measurement of three body compartments.	Body thickness and abnormalities in hydration status (e.g. water retention, heart, kidney, or liver failure) can affect muscle mass measure.[42]
Low precision errors	Very tall and very obese people cannot be measured.
	Cannot quantify fatty infiltration of muscle. It is a bias in the diagnosis of sarcopenia obesity.
	Does not measure skeletal muscle mass in non-limb regions of the body (e.g. trunk).
	Several devices and several software packages and software versions resulting in different results.

Figure 1. 9: A summary with strengths and limitations for muscle mass estimation via DEXA. Abbreviations: CT: Computed Tomography; MRI: Magnetic Resonance Imaging (Taken from Buckinx et al., 2018).

Previous studies (Buckinx et al., 2018) revealed that ALM measured with DEXA is highly associated with the skeletal muscle volume assessed with the MRI and CT (i.e., two reference standard techniques). Notably, the ALMI constitutes a relevant parameter for the diagnosis of sarcopenia (Cruz-Jentoft et al., 2010b; Cruz-Jentoft et al., 2019a).

Therefore, because DEXA is considered a reliable and reproducible measurement of muscle mass, it is widely used in numerous settings and promoted in the guidelines from several working groups for the diagnosis of sarcopenia.

Assessing muscle strength and function: the common techniques in clinical and research settings

There is a growing interest on the influence of aging in reducing muscle strength and physical performance. Several studies have shown a mismatch between muscle quantity and quality, reporting a higher rate loss in favor of muscle strength and function as compared with muscle mass. Therefore, clinicians and researchers started to detect and quantify individuals muscle weakness, trying to find the best tool to implement which comprises of an objective, reliable and sensitive measure that was at the same time accessible for operators as well as easily adaptable to the different needs of patients.

The handgrip dynamometer is widely accepted and used method for muscle strength assessment, both in daily clinical practice and in research protocols. A recent umbrella review (Soysal et al., 2021) of 8 meta-analyses found a high association in handgrip strength (HGS) with all-cause mortality, cardiovascular mortality and disability. In a literature review, Bohannon summarized the evidence regarding the use of handgrip dynamometer in relation with several outcomes in older population; this author concluded that assessing the HGS can be useful for detecting the generalized strength and function and can be a predictive biomarker of specific outcomes: bone mineral density, risk of fractures and falls, malnutrition (Bohannon, 2019a). Other features (e.g., easily to use, portability, affordability) have encouraged experts in this sector to implement the handgrip dynamometer during daily measures in geriatric populations. By contrast, several limitations have also been highlighted. The most significant is related to the kind of protocol that can be performed; with this tool the strength in an isometric modality can be measured, poorly associated with those daily tasks that require expressing strength in dynamic conditions. Furthermore, a systematic review published by Bohannon (Bohannon, 2019b) revealed that a change ranging between 5-6.5 kg should be considered clinically meaningful for patients; in this regard, another important limitation includes the low ability in interpreting the progressive changes over time in longitudinal studies.

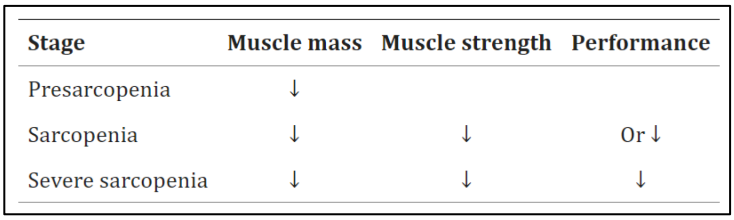
Considering the above-mentioned limitations and the fact that aging mostly affects the function of the lower extremities, other tools and functional tests have been proposed in different settings. The isokinetic devices are mainly used in research for conducting experimental studies, since they allow testing of different muscle groups using various protocols (e.g., isometric, and dynamic conditions, respectively at different angles and speeds of muscle contraction). In addition, with these devices it is simple to standardize the protocol, thus increasing the reproducibility and reliability between sessions. However, several limitations have led experts to prefer alternative tools. As an example, it was reported that in daily practice of geriatric medicine and rheumatology, only 24.2% of the clinicians evaluated lower limb muscle strength with a leg press, whereas 66.4% used the handgrip dynamometer (Olivier Bruyère et al., 2016; Buckinx and Aubertin-Leheudre, 2021).

Another important outcome to monitor in older populations is their physical performance, since it is closely related with other health-conditions like sarcopenia, frailty, sarcopenic obesity and cognitive decline (Buckinx and Aubertin-Leheudre, 2021). Functional tests are often used because they can be performed in every kind of environment (home, hospital, nursing home) without requiring additional equipment, space nor highly qualified operators. It was reported that the 71.4% of clinicians adopt the physical performance where the most common are the following: walking capacity (63.3%), timed up and go (58.6%) and self-reported physical function (58.1%) (Olivier Bruyère et al., 2016; Buckinx and Aubertin-Leheudre, 2021). For instance, the ability from the individuals to cover four meters (i.e., the 4-m walk distance test) has been indicated as a predictor of dependence, severe mobility, and mortality (Abellan Van Kan et al., 2009). Typically, the cut-off under 0.8 m/s indicates a hallmark of poor mobility, whereas a gain between 0.05 and 0.1 m/s is considered a meaningful clinical change (Perera et al., 2006). Despite its simplicity in collecting this outcome, the 4-m walk distance test showed excellent reliability with an ICC of 0.94 (Unver et al., 2017). Finally, one of the most essential tests to measure physical performance is the chair sit to stand (STS) test. The latter is typically described as the ability to perform 5 or 10 repetitions (respectively 5-STS and 10-STS) in the shortest possible time or the maximum number of repetitions in 30 seconds (30s-STS). The STS is considered a feasible measurement, since it is easy to use, quickly and only a chair is required as equipment. In particular, it is reported that the 5-STS is the most common and it is used by ~54% of clinicians in daily practice (Olivier Bruyère et al., 2016; Buckinx and Aubertin-Leheudre, 2021). Interestingly, the 5-STS has been considered a proxy indicator of lower limbs muscles speed and power, hence a great deal of interest is growing around this simple test in research and clinical settings (Buckinx and Aubertin-Leheudre, 2021).

The degree of muscle and functional deterioration can provoke care dependence, increase falls or fractures and hospitalizations. Clinicians should be able to early evaluate and in accurately way these outcomes, especially in those individuals with frailty or sarcopenic condition. One of the major concerns is the low agreement between researchers or clinicians in addressing the best approach to collect this essential information. The different position statements for assessing low muscle mass, muscle weakness and physical performance will be discussed in the next paragraph.

Definitions of sarcopenia and sarcopenic obesity across the world: position statements

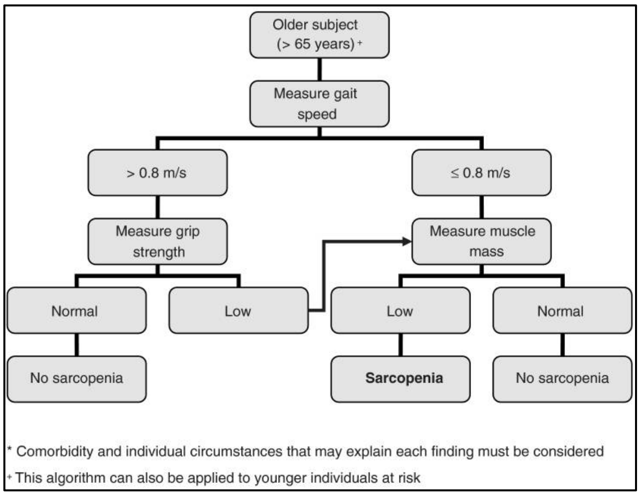
In the last decades, several operational definitions of sarcopenia, including assessments and diagnosis, have been proposed by different task forces and research groups across the world. In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) released a document where sarcopenia was defined as a syndrome characterized by a progressive and generalized loss of skeletal muscle mass and strength (Alfonso J Cruz-Jentoft et al., 2010a). For the first time the concept of "muscle function" appeared in the definition of sarcopenia since muscle strength rather than muscle mass was considered a better predictor of health-related outcomes. According to the EWGSOP, the diagnosis was confirmed by the presence of low muscle mass along with either low muscle strength or physical function. In this regard, three different stages (**Figure 1. 10**) were proposed: i) pre-sarcopenia (presence of low muscle mass); ii) sarcopenia (presence of low muscle mass plus low muscle strength or physical function); iii) severe sarcopenia (presence of low muscle mass, muscle strength and physical function).



Stage	Muscle mass	Muscle strength	Performance
Presarcopenia	↓		
Sarcopenia	↓	↓	Or ↓
Severe sarcopenia	↓	↓	↓

Figure 1. 10: The three different stage of sarcopenia according to the EWGSOP. (Taken from Cruz-Jentoft et al., 2010).

Figure 1. 11 describes the flow chart proposed from the EWGSOP for the sarcopenia diagnosis; they used the gait speed for finding or screening sarcopenia, followed by HGS measurement and then DEXA or BIA to quantify muscle mass.



* Comorbidity and individual circumstances that may explain each finding must be considered
+ This algorithm can also be applied to younger individuals at risk

Figure 1. 11: Algorithm developed by the EWGSOP for sarcopenia diagnosis. (Taken from Cruz-Jentoft et al., 2010).

In 2018, the definition was slightly revised in a new document. In this case, a new algorithm for the diagnosis of sarcopenia was suggested from the EWGSOP2 and structured in four steps: *i)* to find cases of sarcopenia using the Strength, Assistance with walking, Rising from a chair, Climbing stairs and falls (SARC-F) questionnaire; *ii)* to assess muscle strength with the HGS or the STS test; *iii)* to confirm the presence of sarcopenia, the muscle quantity or quality should be detected by body composition techniques according to the purpose. In clinical practice BIA or DEXA are suggested. Otherwise, the DEXA, MRI and CT scan should be preferred for research or specific situations); *iv)* to diagnose a severe condition of sarcopenia, physical performance should be evaluated (**Figure 1. 12**).

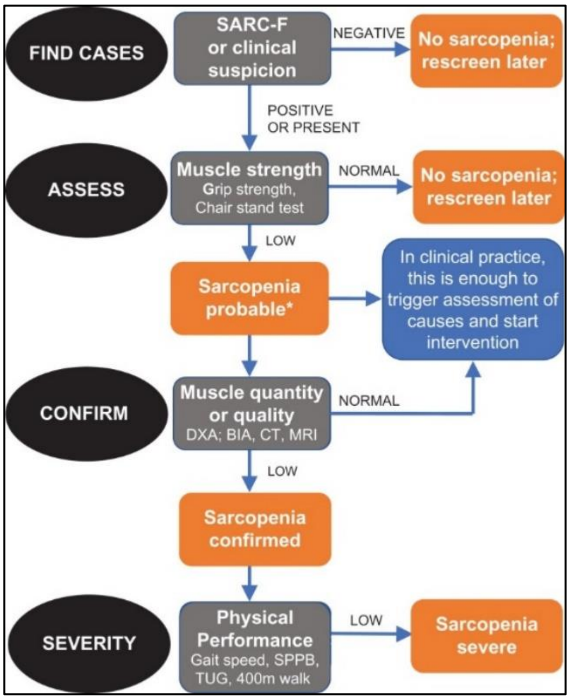
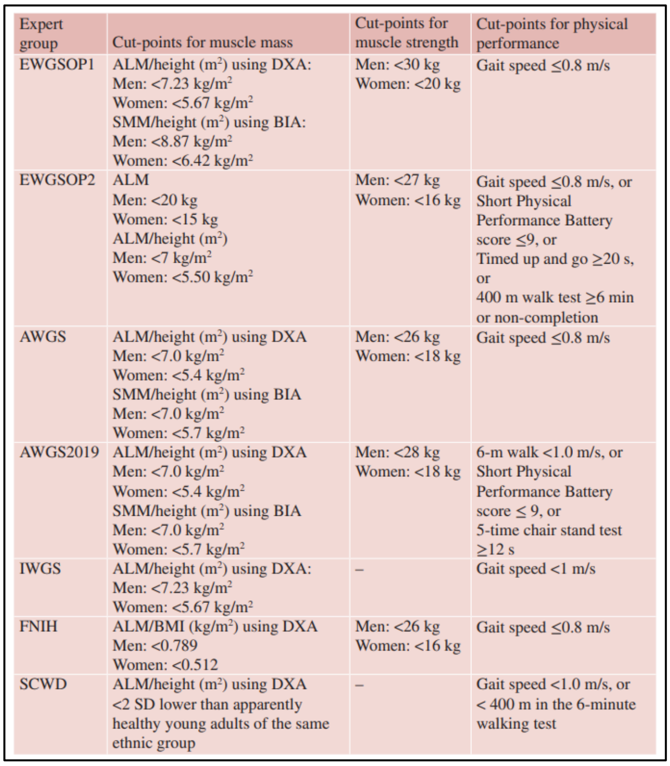


Figure 1. 12: New algorithm developed by the EWGSOP2 for sarcopenia diagnosis (Taken from Cruz-Jentoft et al., 2018). Abbreviations: SARC-F: Strength, Assistance with walking, Rising from a chair, Climbing stairs and falls; DXA: Dual-energy X-ray Absorptiometry; BIA: Bioelectrical Impedance Analysis CT: Computed Tomography; MRI: Magnetic Resonance Imaging.

Other research groups agreed with the EWGSOP and recognized the importance of measuring both muscle mass and function instead of muscle mass alone. In 2014, the Asian Working Group of Sarcopenia (AWGS) released a consensus adopting a similar approach of the EWGSOP with some differences. As an example, due to the differences in ethnicity that distinguish Asian compared to European populations, the cut-offs adopted in terms of body composition were modified. The AWGS recently revised the definition of sarcopenia (i.e., AWGS2019), proposing other functional tests (the 6-minute walking test, short physical performance battery test (SPPB), 5-STS) for measuring the physical performance (Chen et al., 2020).

In parallel with the other two research groups, the Foundation for the National Institutes of Health (FNIH), an organization that included a multidisciplinary approach (e.g., academia, professional, public, and private organizations) worked on a definition of sarcopenia using large datasets instead of a consensus statement. In particular, nine datasets taken from large cohorts were used to identify specific cut-off points for the presence of muscle weakness and low muscle mass. Based on their analysis, this organization identified the low ALM (not adjusted and adjusted by the BMI) combined with the low HGS (in absolute values and adjusted by the BMI) and the gait speed for measuring physical performance.

A summary of the different tools and cut-offs for the diagnosis of sarcopenia is presented in **Figure 1. 13**.



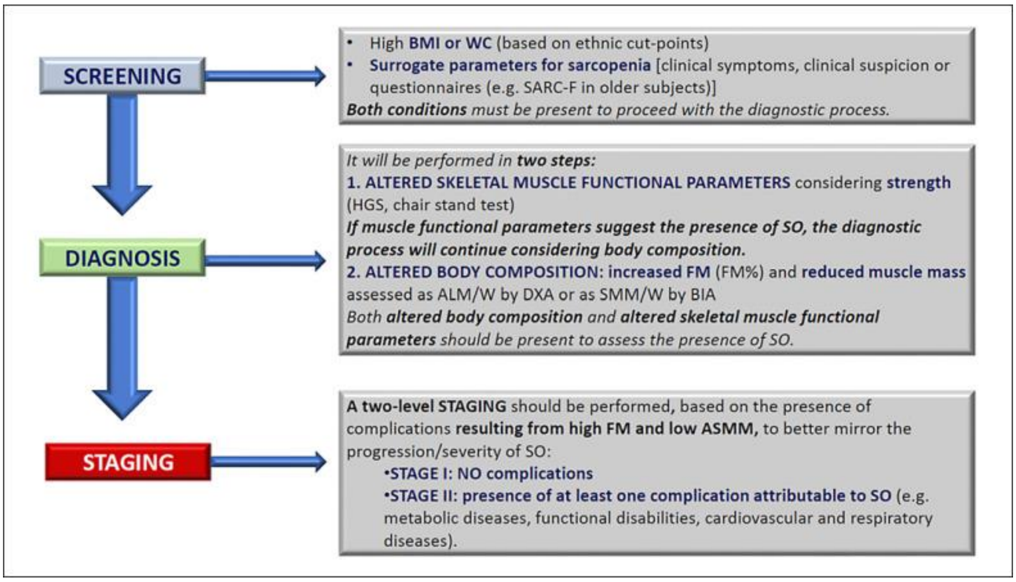
Expert group	Cut-points for muscle mass	Cut-points for muscle strength	Cut-points for physical performance
EWGSOP1	ALM/height (m^2) using DXA: Men: <7.23 kg/m^2 Women: <5.67 kg/m^2 SMM/height (m^2) using BIA: Men: <8.87 kg/m^2 Women: <6.42 kg/m^2	Men: <30 kg Women: <20 kg	Gait speed ≤0.8 m/s
EWGSOP2	ALM Men: <20 kg Women: <15 kg ALM/height (m^2) Men: <7 kg/m^2 Women: <5.50 kg/m^2	Men: <27 kg Women: <16 kg	Gait speed ≤0.8 m/s, or Short Physical Performance Battery score ≤9, or Timed up and go ≥20 s, or 400 m walk test ≥6 min or non-completion
AWGS	ALM/height (m^2) using DXA Men: <7.0 kg/m^2 Women: <5.4 kg/m^2 SMM/height (m^2) using BIA Men: <7.0 kg/m^2 Women: <5.7 kg/m^2	Men: <26 kg Women: <18 kg	Gait speed ≤0.8 m/s
AWGS2019	ALM/height (m^2) using DXA Men: <7.0 kg/m^2 Women: <5.4 kg/m^2 SMM/height (m^2) using BIA Men: <7.0 kg/m^2 Women: <5.7 kg/m^2	Men: <28 kg Women: <18 kg	6-m walk <1.0 m/s, or Short Physical Performance Battery score ≤ 9, or 5-time chair stand test ≥12 s
IWGS	ALM/height (m^2) using DXA: Men: <7.23 kg/m^2 Women: <5.67 kg/m^2	–	Gait speed <1 m/s
FNIH	ALM/BMI (kg/m^2) using DXA Men: <0.789 Women: <0.512	Men: <26 kg Women: <16 kg	Gait speed ≤0.8 m/s
SCWD	ALM/height (m^2) using DXA <2 SD lower than apparently healthy young adults of the same ethnic group	–	Gait speed <1.0 m/s, or < 400 m in the 6-minute walking test

Figure 1. 13: Sarcopenia definitions according to different cut-offs. (Taken from Sabico and Al-Daghri, 2021).

Abbreviations: EWGSOP1: European Working Group on Sarcopenia in Older People; EWGSOP2: revised version of the European Working Group on Sarcopenia in Older People; AWGS: Asian Working Group on Sarcopenia; AWGS2019: Revised version of the Asian Working Group on Sarcopenia; IWGS: International Working Group on Sarcopenia; FNIH: Foundation of the National Institute of Health Sarcopenia Project; SCWD: Society of Sarcopenia, Cachexia and Wasting Disorders; ALM: Appendicular Lean Mass; DXA: Dual X-ray Absorptiometry; BIA: Bioimpedence Analysis; SMM: Skeletal Muscle Mass; BMI: Body Mass Index.

It should be highlighted that the different approaches applied to define sarcopenia have led to relevant differences in the evaluation of the prevalence and of the risk factors associated with sarcopenia. For instance, the authors of a study (Dam et al., 2014a) reported a low agreement between the different definitions and showed a lower prevalence of sarcopenia using the criteria of FNIH (1.3% in men and 2.3% in women) compared to those of the EWGSOP (5.3% in men and 13.3% in women). The discrepancies increase when individuals from different countries are involved. Indeed, given the ethnic differences that characterize individuals of various populations (e.g., anthropometric and body composition variables, lifestyle behavior), these cut-offs should be modified according to the local needs and characteristics (Azzolino et al., 2021).

Inconsistencies increase for the diagnosis of sarcopenic obesity, hence negatively impacting on the ability from clinicians to make an early diagnosis with appropriate intervention strategies. Disparate cut-offs are often used to define the condition of obesity and sarcopenia. However, recently the European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO) highlighted a procedure for sarcopenic obesity identification (**Figure 1. 14**).



- High **BMI or WC** (based on ethnic cut-points)
- **Surrogate parameters for sarcopenia** [clinical symptoms, clinical suspicion or questionnaires (e.g. SARC-F in older subjects)]

***Both conditions** must be present to proceed with the diagnostic process.*

*It will be performed in **two steps:***

1. ALTERED SKELETAL MUSCLE FUNCTIONAL PARAMETERS considering **strength** (HGS, chair stand test)

If muscle functional parameters suggest the presence of SO, the diagnostic process will continue considering body composition.

2. ALTERED BODY COMPOSITION: increased FM (FM%) and **reduced muscle mass** assessed as ALM/W by DXA or as SMM/W by BIA

*Both **altered body composition** and **altered skeletal muscle functional parameters** should be present to assess the presence of SO.*

A two-level STAGING should be performed, based on the presence of complications **resulting from high FM and low ASMM,** to better mirror the progression/severity of SO:

- **•STAGE I: NO complications**
- **•STAGE II: presence of at least one complication attributable to SO** (e.g. metabolic diseases, functional disabilities, cardiovascular and respiratory diseases).

Figure 1. 14: Diagnostic procedure for detecting sarcopenic obesity. Abbreviations: BMI: Body Mass Index; WC: Waist Circumference, SARC-F: Strength, Assistance with walking, Rising from a chair, Climbing stairs and falls; HGS: Handgrip Strength; SO: Sarcopenic Obesity; FM: Fat mass; ALM/W: Appendicular Lean Mass normalized for Body Weight; DXA: Dual Energy X-Ray Absorptiometry; SMM/W: Total Skeletal Muscle Mass normalized for Body Weight; BIA:

Bioelectrical Impedance Analysis; ASMM: Absolute Skeletal Muscle Mass (Taken from Donini et al., 2022).

In this consensus statement, the authors defined sarcopenic obesity as the "co-existence of obesity and sarcopenia" (Donini et al., 2022). The procedure for finding and diagnosing individuals with sarcopenic obesity is structured in different steps:

i) Screening: it includes the combined presence of obesity assessed with high BMI levels or waist circumference according to specific cut offs based on the individual's ethnicity (Caucasian or Asian populations) and surrogate indicators of sarcopenia or questionnaires (e.g., SARC-F).

ii) Diagnosis: it includes the assessment of HGS (adjusted by body weight), or chairs stand test (i.e., 5-STS test or 30 s STS), with cut-off points that account individual characteristics (sex, ethnicity, and age). If muscle weakness is detected, the diagnosis continues assessing body composition with DEXA (or BIA when other tools are not available). As an alternative, psoas muscle area as evaluated by CT scan should be employed in special conditions (e.g., in the oncology field).

iii) Staging: it occurs when the sarcopenic obesity diagnosis is established and individuals with sarcopenic obesity are classified in stage I (no complications attributed to muscle weakness or alterations in body composition) or stage II (the existence of at least one complication such as metabolic, cardiovascular, or respiratory diseases, disability linked which cause impairments in muscle strength or body composition).

To summarize, this position statement provided new insights of sarcopenic obesity. These authors considered relevant to evaluate skeletal muscle mass, quality, and muscle function. The latter has been recognized as an important component for the definition and the diagnostic procedure. However, the assessment should differ in clinical and research environments, searching for the best approach which considers a balance between practicality (costs, time, availability), specificity and sensitivity of evaluations. Finally, more evidence is required to find and treat individuals affected by sarcopenic obesity. Regarding the treatment, an overview will be provided in the proceeding paragraphs.

The role of exercise in older population with obesity or sarcopenic obesity

Physical inactivity is one of the most significant risk factors for developing obesity and sarcopenia which may be preventable and modifiable. In a previous review which involved 23 reports from seven countries, showed that 65% of adults above 60 years were sedentary with a total amount of 9 hours per day (Sabico and Al-Daghri, 2021). It is not surprising that this problem is more common amongst the older population, which tends to less tolerate the effort during different tasks, discouraging the daily movement with a consequent reduction in energy expenditure, an increase in fat compartments with loss of muscle mass.

Physical activity defined as all the bodily movements produced by skeletal muscles that leads to an increase in energy expenditure, has been previously endorsed (Montero-Fernández and Serra-Rexach, 2013). Exercise represents a subset of physical activity with more specific features. Exercise is planned, repetitive and structured and has the purpose to improve or maintain the health-related physical fitness components (i.e., endurance, strength, flexibility, body composition) (Montero-Fernández and Serra-Rexach, 2013). In older population, to induce beneficial effects on health and function different kinds of exercise might be proposed: aerobic, resistance (or power) training, a combination of aerobic and resistance training, balance/gait training. In addition, the prescription of each exercise modality should include intensity, volume, frequency and progression of training (Chodzko-Zajko et al., 2009).

Aerobic training is the ability to perform dynamic exercises from a moderate to a vigorous intensity, involving large muscle groups over a long period of time. This modality can be prescribed in several ways that includes brisk walking, nordic walking, running, or cycling, swimming. In older adults, aerobic training can be beneficial for cardiovascular fitness and endurance capacity, body composition, cardiometabolic health and chronic inflammation (Montero-Fernández and Serra-Rexach, 2013). Amongst the older population with obesity and sarcopenia, one study found that after eight weeks of aerobic exercise (i.e., ~10 minutes of dynamic exercise plus ~45 minutes of a combination of dance steps movements) participants significantly decrease body fat mass (-0.7 kg), visceral fat (-6 cm^2) and maintained skeletal muscle mass (+0.1 kg) compared to the control group (Chen et al., 2017).

Progressive resistance training (RT) is a form of structured exercise that requires muscles to apply force to move or resist against weight (Montero-Fernández and Serra-Rexach, 2013). Some examples include resistance machines, free weights or exercise using individual body weight and elastic resistance therabands. In terms of prescription, this modality comprises the number of repetitions (volume), the number of training sessions (frequency) and the percentage of one repetition maximum (1-RM) (intensity). Robust evidence demonstrating that progressive RT can improve muscle strength, performance and lean mass in older adults (Chodzko-Zajko et al., 2009). Recently, a therapeutic strategy for counteracting sarcopenia has been established (Hurst et al., 2022). Despite the potential beneficial effects of RT, its role in individuals with sarcopenic obesity is not well-examined, particularly regarding the potential impact on muscle mass and muscle function (Trouwborst et al., 2018). For example, after 10 weeks of resistance training, a previous study (Vasconcelos et al., 2016) did not find improvements to physical function, strength and power in older women with sarcopenic obesity. By contrast, after 8 weeks of RT, the patients with sarcopenic obesity maintained skeletal muscle mass, despite the reduction of fat mass and increased HGS (Chen et al., 2017). Similarly, compared to the control group, other authors (Gadelha et al., 2016; Liao et al., 2017a) reported a positive impact on muscle mass, muscle strength, muscle quality and physical capacity after a different period of intervention (i.e., 12 or 24 weeks). Hence, the majority of previous research underscored the importance of RT. Nevertheless, several components of exercise prescriptions that can drive clinicians and kinesiologists to prevent and treat sarcopenic obesity are less clear.

Another important aspect to consider is that in those older adults with obesity or sarcopenic obesity, it is crucial to encourage weight loss with a concomitant increase or at least preservation of lean mass. It was suggested that a combination of aerobic and RT (i.e., the concurrent training) or RT combined with a nutritious diet, might constitute more promising interventions (Trouwborst et al., 2018). Regarding concurrent training, some literature exists in older frail individuals with obesity, but limited studies are shown in populations with sarcopenic obesity

(Trouwborst et al., 2018). In a sample of older sarcopenic obese women, a randomized control trial reported that 12 weeks of concurrent training (60 minutes/session, two times per week) led to an increase in knee extensor (KE) muscle strength, a gain in leg and arm lean mass accompanied with a loss of total body fat mass. In another work (Villareal et al., 2017) the authors have evaluated the effects of 6 months of hypocaloric diet combined with a progressive RT, or aerobic training or concurrent training in frail older adults with obesity. After intervention, all the three groups had a significant weight loss (9%), but there was also a reduction of skeletal muscle mass (~3 kg) which was less pronounced in the resistance and concurrent training groups compared to the aerobic group. Furthermore, RT or concurrent training led to improvements in muscle strength and physical performance; the latter increased more in those individuals who attended the concurrent training. The authors suggested that functional status can enhance if the exercise prescription includes both aerobic and strength training, yet it might not be enough for maintaining the lean muscle mass which is relevant for the treatment of sarcopenic obesity. For these reasons, other potential therapies may be implemented in order to enhance positive adaptations on body composition, muscle function and performance.

Nutrition and supplementation in older population with obesity or sarcopenic obesity

Among the metabolic impairments associated with obesity, protein metabolism can also be affected. Muscle quantity and quality depend on the protein turnover rate (i.e., protein synthesis and protein breakdown) by regulating the amount of proteins and their post-translational changes in skeletal muscle. In this process, hormones, nutrients, and physical exercise play a role in protein metabolism regulation.

Individuals with obesity often present alterations of protein metabolism, attributed to a lower inhibition of proteolysis and a normal or lower stimulation by insulin and amino acids in the body. In the skeletal muscle, obesity is linked to a reduction in the rate of fasting protein synthesis and its response to elevated plasma amino acids concentrations and to caloric restriction or exercise. Hence, different dietary approaches which include the intake of adequate amounts of protein and amino acids might be extremely relevant for those people with obesity that need to achieve weight loss.

A diet that includes an adequate amount of protein was demonstrated important for conserving lean muscle mass in older adults that are under caloric restriction. In this regard, a previous randomized control trial (Beavers et al., 2019) involving older (≥65 years) men and women with obesity (class I and class II) followed a 6-month caloric restriction combined with a daily protein amount ranging from 1.2 to 1.5 g/kg body weight. After the intervention, the average weight loss was low (1.16 kg), however 87% of patients showed a reduction in fat mass, preserving the lean mass and slightly improving mobility. Another study (Weaver et al., 2019) found that a high protein diet promoted the maintenance of bone density and quality, therefore indicating beneficial effects on different body composition compartments. An important factor relevant for preserving lean muscle mass during weight loss is the quality of protein (Simonson et al., 2020). Whey protein can stimulate the postprandial protein synthesis ascribed to its fast digestion and absorption kinetics in combination with the high content in leucine (Simonson et al., 2020). Some studies (Layman and Walker, 2006; Paddon-Jones and Rasmussen, 2009) have indeed reported that leucine, an essential amino acid (EAA), is able to stimulate the postprandial muscle protein synthesis in older adults. In regard with the role of supplementation, conflicting findings were reported from a recent meta-analysis in older adults affected by sarcopenic obesity (Hsu et al., 2019). A nutrition intervention alone showed a decrease in fat mass with no improvements or reduction in lean mass nor significant gains in muscle strength (evaluated with handgrip dynamometer).

Beyond protein intake, the EAA have an important role in protein nutritional status. Particularly, the branched-chain amino acids (BCAA) (leucine, isoleucine, and valine) promote protein synthesis in the muscles through several pathways. They are taken up by skeletal muscle in response to a meal and their uptake is not directly linked by insulin. During the postprandial phase, they signal a reduction in protein breakdown and an increase in protein synthesis, thus stimulating the accretion of protein inside the muscles and controlling the amino acids plasma concentration. Mechanistically, amino acids are involved in the insulin signaling pathway through the interaction with the target of rapamycin (mTOR) complex (Simonson et al., 2020). The protein synthesis is induced by the complex 1 of mTOR which mediates the efflux of different amino acids that include the leucine. A high amount between 10-15 g of BCAA, or at least 3 g of leucine per meal, may counteract aged muscle loss, therefore ameliorating the onset of sarcopenia (Argilés et al., 2016). By contrast, other evidence (Breen and Phillips, 2011) reported that aging can lead to a reduction in the muscle protein synthesis. This phenomenon is called “anabolic resistance” and is defined as the low ability from skeletal muscles to increase protein synthesis in response to various stimuli which include amino acids and protein, insulin, or physical exercise (Moro et al., 2018).

Interestingly, the relationship between sarcopenic obesity and amino acids should be clarified since these population of interest might present an elevated or reduced content in BCAA as a consequence of obesity or sarcopenia, respectively (Le Couteur et al., 2021). A recent study (Le Couteur et al., 2021) investigated the amino acid profile in older men with obesity, sarcopenia or sarcopenic obesity. In the sarcopenic obesity group, the authors observed an intermediate content of amino acids compared to the other two groups, whereas BCAA were lower than the older men with obesity and close to the content of those with sarcopenia. It appears that for the management of sarcopenic obesity even the supplementation of specific amino acids may be a promising therapy to implement when the goal is to stimulate protein synthesis to increase muscle mass and muscle function. This might be more useful when the supplementation is combined with physical exercise and resistance training in particular.

Exercise plus nutrition in older population with obesity or sarcopenic obesity

Nutrition can represent an important element to counteract metabolic alterations associated with aging, however, seems insufficient to eliminate or reverse protein breakdown in muscles. Protein synthesis starts following the muscle’s contraction. Physical exercise is a key factor to induce a number of anabolic signaling pathways, hence reducing the degradation of muscle protein. On the contrary, the lack of physical activity and exercise reduce the promotion of muscle’s anabolism and in particular, the synthesis of proteins from amino acids. Through the exercise modalities, RT seems essential to treat or prevent muscle atrophy. As reported in

Figure 1. 15 resistance exercise combined with an adequate amount of protein or amino acids are powerful elements for promoting the protein synthesis in the muscles in older adults.

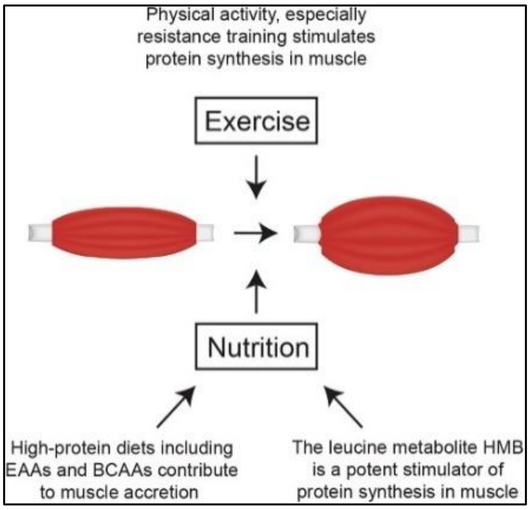
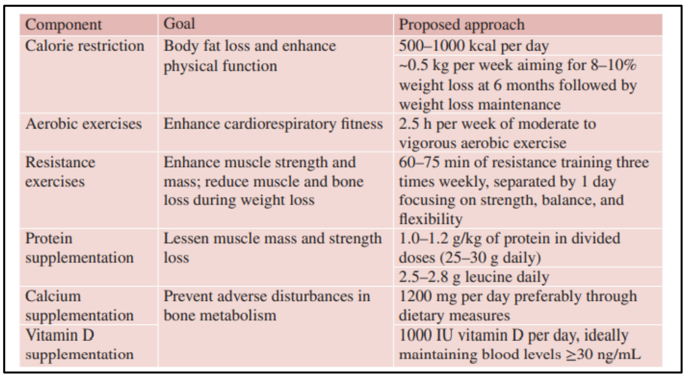


Figure 1. 15: Individuals with a high risk of sarcopenia are recommended to consume a diet high in protein, to include resistance training and to take supplements of the leucine metabolite HMB. Abbreviations: EEAs: Essential Amino Acids; BCAAs: Branched-chain amino acids, HMB: metabolite β-hydroxy β-methylbutyrate. (Taken from Argiles et al., 2016).

A recent umbrella review (Gielen et al., 2021) concluded that a combination of protein supplementation with RT was recommended to increase muscle mass and strength, particularly for people with obesity who followed 24 weeks of training. Instead, no clear additive effects were shown for improving physical performance. These authors further reported insufficient evidence to state that overall physical exercise combined with essential amino acids increase muscle strength, muscle mass and physical performance in older adults with sarcopenia.

Regarding the combination of nutrition and exercise in adults with sarcopenic obesity, the literature is scarce. In a previous meta-analysis (Hita-Contreras et al., 2018) the authors concluded that dietary protein supplements plus exercise led to positive improvements on fat mass and ALM as well as HGS and gait speed. Similarly, another recent meta-analysis (Yin et al., 2020) indicated that exercise alone or combined with nutritional interventions were effective strategies to improve body composition, HGS and gait speed. However, these authors also added that the quality of the previous randomized control trials were from very low to moderate, suggesting the need of further exploration (Yin et al., 2020).

In contrast with these conclusions the meta-analysis of other research groups (Hsu et al., 2019) showed that the protein supplementation did not provide additional benefits on inflammatory biomarkers, body composition, strength and physical function in adults with sarcopenic obesity. In this work the authors focused their attention on the different exercise modalities in combination with nutritional supplementation. For example, considering the amino acids supplementation, only one randomized control trial (Kim et al., 2016) investigated the effects of 12 weeks of concurrent training (60 minutes/session, 2 times/week) with a supplementation of 3 g of amino acids (where 1.3 g of leucine was included). Compared to the control group the participants with sarcopenic obesity significantly reduced fat mass (-5.5 kg) with no changes in muscle mass and physical function. Another work (Yamada et al., 2019) found that RT training in combination with Vitamin D3 and protein increased muscle strength and muscle quality compared to the two modalities proposed alone. To summarize, different therapies have been proposed for the treatment of sarcopenic obesity (**Figure 1. 16**).



Component	Goal	Proposed approach
Calorie restriction	Body fat loss and enhance physical function	500–1000 kcal per day
		~0.5 kg per week aiming for 8–10% weight loss at 6 months followed by weight loss maintenance
Aerobic exercises	Enhance cardiorespiratory fitness	2.5 h per week of moderate to vigorous aerobic exercise
Resistance exercises	Enhance muscle strength and mass; reduce muscle and bone loss during weight loss	60–75 min of resistance training three times weekly, separated by 1 day focusing on strength, balance, and flexibility
Protein supplementation	Lessen muscle mass and strength loss	1.0–1.2 g/kg of protein in divided doses (25–30 g daily)
		2.5–2.8 g leucine daily
Calcium supplementation	Prevent adverse disturbances in bone metabolism	1200 mg per day preferably through dietary measures
Vitamin D supplementation		1000 IU vitamin D per day, ideally maintaining blood levels ≥30 ng/mL

Figure 1. 16: The major proposed therapies to counteract sarcopenic obesity. (Taken from Veronese et al., 2021).

Weight loss reached through caloric restriction plays a key role for the management of obesity, but the implementation of aerobic and/or RT might constitute harmful tools to enhance physical function, strength and several outcomes related to sarcopenia. Appropriate dietary proteins which include EAA might stimulate muscle protein synthesis, ameliorating the preservation of muscle mass after the caloric restriction. However, the optimal strategies in terms of exercise modality and prescription (intensity, frequency, volume, progression of training) or the specific amount and distribution (e.g., before or after exercise sessions) of protein or amino acids supplementation to prevent or reduce the prevalence of sarcopenic obesity, is still to be established. Furthermore, the few studies available mainly focused on simple clinical tests to measure the improvements of upper and lower limb function, however no studies analyzed the force-velocity and power-velocity relationships which may be crucial components to monitor during aging.

SUMMARY AND GOALS OF THIS PHD THESIS

In the previous chapter, it was provided an overview of the impact of obesity and sarcopenia in older population, highlighting the importance to preserve, monitor and counteract the loss of muscle strength, quality, and physical function. Therefore, the purpose of this thesis is to analyse the impact of obesity on muscle strength and muscle function, the contribution in assessing these outcomes to screen muscle weakness and to evaluate the effectiveness of physical exercise in combination with other strategies (e.g., caloric restriction, supplementation) in older men and women with sarcopenic obesity. In further detail:

1. In the second chapter the goal will be to determine the differences in lower knee extensors and flexors muscle strength, muscle power and muscle quality in a sample of older adults affect by obesity compared to the older normal weight counterpart of both sexes. Specifically, an analysis of the force-velocity and power-velocity relationships will be considered in this kind of population.
2. In the third chapter the goal will be to summarise the evidence of previous studies which investigated the associations between handgrip dynamometer with lower limbs muscle strength and physical function. Furthermore, a cross-sectional study will be conducted on a sample of older adults with obesity to understand if the handgrip dynamometer can be used alone to evaluate the lower limbs muscle strength and function or if a specific assessment is needed to identify lower limbs muscle weakness.
3. In the fourth chapter the goal will be to propose a multidisciplinary intervention, investigating the effectiveness of diet in combination with a strength training protocol with or without the amino acids’ supplementation in older men and women affected by sarcopenic obesity. Several health-related outcomes will be assessed: anthropometric and body composition, metabolic profile, upper and lower limbs muscle strength, lower limbs muscle power, muscle quality, and physical performance.

Proceeding these chapters, a discussion and conclusion will be provided with future considerations to acknowledge for future studies on these relevant topics.

CHAPTER 2: THE IMPACT OF OBESITY ON MUSCLE FUNCTION IN OLDER ADULTS

EXPERIMENTAL RESEARCH: STUDY 1

Full characterisation of knee extensors' function in ageing: effect of sex and obesity

Valentina Muollo[1], Andrea P Rossi[2], Andrea Zignoli[3], Massimo Teso, Chiara Milanese[4], Valentina Cavedon[4], Mauro Zamboni[2], Federico Schena[4,5], Carlo Capelli[4], Silvia Pogliaghi[4]

[1] Department of Medicine, University of Verona, Verona, Italy

[2] Department of Medicine, Section of Geriatrics, Healthy Aging Center Verona, Verona, Italy

[3] Department of Industrial Engineering, University of Trento, Trento, Italy

[4] Department of Neuroscience, Biomedicine and Movement, University of Verona, Verona, Italy

[5] CeRiSM, Sport, Mountain and Health Research Center, University of Verona, Rovereto, Italy

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Abstract

Background and aims: Muscle function is a marker of current and prospective health/independence throughout life. The effects of sex and obesity on the loss of muscle function in ageing remain unresolved, with important implications for the diagnosis/monitoring of sarcopenia. To characterise *in vivo* knee extensors' function, we compared muscles torque and power with isometric and isokinetic tests in older men and women, with normal range of BMI and obesity.

Methods: In 70 sedentary older men and women (69±5 yrs) with normal weight and obesity (i.e., BMI < 30 kg/m^2 and ≥ 30 kg/m^2, respectively) we tested the right knee's extensor: *i)* isometric torque at 30, 60, 75, 90° knee angles; *ii)* isokinetic concentric torque at 60, 90, 150, 180 and 210$°\cdot s^{-1}$ angular speeds. Maximal isometric torque-angle, maximal isokinetic knee-extensor torque-velocity, theoretical maximal shortening velocity, maximal power, optimal torque, and velocity were determined in absolute units, normalised by body mass (BM) and right leg lean mass (LLM_R) and compared over sex, BMI categories and angle or angular speeds by 3-way ANOVA.

Results: In absolute units, relative to BM and LLM_R, sex differences were found in favour of men for all parameters of muscle function (main effect for sex, $p<0.05$). Obesity did not affect either absolute or relative to LLM_R isometric and isokinetic muscle function (main effect for BMI, $p>0.05$); however, muscle function indices, when adjusted for BM, were lower in both men and women with obesity compared to the normal weight counterparts ($p<0.05$).

Conclusions: We confirmed sex differences in absolute, relative to BM and LLM_R muscle function in favour of men. While overall muscle function and muscle contractile quality is conserved in individuals with class I obesity, muscle function normalised for BM, that defines the ability to perform independently and safely the activities of daily living, are impaired in comparison with physiological ageing.

Introduction

Muscle strength and power are two key components of physical performance (Macaluso and De Vito, 2004) and, when expressed relative to BM, they determine the individual’s ability to cope independently with the requirements of activities of daily living and to remain safe from the risk of falling (Landi et al., 2012). Furthermore, absolute muscle strength, due to its strong correlation with both total muscle mass and mortality, is an index of current and prospective health (M. O. Harris-Love et al., 2018).

Maximal strength and power are reached at ~25 years of age, with a gradual decline thereafter (Keller and Engelhardt, 2013). A further reduction in force of 1.5% and power of 3-4% per-year is expected after 50, with an even steeper loss over 64 years (SKELTON et al., 1994). The main cause of the loss of muscle strength and power observed with ageing is a “multi-faced geriatric syndrome” known as sarcopenia (Alfonso J Cruz-Jentoft et al., 2010b) and defined as a decrease of skeletal muscle mass associated with aging (Cooper et al., 2013). In addition, the selective atrophy of fast fibres and the deterioration of the contractile properties of muscles tissue are also implicated, particularly in the loss of muscle power (Narici and Maffulli, 2010). Other factors, such as immobility or sedentary lifestyle, endocrine dysfunction, chronic disease and nutritional deficiencies (Alfonso J Cruz-Jentoft et al., 2010b) may contribute to the detrimental effects of sarcopenia.

When ageing is accompanied by obesity (i.e., sarcopenic obesity (Zamboni et al., 2008)), the age-related decline in muscle mass and contractile properties are exacerbated by an accumulation of intramuscular fat that can lead to a chronic muscle inflammation (Delmonico et al., 2009). In turn, the release of different cytokines (e.g. TNF-alfa, IL-1 and IL-6), facilitates protein muscle degradation, impairs protein synthesis and favours muscle atrophy (Tomlinson et al., 2016). In addition, obesity may be associated with an impairment of the contractile properties of the surviving muscle mass due to intramuscular fat infiltration and fibrosis (Tomlinson et al., 2016). In this case, the marked loss of muscle strength and power has a further impact on independence and function, and it may lead to a vicious cycle, where a reduction of exercise tolerance, spontaneous physical activity and daily energy expenditure concur for a further loss of muscle mass, function and weight gain (Zamboni et al., 2008). However, a controversial theory proposes that the excess in BM that characterises individuals with obesity may constitute a natural overload and a positive training stimulus that may protect them from the age-related decline of muscle mass (Tallis et al., 2018). Indeed, higher absolute values of isometric and isokinetic knee extensors muscle strength and power were reported in adolescents with obesity (Bollinger, 2017a). However, little is known about the impact of obesity on the muscle mass and contractile quality in elderly adults (Tallis et al., 2018; Valenzuela et al., 2020) and the few available studies do not confirm higher strength values in older adults with obesity compared to normal weight age-matched controls (Tomlinson et al., 2014; Zoico et al., 2004).

In the daily clinical practice, muscle strength is typically assessed by handgrip dynamometry (M. O. Harris-Love et al., 2018). This approach is time and cost-effective (M. O. Harris-Love et al., 2018) but it can be adopted to evaluate the isometric strength of upper extremities only at a single muscle length and with no account of the speed of strength expression (Buckinx and Aubertin-Leheudre, 2019). However, the ability to express strength, depends on the muscle length and consequently on the joint angle from which contraction is initiated and on the speed of movement. In real life, the age-related loss of strength generating capacity can have a different impact on ability to perform the activities of daily living depending on the modifications of both length/force and strength/speed profiles at the individual level (Lanza et al., 2003; Thompson et al., 2018). It is currently unknown if and to what extent obesity may interfere with the age-related modification of the length/force and strength/speed profiles (Tallis et al., 2018). With regard to the above considerations, the handgrip evaluation may provide a rather simplistic picture of muscle function (M. O. Harris-Love et al., 2018). Furthermore, it may not accurately reflect the variability in strength loss in different body districts, nor the most functionally relevant changes with ageing (Buckinx and Aubertin-Leheudre, 2019; M. O. Harris-Love et al., 2018; Maffiuletti et al., 2013). Finally, it appears unsuitable as an outcome measure because it fails to accurately track the changes in total body strength resulting from training interventions (M. O. Harris-Love et al., 2018).

A full characterisation of muscle function can be obtained using isokinetic dynamometers. This allows to derive torque-angle, torque-velocity, and power-velocity relationships and, through these, to calculate the maximal isometric torque (Tmax), theoretical Vmax, Pmax and the corresponding optimal angle, Vopt and Topt. The aforementioned variables provide quantitative and qualitative information on the total skeletal muscle function (S. Barbat-Artigas et al., 2012; Raj et al., 2010). Furthermore, torque and power can be expressed relative to BM, providing the "useful" force or power, i.e. an index of the subject's ability to move their own BM in ordinary actions (S. Barbat-Artigas et al., 2012). The force and power normalised for muscle mass inform us on the muscle quality, i.e. the muscle's ability to generate force/power per unit of muscle mass ("specific" force/power) (14, 16), an index of the morphological deterioration of the surviving muscle mass and of the quality of the neuromuscular control (Raj et al., 2010). Finally, the exploration of a wide range of joint angles and angular speeds allows to understand the impact of obesity on the force expression of lower extremities in real-life tasks. This approach may provide a mechanistic insight into the possible causes of a deterioration of muscle function in obesity, as the force expression profiles at the individual level can assist in tailoring the training prescription towards safety and independency in the movement tasks of daily living (Alcazar et al., 2018b).

In summary, the extent of the loss of muscle force and power, in people with obesity is still not fully elucidated (Tallis et al., 2018) and the effects of the interaction between sex, ageing and obesity on the conservation of muscle function remains unresolved (Tallis et al., 2018). Therefore, the aim of this study was to characterise the knee extensors' muscle function *in vivo* through the determination of the ability to develop strength at different muscle length and the ability to produce strength and power across different angular speeds, in absolute units, relative to BM and relative to leg lean mass in a population of elderly men and women in normal weight and with obesity. We hypothesised that absolute strength and power were higher, while useful and specific force and power were impaired in individuals with obesity compared to normal weight controls.

Methods

Participants

Seventy older adults aged 60-80 years, resident in Verona (Italy), volunteered for this study. The participants were divided in four groups based on sex and BMI: women (n=16) and men (n=18) with normal weight (BMI ≥18.5 and <30 kg/m^2); women (n=18) and men (n=18) with obesity (BMI≥30 kg/m^2). Participants were excluded from the study in case of acute injuries, chronic symptomatic conditions, joint instability, prosthesis, <6 months or pain in the lower extremities or any neurological condition that could interfere with the expression of maximal force. The habitual physical activity level of each participant was evaluated by means of the International Physical Activity Questionnaire (IPAQ) (Lee et al., 2011), along with the history of falls or near-falls of the past year. The study was approved by the Ethics board of the University of Verona (Prog. n 739CESC, prot. n 79152 December 12th, 2018) and participants gave their written informed consent.

Anthropometric and body composition measurements

In the morning, in a fasted state, body mass was assessed with an electronic scale (Tanita electronic scale BWB-800 MA) and stature was measured with a Harpenden stadiometer (Holtain Ltd., Crymych, Pembs. UK). BMI was calculated as weight (kg)/height (m)^2 (Visser et al., 1999). Total body and regional body composition (lean mass and body fat) were evaluated by means of a DEXA and a total body scanner (QDR Horizon W, Hologic, MA, USA; Fan-Bean Technology, ver. 12.4.2) accordingly to the manufacturer’s procedures. The LLM$_R$ was used in the normalisation of the torque and power data (Andrew J. Skalsky et al., 2009). ALM and ALMI were calculated as the sum of lean mass of arms and legs and as ALM divided by height squared, respectively (Cruz-Jentoft et al., 2019a).

Muscle strength measurements

On the same day, an isokinetic dynamometer (CMSi Cybex Humac Norm Dynamometer, Lumex, Ronkokoma, NY, USA) was used to assess the maximal isometric and isokinetic torque of the quadriceps femoris of the right leg. The device was calibrated, and the gravity correction executed accordingly to the manufacturer's procedures.

After familiarisation and preliminary identification of the full range of motion, the participants seated on the dynamometer chair (90° at the hip) with the mid-thigh, hip and trunk secured with straps. The knee-joint centre was aligned with the rotational axis of the dynamometer and the leg was fixed with a length-adjustable lever arm. Maximal isometric trials were conducted in a random sequence separated by a 5-min recovery, at 30°, 60°, 75° and 90° knee joint angles. Each trial consisted in three maximal contractions with 60 s-recovery. After 10 min, maximal isokinetic knee extension-flexion tests were also performed in a randomised sequence, separated by a 5-min recovery, at 60, 90, 150, 180 and $210°\cdot s^{-1}$. Each trial consisted in three knee extension-flexion movements with 60 s-recovery.

Muscle isometric and isokinetic strength analysis

The angle and torque signals were sampled at 1000 Hz. A custom written optimal filter was used to maximise the signal-to-noise ratio and to smooth the signal. The highest isometric and isokinetic torque values were considered for the analysis (Mullineaux et al., 2001) and expressed in absolute units (Nm), relative to BM (Nm/kg) and to right leg lean mass ($Nm/kg_{Leglean}$) (Lee and Dierickx, 2018). The window for calculating the maximal torque in isometric conditions was 0.2 seconds, whilst the window for calculating the maximal torque in dynamic conditions was 0.02 seconds.

Individual values of maximal isometric torque ($T_{(30-90)}$) were fitted with a second order polynomial function, i.e. the torque-angle relationship and the three parameters of the quadratic function that best fitted the experimental data were identified with Matlab (Mathworks, ver. 2018b) built-in nonlinear least-square solver *lsqcurvefit* (Coleman and Li, 1996). These were used to compute the vertex of the quadratic function, that provided the individual maximal isometric torque (Tmax) and the corresponding angle (Ferri et al., 2003) (**Figure 2. 1**, panel A).

The values of maximal isokinetic knee-extensor torque at different velocities ($T_{v\ (60-210)}$) were fitted with the Hill's hyperbolic function (Hill, 1938), which describes the change in the muscle force expression capacity with speed of contraction. Hill's function $T_v = (T_0 \cdot b - a \cdot v)/(v+b)$ was fitted using *lsqcurvefit* (Coleman and Li, 1996) and the estimated maximal isometric torque T_0 (i.e. T_v in $v = 0$), *a* and *b* parameters were quantified. The value of Fmax was used as a first-guess for T_0 during the fitting process. The individual theoretical Vmax was obtained by the Hill's equation for $T_v = 0$, i.e.: $Vmax = (T_0 \cdot b)/a$ (**Figure 2. 1**, panel B). The power was calculated as the product between torque and velocity. The Pmax, the Vopt (vopt, i.e., the contraction velocity at Pmax) and torque (Topt, i.e., the torque expressed at Pmax), were also calculated (**Figure 2. 1**, panel C).

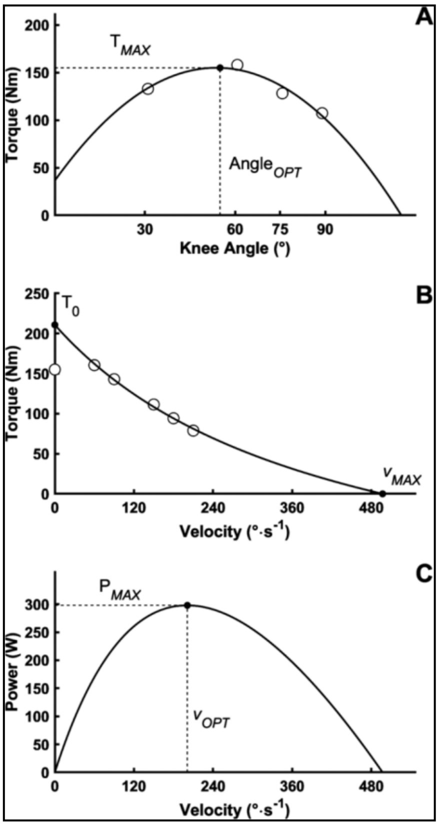

Figure 2. 1: The experimental data points of maximal isometric torque at different angles (panel A), torque-velocity (panel B) and power velocity (panel C) in a representative subject were fitted using Hill's equation. (Taken from Muollo et al., 2021).

Statistical Analysis

After checking for normality (Shapiro-Wilks for normal distribution, Brown-Forsythe for homogeneity of variance), a three-way ANOVA was used to compare the different groups for isometric (sex x BMI x angle) and isokinetic (sex x BMI x velocity) outcomes (expressed in absolute values, relative to body mass and leg lean mass). A two-way ANOVA (sex x BMI) was used for anthropometric and body composition variables and parameters estimated with the Hill's equation. A paired multiple comparison was applied by means of the Holm-Sidak method.

Data are reported as mean ± standard deviation. Statistical analyses were performed with SigmaPlot 14.0 with a level of significance set at $p \leq 0.05$.

Based on variances in T_0 measured in our laboratory in control participants (between-participants coefficient of variation = 25%), using a power of 0.8 and a p > level of 0.05, the sample size analysis for a two-way ANOVA (Sigma Stat version 1; Jandel Scientific, S. Raphael, CA) indicated that the minimum number of participants required to detect a significant difference between the 4 sex/BMI groups (i.e., a 30% difference between groups) was 16 per group.

Results

Anthropometric and body composition characteristics

In **Table 2. 1** the characteristics of participants are reported. The four groups did not differ in terms of age and PAL ($p > 0.05$) and none of the participants reported a positive fall and near-fall history in the previous year. A significant main effect for sex was found for all the body composition parameters, with exception for BMI and total body fat (expressed in kg). A significant main effect for BMI was found for total body fat (expressed in kg and %) and lean mass, ALM, ALMI, leg lean mass and LLM_R. A sex x BMI interaction was found for total body fat (expressed in %) ($p = 0.036$), total lean mass ($p = 0.049$), ALM ($p = 0.021$) and ALMI ($p = 0.045$). The pairwise multiple comparisons showed that both women and men with obesity had higher values for total body fat expressed in kg and %, total lean mass (10% vs 16%, $p = 0.001$), ALM (12%, $p = 0.034$; 20%, $p = 0.001$), ALMI (11% and 18%, $p = 0.001$), leg lean mass (14%, $p = 0.010$; 19%, $p = 0.001$), LLM_R (15%, $p = 0.010$; 19%, $p = 0.001$) than the normal weight of the same sex.

Table 2. 1: Anthropometric and body composition characteristics of study participants

Outcomes	OB$_W$ (n=18)	NW$_W$ (n=16)	OB$_M$ (n=18)	NW$_M$ (n=18)	Sex effect	BMI effect	Sex x BMI
Age (years)	69.3 ± 4.4	68.4 ± 5.2	67.1 ± 6.0	70.3 ± 5.6	p = 0.918	p = 0.377	p = 0.105
BM (kg)	83.4 ± 8.7	56 ± 5.9 *	100.1 ± 17.2 °	71.4 ± 4.8 *°	p < 0.001	p < 0.001	p = 0.795
Height (m)	1.57 ± 6.0	1.57 ± 4.0	1.72 ± 6.0 °	1.71 ± 5.0 °	p < 0.001	p = 0.551	p = 0.725
BMI (kg/m²)	33.8 ± 2.8	22.8 ± 1.9 *	33.7 ± 4.3	24.4 ± 1.0 *	p = 0.269	p = 0.001	p = 0.190
	Class I (61%)	< 18.5 (0%)	Class I (83%)	< 18.5 (0%)			
	Class II (33%)	18.5 - 29.9 (100%)	Class II (11%)	18.5 - 29.9 (100%)			
	Class III (6%)		Class III (6%)				
PAL (METs·min·week)	925.8 ± 900.8	1015.5 ± 767.3	1184.1 ± 937.2	1365.8 ± 712.3	p = 0.133	p = 0.500	p = 0.819
Total BF (kg)	41.7 ± 5.6	18.9 ± 3.9 *	39.2 ± 14	18.4 ± 2.7 *	p = 0.412	p = 0.001	p = 0.605
Total BF (%)	50.5 ± 2.4	33.6 ± 3.6 *	38.3 ± 7.1 °	25.7 ± 2.9 *°	p = 0.001	p = 0.001	p = 0.036
Total LM (kg)	38.7 ± 3.5	35.2 ± 3.2 *	58.1 ± 7.0 °	50.3 ± 3.3 *°	p = 0.001	p = 0.001	p = 0.049
ALM (kg)	15.9 ± 1.8	14.23 ± 1.5 *	25.9 ± 3.7 °	21.6 ± 1.5 *°	p = 0.001	p = 0.001	p = 0.021
ALMI (kg/m²)	6.5 ± 0.7	5.8 ± 0.6 *	8.7 ± 1.1 °	7.4 ± 0.4 *°	p < 0.001	p < 0.001	p = 0.045
LLM (kg)	12.2 ± 1.2	10.7 ± 1.1 *	19.0 ± 2.8 °	16.0 ± 1.1 *°	p = 0.001	p = 0.001	p = 0.056
LLM$_R$ (kg)	6.2 ± 0.6	5.4 ± 0.6 *	9.6 ± 1.5 °	8.1 ± 0.5 *°	p = 0.001	p = 0.001	p = 0.073

**** vs OB of the same sex at p < 0.05; ° vs women of the same category at p < 0.05***

OB$_W$: Obese women; NW$_W$: Normal weight women; OB$_M$: Obese men; NW$_W$: Normal weight women; BMI: Body Mass Index; PAL: Physical Activity Level; MET: Metabolic Equivalent; BF: Body Fat; LM: Lean Mass; ALM: Appendicular Lean Mass; ALMI: Appendicular Lean Mass Index; LLM: Leg Lean Mass; LLM$_R$: Right Leg Lean Mass

Isometric and isokinetic measurements

In absolute units

Maximal isometric torque for every tested angle is presented in **Figure 2. 2**, Panel A. The ANOVA resulted in a main effect for sex ($p < 0.001$), BMI ($p = 0.001$) and angle ($p < 0.001$) with no three-way ($p = 0.969$) or two-way interactions for BMI x sex ($p = 0.974$), BMI x angle ($p = 0.951$) and sex x angle ($p = 0.069$).

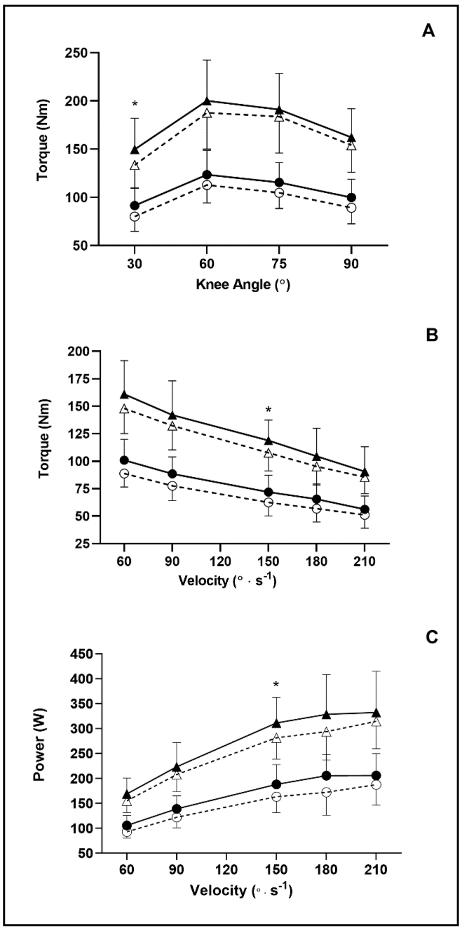

Figure 2. 2: Average ± standard deviation absolute values of maximal isometric torque at different angles (panel A), torque-velocity (panel B) and power velocity (panel C) in obese (continuous lines) women (●) and men (▲) and in normal weight (dashed lines) women (○) and men (△). * vs obese men at $p < 0.05$. (Taken from Muollo et al., 2021).

In regards of the absolute isokinetic torque (**Figure 2. 2**, Panel B), there was a main effect for sex ($p < 0.001$), BMI ($p < 0.001$) and velocity ($p < 0.001$), with no three-way ($p = 1.000$) or two-way interactions for BMI x sex ($p = 0.923$), BMI x velocity ($p = 0.818$), but a significant sex x velocity interaction ($p < 0.001$). This latter significant interaction indicates that the differences in torque at the different velocities are affected by sex.

In regards of the absolute isokinetic power (**Figure 2. 2**, Panel C), there was a main effect for sex ($p < 0.001$), BMI ($p < 0.001$) and velocity ($p < 0.001$), with no three-way ($p = 1.000$) or two-way interactions for BMI x sex ($p = 0.912$), BMI x velocity ($p = 0.650$), but a significant sex x velocity interaction ($p < 0.001$). This latter significant interaction indicates that the differences in power at the different velocities are affected by sex.

Per unit of body mass

In regards of the isometric torque relative to BM (**Figure 2. 3**, Panel A) there was a main effect for sex ($p < 0.001$), BMI ($p < 0.001$) and angle ($p < 0.001$) with no three-way ($p = 0.979$) or two-way interactions for BMI x sex ($p = 0.251$), BMI x angle ($p = 0.178$) and sex x angle ($p = 0.328$).

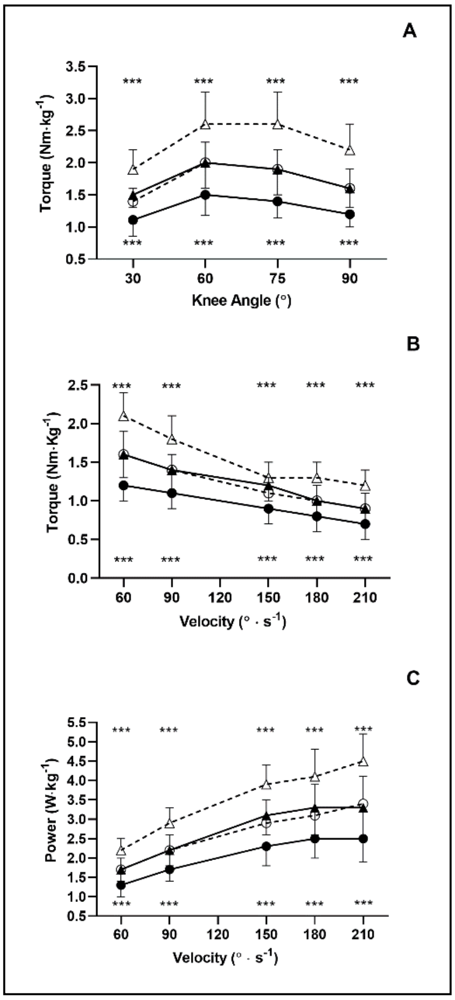

Figure 2. 3: Average ± standard deviation values normalised for body mass of maximal isometric torque at different angles (panel A), torque-velocity (panel B) and power velocity (panel C) in obese (continuous lines) women (●) and men (▲) and in normal weight (dashed lines) women (○) and men (△). *** vs obese men and obese women at p < 0.001. (Taken from Muollo et al., 2021).

Per unit of muscle mass

For the isometric torque relative to the right leg lean mass (**Figure 2. 4**, Panel A), there was a main effect for sex ($p < 0.001$), BMI ($p = 0.003$) and angle ($p < 0.001$) with no three-way ($p = 0.979$) or two-way interactions for BMI x sex ($p = 0.087$), BMI x angle ($p = 0.698$), sex x angle ($p = 0.841$).

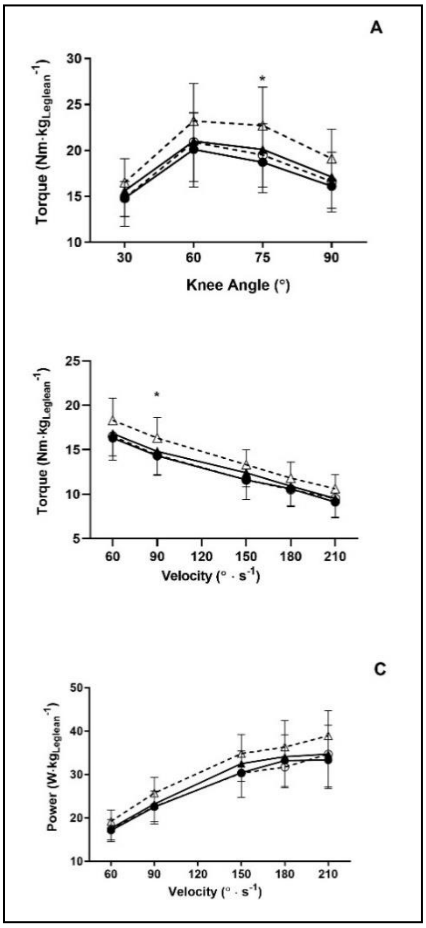

Figure 2. 4: Average ± standard deviation values normalised for the right leg lean mass of maximal isometric torque at different angles (panel A), torque-velocity (panel B) and power velocity (panel C) in obese (continuous lines) women (●) and men (▲) and in normal weight (dashed lines) women (○) and men (△). * vs obese men at p < 0.05. (Taken from Muollo et al., 2021).

For isokinetic torque relative to LLM_R (**Figure 2. 4**, Panel B), the ANOVA reported a main effect for sex ($p < 0.001$), BMI ($p = 0.004$) and velocity ($p < 0.001$) with no three-way ($p = 0.985$) or two-way interactions for BMI x velocity ($p = 0.946$), sex x velocity ($p = 0.915$), but a significant interaction for BMI x sex ($p = 0.013$). This latter significant interaction indicates that the differences in torque at the different velocities are affected by sex and BMI.

For isokinetic power relative to LLM_R (**Figure 2. 4**, Panel C) the ANOVA reported a main effect for sex ($p < 0.001$), BMI ($p = 0.021$), velocity ($p < 0.001$) with no three-way ($p = 0.977$) or two-way interactions for BMI x velocity ($p = 0.707$), sex x velocity ($p = 0.771$), but a significant interaction for BMI x sex ($p = 0.022$). This latter significant interaction indicates that the differences in power at the different velocities are affected by sex and BMI.

Parameters estimated with the Hill’s equation

Compared to the women of the same category, men had significant higher Tmax and T_0 (in absolute values and relative to BM), Vmax, Vopt and Topt (in absolute values and relative to BM) (**Table 2. 2**).

Table 2. 2: Parameters of the torque-velocity and power-velocity relationship

	Outcomes	OB$_W$	NW$_W$	OB$_M$	NW$_M$	Sex effect	BMI effect	Sex x BMI
	T_{MAX} (Nm)	125.8 ± 20.8	115.4 ± 14.1	203.1 ± 38.2 °	190.4 ± 97.9 °	$p < 0.001$	$p = 0.115$	$p = 0.871$
	T_{MAX} (Nm/kg) [a]	1.5 ± 0.3	2.1 ± 0.3 *	2.0 ± 0.3 °	2.7 ± 0.5 *°	$p < 0.001$	$p < 0.001$	$p = 0.753$
	T_{MAX} (Nm/kg$_{Leglean}$) [b]	20.4 ± 3.3	21.5 ± 3.4	21.3 ± 4.0	23.5 ± 4.1	$p = 0.103$	$p = 0.066$	$p = 0.541$
	Angle$_{OPT}$	61.9 ± 6.6	64.8 ± 10.0	63.1 ± 7.1	64.7 ± 6.1	$p = 0.764$	$p = 0.217$	$p = 0.729$
B	T_0 (Nm)	134.6 ± 22.5	119.7 ± 15.7 *	208.4 ± 37.4 °	191.0 ± 28.9 °	$p < 0.001$	$p = 0.017$	$p = 0.858$
	T_0 (Nm/kg) [a]	1.6 ± 0.3	2.2 ± 0.3 *	2.1 ± 0.4 °	2.7 ± 0.4 *°	$p < 0.001$	$p < 0.001$	$p = 0.759$
	T_0 (Nm/kg$_{Leglean}$)[b]	21.8 ± 3.0	22.2 ± 2.7	21.8 ± 3.0	23.7 ± 3.2	$p = 0.326$	$p = 0.110$	$p = 0.313$
	v_{MAX} (°/s)	531.3 ± 69.5	502.5 ± 66.0	696.2 ± 170.5 °	671.1 ± 80.8 °	$p < 0.001$	$p = 0.295$	$p = 0.943$
C	P_{MAX} (W)	198.6 ± 41.2	171.6 ± 38.8	351.3 ± 88.0 °	315.8 ± 60.5 °	$p < 0.001$	$p = 0.036$	$p = 0.769$
	P_{MAX} (W/kg) [a]	2.4 ± 0.5	3.1 ± 0.7 *	3.5 ± 0.8 °	4.4 ± 0.7 *°	$p < 0.001$	$p < 0.001$	$p = 0.527$
	P_{MAX} (W/kg$_{Leglean}$) [b]	32.1 ± 5.8	31.7 ± 6.1	36.5 ± 7.7	39.0 ± 6.3 °	$p < 0.001$	$p = 0.495$	$p = 0.364$
	v_{OPT} (°/s)	211.2 ± 23.3	202.1 ± 22.0	259.6 ± 56.5 °	252.1 ± 28.9 °	$p < 0.001$	$p = 0.339$	$p = 0.924$
B-C	T_{OPT} (Nm)	53.6 ± 8.8	48.1 ± 5.2 *	78.2 ± 14.2 °	71.7 ± 10.3 °	$p < 0.001$	$p = 0.017$	$p = 0.850$
	T_{OPT} (Nm/kg) [a]	0.6 ± 0.1	0.9 ± 0.1*	0.8 ± 0.1 °	1.0 ± 0.1 *°	$p < 0.001$	$p < 0.001$	$p = 0.981$
	T_{OPT} (Nm/kg$_{Leglean}$) [b]	8.7 ± 1.2	8.9 ± 1.0	8.2 ± 1.2	8.9 ± 1.1	$p = 0.299$	$p = 0.074$	$p = 0.407$

A-C correspond to the parameters obtained in the isometric and isokinetic trials. * vs OB of the same sex at $p < 0.05$; ° vs women of the same category at $p < 0.05$; [a] relative to body mass; [b] relative to right leg lean mass. Abbreviations: OB: Obese; NW: Normal Weight; W: Women; M: Men; T_{MAX}: maximal isometric torque; Angle$_{OPT}$: optimal angle; T_0: maximal torque at velocity equal to zero; v_{MAX}: theoretical maximal velocity at torque equal to zero; P_{MAX}: maximal power; v_{OPT}: optimal velocity; T_{OPT}: optimal force. A, B, C correspond to the parameters obtained in the isometric and isokinetic trials.

In absolute values and adjusted for BM, Pmax was larger in men than women of the same category, whereas relative to the leg lean mass, was higher in the normal weight men than normal weight women ($p = 0.002$), with a trend in the obese men compared to the obese women ($p = 0.059$). $Angle_{OPT}$, Tmax, T_0 and Topt relative to LLM_R did not differ significantly between men and women. Relative to BM, obese men and women had lower Tmax (-27% and -23%, respectively), T_0 (-24% and -21%, respectively), Pmax (-22% and -20%, respectively) and Topt (-25% and -22%, respectively) compared to the normal weight counterparts.

Discussion

This is the first study that provides a complete picture of the impact of sex and obesity on isometric and isokinetic strength and power during ageing. The study confirmed sex differences in body composition, strength, and power in favour of men, in both BMI groups. Moreover, in line with our hypothesis, the ability to express isometric maximal torque, isokinetic torque and power changed with different muscle lengths and speeds of contraction, but, with a similar profile in both BMI groups. Contrary to our hypothesis, absolute values of strength, power and speeds were not different among BMI groups; however, people with obesity had lower values of strength and power relative to BM, i.e., useful strength/power, suggesting physical limitations when moving their body into the space. Finally, in contrast with previous studies conducted in participants with severe obesity, the overall intrinsic skeletal muscle's ability of producing torque and power, i.e., the specific strength/power, seemed preserved in our study sample, mainly composed of individuals with class I of obesity, compared to normal weight peers.

Only 1/3 of the women and 1/6 of the men showed a class of obesity > I, in line with the prevalence of this condition in Italian population as compared with North American one (Marques et al., 2018; Ogden et al., 2017). Furthermore, the prevalence of sarcopenia defined by ALMI (Cruz-Jentoft et al., 2019a) was lower in obese than the normal weight group (Johnson Stoklossa et al., 2017; Perna et al., 2017). As such, the present study sample is representative of sedentary Italian elders' population with normal weight and with obesity (Perna et al., 2017). Finally, our study confirmed previously observed sex differences in body composition

(Lafortuna et al., 2005), i.e. a higher percentage of total body fat and lower levels of total lean mass and appendicular lean mass in women compared to men.

Maximal isometric torque is a marker of current and prospective health that has been linked to healthy ageing (McLeod et al., 2016b) and independent living (Buckinx and Aubertin-Leheudre, 2019; Tallis et al., 2018). In addition, maximal isometric strength is strongly associated with total lean mass, so leg extensors strength measurements can be used as a proxy of muscle mass. In agreement with the existing literature, absolute torque was found to be higher in men at all knee angles, reaching higher Tmax compared to women, with no significant differences in optimal angle. The sex-differences in torque-angles and Tmax found in our study might be explained by the higher total and regional lean mass of men over women (Barbat-Artigas et al., 2013). On the other hand, in agreement with previous studies, our results showed similar absolute Tmax and torque-angles between the participants with obesity and the normal weight group (Miyatake et al., 2000; Zoico et al., 2004). Interestingly, our study found that men with obesity exhibited higher torque (+12%) than normal weight group at short muscle's length in agreement with Maffiuletti et al., who tested a population of young adolescents with OB (Maffiuletti et al., 2008). Indeed, it has been reported that with increasing class of obesity, compensatory strategies are adopted to perform daily activities that involve lower extremities (e.g. chair stand, knee to stand, stair ascent and descent) (Naugle et al., 2012). In particular, people with obesity tend to avoid those movements that may require deep knee flexions and large range of motion (and therefore long muscle lengths), in order to reduce the biomechanical burden on the joint of lower extremities. These compensatory strategies may explain a better preservation of performance of the leg muscles at low compared to the larger angles.

Our data constitute a valuable reference for muscle dynamic torque and power in older adults (see e.g. (Macaluso and De Vito, 2004)). Isokinetic testing allows the characterisation of the dynamic expression of force, i.e., strength and power in dynamic movements or in situations that require a prompt response to a loss of balance. In agreement with previous studies (Buckinx and Aubertin-Leheudre, 2019; Leblanc et al., 2015), the results confirmed that men expressed higher isokinetic torque and power across all the tested velocities compared to women.

Moreover, participants with obesity showed similar absolute isokinetic torque and power compared to the normal weight group, therefore suggesting that obesity does not impair the overall ability to produce strength and power in dynamic conditions. Conversely, Villareal et al. (Dennis T Villareal et al., 2004) found a deterioration of isokinetic torque (tested at $60^{\circ}\cdot s^{-1}$) in a group of sedentary elders with a more severe obesity (i.e. class II) compared to our study sample.

Torque and power relative to BM are important components of mobility since several tasks of the daily living require the movement of the body in the space. For example, extensor torque values of ~0.7-1.5 $Nm\cdot kg^{-1}$ are required for walking upstairs (Hortobágyi et al., 2003; Kowalk et al., 1996) and of ~1.5-2.0 $Nm\cdot kg^{-1}$ for descending stairs (Startzell et al., 2000). Furthermore, to stand up from a seated position, the average knee torque needed is 111-186 Nm (~1.7-2.9 $Nm\cdot kg^{-1}$) (PAI and ROGERS, 1991). The useful strength values in our participants with obesity and controls were all above the minimum requirement for independent household activity. However, the current strength (in $Nm\cdot kg^{-1}$) was only 1.1±0.2 and 1.4±0.2 folds the minimum requirements for independent living respectively in obese men and women, and significantly lower (i.e., 1.4±0.2 and 1.8±0.3 respectively in women and men) compared to the normal weight counterparts. This may suggest that a smaller "safety margin" for independent living might be associated with the condition of obesity. Hypothesising a physiological rate of decline of 0.6% and 1% per year in women and men respectively (Hughes et al., 2001), this entails a shorter independence time margin (-3.2 and -1.6 years in women and men) in the individuals with obesity compared to normal weight controls. Importantly, any increase in BM and/or acute reductions of strength could accelerate the autonomy decline in these individuals.

In agreement with previous studies (Bollinger, 2017a), our work confirmed that isometric torque per unit of body mass at different knee angles was ~20-30% lower in individuals with obesity compared to normal weight. Furthermore, across all the tested velocities, muscle isokinetic torque and power normalised for BM resulted 20 to 26% lower in participants with obesity with reference to the control group. These differences are smaller compared to previous work in adolescents (Maffiuletti et al., 2007) and adults (Lafortuna et al., 2005), characterised by a higher level of obesity. Moreover, the increase in power as a function of speed that is observed in normal weight groups appears dampened in individuals with obesity of both sexes, particularly so at the higher speeds (i.e., above 150°s^{-1}).

Participants with low muscle strength and power of the lower limb muscles have higher risk of falling (Hortobágyi et al., 2003). For instance, a previous study (Han and Yang, 2015) showed that young individuals that fell after a postural perturbation express lower power values (~2.0 at low speed and 4.5 W·kg^{-1} at high speed) compared to the group that recovered (~2.5 at low speed and 5.5 W·kg^{-1} at high speed) after the perturbation. Therefore, assessing isokinetic torque and power may allow to quantify the ability to react quickly to a postural perturbation or to support body mass during reactive stepping. Compared to the values reported in the aforementioned study, the isokinetic power normalised for body mass in this sample was appreciably lower than the one required to recover from a postural perturbation; this suggests a potential high risk of incurring in falls and injuries in both normal weight (normal weight women 1.7-3.1, normal weight 2.2-4.1 W·kg^{-1}, at low and high speed respectively) and obesity (obese women 1.3-2.5, obese men 1.7-3.3 W·kg^{-1}, at low and high speed respectively).

Specific torque and power, reflect muscle quality (S. Barbat-Artigas et al., 2012) and a warning signal of muscles deterioration towards the early diagnosis of sarcopenia (25,48,49). Among the factors that may contribute to a low specific force and power there are selective atrophy of type II fibres, increase in fat infiltration, connective tissue proliferation and fibrosis (McGregor et al., 2014), all of which have been described with ageing and obesity (Tallis et al., 2018). Interestingly, poor muscle quality was previously found only in participants with obesity and metabolic syndrome, but not in those with a healthy metabolic profile (Sébastien Barbat-Artigas et al., 2012; Poggiogalle et al., 2019) and in middle aged and elderly people with class II or III of obesity (Maria Hulens et al., 2001; Valenzuela et al., 2020; Dennis T Villareal et al., 2004). These findings suggest that the occurrence of lower muscle quality may depend on the presence/absence of metabolic syndrome and on the class of obesity. This may be the reason why in our study, that included mostly individuals with class I of obesity and no metabolic syndrome, specific torque and power were not different between the two BMI groups. Future studies need to include individuals with different class of obesity and specifically address the impact of metabolic health on the conservation of muscle quality with ageing. This is the first study to provide estimates of T_0, Vmax, Topt and Vopt in participants with obesity; these indexes allow the prioritisation of training objectives according to the prevailing deficit (strength or speed) in each individual. In agreement with previous studies (S. Barbat-Artigas et al., 2012), our results showed higher absolute values in T_0, Vmax, Topt and Vopt in men compared to women. As expected, all the parameters appear lower in the elderly group compared to the values of young individuals reported elsewhere, reflecting the well-known age-related changes in muscle's fibre type and architecture (Bollinger, 2017a; Raj et al., 2010). However, all key parameters of muscle power characterising the Hill's equation (i.e., Vmax, Topt and Vopt) did not differ among BMI groups, suggesting no specific impact of the weight excess on the torque-velocity profile of muscle function.

The present study has some limitations. First, we recruited a relatively homogeneous population in terms of class of obesity (most of our participants had a class I of obesity), physical activity level (low levels of physical activity) and age (60-80 years). This was done to contain the between-participants variability and the effect of these confounding variable on muscle strength and power. This on one hand might have reduced the differences among the BMI groups of both sexes and on the other hand might reduce the generalisability of our results in a more heterogeneous sample. Finally, although DEXA is the most used tool in clinical setting for the assessment of total and compartmental lean mass, other more accurate methods (i.e. magnetic resonance imaging or computed tomography scan) better describe the intermuscular fat content and allow to pick up subtler differences in muscle quality among BMI groups (Erlandson et al., 2016).

Conclusion

In conclusion, this study confirmed sex differences between men and women in producing torque and power in absolute values and adjusted for body mass or leg lean mass. Obesity reduced the useful torque/power at different muscle lengths and angular speeds that may lead to a potential loss of autonomy. However, muscle quality seems to be preserved, suggesting that the intrinsic skeletal contraction ability is not impaired in individuals with a class I of obesity.

EXPERIMENTAL RESEARCH: STUDY 2

Knee flexor and extensor torque ratio in elderly men and women with and without obesity: a cross-sectional study

Valentina Muollo[1], Andrea Zignoli[2], Laura Ghiotto[3], Chiara Milanese[3], Mauro Zamboni[4], Federico Schena[3,5], Andrea P Rossi[4]

[1] Department of Medicine, University of Verona, Verona, Italy
[2] Department of Industrial Engineering, University of Trento, Trento, Italy
[3] Department of Neuroscience, Biomedicine and Movement, University of Verona, Verona, Italy
[4] Department of Medicine, Section of Geriatrics, Healthy Aging Center Verona, Verona, Italy
[5] CeRiSM, Sport, Mountain and Health Research Center, University of Verona, Rovereto, Italy

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Abstract

Background and aims: With aging and obesity lower limb torque deteriorates. Importantly, the ratio between knee flexor (KF) and extensor (KE) torque is an indicator of joint stability. We compared KF torque and KF/KE ratio in older subjects of both sexes with or without obesity.

Methods: The maximal torque during KE and KF isokinetic contractions were evaluated at: 60, 90, 150, 180 and 210 deg/s in 89 elderly (68 ± 5 years) subjects with normal weight (BMI < 30 kg/m^2) and obesity (BMI ≥ 30 kg/m^2). Values were normalised for BM and leg lean mass (i.e., muscle quality).

Results: At all speeds men had higher absolute KF values ($p < 0.001$). When values were normalised for BM, sex differences remain in favour of men ($p < 0.001$) with lower values in both groups with obesity than normal weight ($p < 0.001$). Muscle quality and KF/KE ratio were lower in obese than normal weight participants ($p < 0.001$).

Conclusions: The KF torque and KF/KE ratio decline with aging and with obesity. In all groups, the KF/KE ratio was below the joint stability threshold. Thus, exercise physiologists should include exercises designed to train both KE and KF in older subjects with obesity.

Introduction

The prevalence of obesity in elderly adults is progressively increasing worldwide (Kelly et al., 2008). The factors that contribute to a reduction in functional disability are mainly at the cardiovascular, metabolic, and musculoskeletal levels (Borges et al., 2015). Older subjects with obesity commonly show an insufficient level of skeletal muscle mass, torque, and quality (i.e., muscle torque per unit of lean mass) that increase the risk of frailty and the loss of independence (Buckinx et al., 2019; Rossi-Izquierdo et al., 2016).

In the elderly, lower extremities are compromised due to a natural detrimental physiological effect of aging and sedentary lifestyle (Bollinger, 2017a). Commonly, muscle maximal mechanical output deteriorates, with consequences on gait mechanics and balance maintenance (Borges et al., 2015). Several studies (Bollinger, 2017a) reported torque decline specifically in KE muscles. In comparison, the KF received little attention (Bollinger, 2017a; Borges et al., 2015) even if they might be equally important for several tasks of daily life (de Zwart et al., 2015).

The ratio between maximal isokinetic concentric KF and KE torque is a parameter applied in injury prevention and rehabilitation (da Rosa Orssatto et al., 2018). From a clinical standpoint, a conventional value of 0.5 (i.e., KE muscles twice as strong as KF) demarcates a critical level for joint stability and risk of joint degeneration (e.g., osteoarthritis) (Behan et al., 2018; da Rosa Orssatto et al., 2018)). Osteoarthritis is a pathology that can lead to a reduction in physical exercise, muscle torque and sarcopenia, and contributes to an increase in the risk of falling and hospitalization (Behan et al., 2018). Moreover, obesity alone is known to raise the risk of musculoskeletal injuries and lower extremities osteoarthritis (Bollinger, 2017a; Segal et al., 2012).

We already conducted a full characterization of knee extensors isometric, isokinetic torque, and power in sedentary elderly subjects with obesity and without obesity of both sexes (Muollo et al., 2021). Our results revealed similar muscle torque and power expressed in absolute units, with no alteration in muscle quality (in line with the existing literature (Bollinger, 2017a)). However, knee extensors muscle torque and power relative to BM was lower in elderly subjects with obesity of both sexes than the normal weight.

To our knowledge, limited data is available on the possible effects of obesity on KF muscles functioning in the elderly (Bollinger, 2017a). The purposes of our study were: *1)* to provide reference values for KF muscles torque and *2)* to compare KF/KE ratio in elderly subjects of both sexes with or without obesity. We expected similar KF values for individuals with normal weight and obesity, but lower KF/KE ratios in the groups with obesity. We hypothesised that lower KF/KE ratios in the groups with obesity could be due to a disproportionate KE torque rather than to a KF deficiency.

Methods

Participants

A total of 89 Caucasian sedentary elderly (60-80 years) men and women with normal weight (N = 34, (BMI < 30 kg/m^2) and obesity (N = 55, BMI ≥ 30 kg/m^2) were recruited (**Table 2. 3**) from Verona (Italy) metropolitan area. Participants were excluded if they had a recent history (< 6 months) of musculoskeletal injuries or any other pathology that could interfere with the maximal individual's torque expression capacity. The minimum sample size required to detect significant differences between BMI-sex groups (power of 90%, significance value of 0.05, minimum detectable difference in means computed as 25% of the coefficient of variation of the KF/KE ratios in a control group) was 80. The study was approved by the Ethics Board of the University of Verona (Prog. n 739CESC, prot. n 79152, 2018). All participants gave written consent.

Table 2. 3: Anthropometric, body composition variables in men and women with and without obesity

Outcomes	**OB group (n = 55)**		**NOB group (n = 34)**	
	OB$_W$ (n = 30)	**OB$_M$ (n = 25)**	**NOB$_W$ (n = 16)**	**NOB$_M$ (n = 18)**
Age (years)	67.8 ± 4.6	67.8 ± 6.1	68.4 ± 5.1	70.3 ± 5.6
BW (kg)	80.8 ± 9.3 *	99.8 ± 16.1 §*	56.0 ± 5.9	71.4 ± 4.8 §
Height (m)	1.6 ± 0.1	1.7 ± 0.1	1.6 ± 0.0	1.7 ± 0.0
BMI (kg/m^2)	32.6 ± 3.1 *	33.5 ± 4.0 *	22.8 ± 1.9	24.4 ± 1.0 §
Total FM (kg)	38.1 ± 6.2	37.7 ± 12.0	18.9 ± 3.9	18.4 ± 2.7

Total LM (kg)	39.7 ± 4.7	58.9 ± 7.0	35.2 ± 3.2	50.3 ± 3.3
Right LLM (kg)	6.3 ± 0.7	9.6 ± 1.3	5.4 ± 0.5	8.1 ± 0.5
Right TLM (kg)	4.5 ± 0.7	6.4 ± 1.0	3.7 ± 0.4	5.6 ± 0.4

§denotes significant (p<0.01) differences: men vs women of the same sex; *denotes significant (p<0.01) differences: men vs women of the same sex. Abbreviations: OB: obesity; NOB: without obesity; W: women; M: men; BMI: body mass index; FM: total fat mass; LM: total lean mass; ALM: appendicular lean mass; LLM: leg lean mass; TLM: thigh lean mass

Anthropometric and body composition analysis

BM was taken with an electronic scale (Tanita electronic scale BWB-800 MA) and height was measured with a Harpenden stadiometer (Holtain Ltd., Crymych, Pembs. UK) for assessing the BMI. Total and regional body lean, and fat mass were measured by DEXA using a total body scanner (QDR Horizon W, Hologic, MA, USA; Fan-Bean Technology, ver. 12.4.2). A specific region of interest labelled “thigh” was identified for the tested right leg by tracing an oblique line passing through the femoral neck to the horizontal line passing through the knee (Andrew J Skalsky et al., 2009).

Muscle strength protocol and analysis

In a single laboratory session, KE and KF isokinetic torque of the right leg were assessed with an isokinetic testing dynamometer (CMSi Cybex Humac Norm Dynamometer, Lumex, Ronkokoma, NY, USA). The protocol is described above in more details (Muollo et al., 2021). After 5-min of familiarisation, three maximal knee concentric extensions and flexions tests were performed at: 60, 90, 150, 180 and 210 deg/s. All the trials were randomised and interspersed by 60s-recovery. The best performances reported in each muscle group contraction for KE and KF torque were used for the analysis in absolute units (Nm), relative to BM and to the thigh lean mass (Nm/kg) (Segal et al., 2012). The KF/KE ratio was computed by dividing the maximal torque values of KF and KE torques as previously reported (Capodaglio et al., 2009; da Rosa Orssatto et al., 2018) .

Statistical analysis

The values are expressed as mean ± standard deviation. The normality of the distribution and the homogeneity of variance were checked with Shapiro-Wilk and

Brown-Forsythe tests. A three-way ANOVA was used to assess the influence of sex, BMI, and isokinetic velocity on torque production ability. If interaction was reported, the Holm-Sidak method was used to conduct the post hoc analysis. Significance was set at $p<0.05$. All statistical analysis was performed using SigmaPlot 12.5.

Results

For the absolute KF torque, the KF torque relative to BM and the KF torque relative to thigh lean mass, results of the ANOVA and the post-hoc analyses are reported in **Table 2. 4**.

Table 2. 4: Isokinetic torque of the knee flexor in elderly men and women with and without obesity

Outcomes	**Torque**					**Main effect**			**Interaction**			
	60 (deg/s)	**90 (deg/s)**	**150 (deg/s)**	**180 (deg/s)**	**210 (deg/s)**	**Sex**	**BMI**	**Velocity**	**Sex x BMI**	**Sex x velocity**	**BMI x velocity**	**Sex x BMI x velocity**
Absolute values (Nm)												
OB$_W$	42.4± 12.3	36.4 ± 13.2	29.4 ± 9.2	27.2 ± 7.8	24.8 ± 5.9	p<0.001	p=0.266	p<0.001	p=0.322	p=0.005	p=0.936	p=0.954
NOB$_W$	41.1 ± 8.1	37.1 ± 9.5	30.2 ± 7.1	27.4 ± 6.4	23.6 ± 5.2							
OB$_M$	67.1 ± 22.8§	61.1 ± 21.9§	47.0 ± 15.6§	44.0 ± 12.0§	39.8 ± 11.5§							
NOB$_M$	65.1 ± 15.2§	61.0 ± 13.2§	45.2 ± 11.2§	38.0 ± 11.7§	36.7 ± 9.9§							
Relative to BW (Nm/kg)												
OB$_W$	0.5 ± 0.1	0.5 ± 0.2	0.4 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	p<0.001	p<0.001	p<0.001	p=0.095	p=0.096	p=0.027	p=0.819
NOB$_W$	0.7 ± 0.1*	0.7 ± 0.2*	0.5 ± 0.1*	0.5 ± 0.1*	0.4 ± 0.1*							
OB$_M$	0.7 ± 0.2§	0.6 ± 0.2§	0.5 ± 0.2§	0.4 ± 0.1§	0.4 ± 0.1§							
NOB$_M$	0.9 ± 0.2§*	0.9 ± 0.2§*	0.6 ± 0.1*	0.5 ± 0.2	0.5 ± 0.1§*							
Relative to TLM (Nm/kg)												
OB$_W$	9.5 ± 2.8	8.1 ± 2.9	6.6 ± 2.2	6.1 ± 1.7	5.5 ± 1.3	p = 0.013	p<0.001	p<0.001	p=0.114	p=0.618	p=0.512	p=0.953
NOB$_W$	11.1 ± 2.2	10.0 ± 2.5*	8.2 ± 2.0*	7.4 ± 1.9*	6.4 ± 1.6							
OB$_M$	10.6 ± 3.9	9.5 ± 3.1	7.4 ± 2.5	6.9 ± 1.7	6.2 ± 1.8							
NOB$_M$	11.7 ± 2.9	11.0 ± 2.4	8.1 ± 1.9	6.8 ± 2.0	6.6 ± 1.8							

§***denotes significant (p<0.01) differences: men vs women of the same sex; *denotes significant (p<0.01) differences: men vs women of the same sex. Abbreviations: OB: obesity; NOB: without obesity; W: women; M: men; BMI: body mass index; BW: body weight; TLM: thigh lean mass***

The KF/KE ratio in men and women with obesity and normal weight are reported in **Figure 2. 5**. The ANOVA showed a main effect for BMI (p < 0.001) with no main effect for sex (p = 0.174) and velocity (p = 0.809). A significant sex x BMI interaction (p < 0.01) was found with no other significant interactions (p > 0.05). Post hoc analysis showed that at 150 and 180 deg/s obese women had a lower KF/KE ratio (~18%, p < 0.01) compared to their normal weight peers, with no differences in the groups of men (p = 0.587). A similar KF/KE ratio was found in the group of elderly of both BMI.

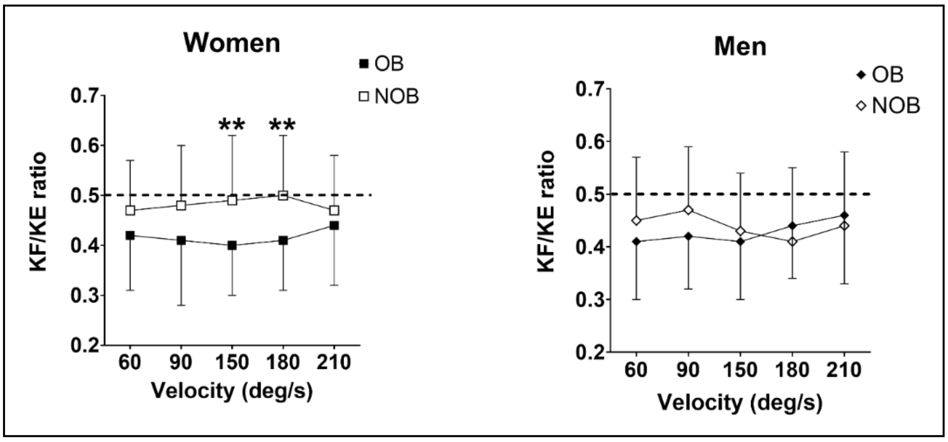

Figure 2. 5: Conventional ratio in elderly men and women with and without obesity. Knee flexor/extensor ratio at different speeds between elderly men and women with obesity and normal weight. Dashed line indicates the critical threshold below which the risk of knee joint injuries increases. ** p < 0.01, denotes differences between women with obesity and normal weight. Abbreviations: KE: knee extensors; KF: knee flexors; NOB: without obesity; OB: obesity.

Discussion

Few studies investigated the effects of aging and obesity on KF muscle torque in older subjects (HIROSHI Akima et al., 2001; Borges et al., 2015). In agreement with previous findings (HIROSHI Akima et al., 2001; Capodaglio et al., 2009), absolute KF torque decreased similarly in all groups at all speeds and displayed lower values (35-40%) in women, probably due to smaller absolute KF muscles sizes (Behan et al., 2018). On average, the torque delivered by the KF was about half of that of the KE muscles in all groups and showed similar values between the BMI groups. Our findings, in line with previous works (Capodaglio et al., 2009; Maria Hulens et al., 2001), might be explained by the fact that obesity can act as a training stimulus only for antigravitational muscles (e.g., KE) (Bollinger, 2017a).

During everyday activities (e.g., walking and stairs descending (Samuel et al., 2013)), a minimal level of torque is required in KE and KF muscles. Elderly subjects of both sexes with obesity had lower KF values per unit of BM than the non-obese subjects at all speeds, in accordance with a prior study conducted on young adults with obesity (Capodaglio et al., 2009). This necessarily entails impairments in mobility and joint stability, ultimately increasing the risk of falling in elders with obesity, especially in those functional tasks that require a quick reaction to the external perturbations of the body (Rossi-Izquierdo et al., 2016).

The KF torque relative to thigh lean mass (i.e., muscle quality) was different between men and women and the obese and non-obese groups. Similarly to what is reported by Hulens et al. (Maria Hulens et al., 2001) in middle-aged adults with obesity, our sample of men and women with obesity showed lower values compared to the normal weight group, indicating that muscle quality might be compromised with obesity. In our sample, this was particularly highlighted only in the women group with obesity that showed lower (~19%) muscle quality at different speeds of contraction (i.e., from 90 to 180 deg/s) compared to the normal weight counterpart. Although our results showed a loss in KF muscle quality more pronounced in women, future research are needed to confirm and better understand the possible sex-specific response associated with these differences.

The KF muscles are important in preventing knee hyper-extension and stabilise the knee joint across the entire range of motion (da Rosa Orssatto et al., 2018). Imbalances between KF and KE torque can cause joint instability with consequences on frailty and injuries. The evaluation of KF/KE ratio is used as an indicator of knee joint antero-posterior stability (da Rosa Orssatto et al., 2018), where the normal healthy range is between 0.5-0.8 (Borges et al., 2015; da Rosa Orssatto et al., 2018). In our sample, the average KF/KE ratio was lower than 0.5, with differences in obese women than the normal weight group (Figure 1). In our study, people with obesity displayed a larger imbalance between KF and KE. Notably, the imbalance seemed not to be related with KF weakness, but rather with disproportionate KE torque. This means that their KF might not be able to effectively counteract the action of the KE during extension movements, hence exposing the joint to the development of musculoskeletal conditions like osteoarthritis. In RT, exercise physiologists tend to give priority at KE over KF development (e.g., leg extension or leg press) (da Rosa Orssatto et al., 2018), hence potentially worsening KF/KE. Our results support the notion that it might be beneficial to include exercises for KF muscles torque development and preservation, particularly in exercise programmes for elderly adults. For instance, kinesiologist should also include KF exercises on isotonic machines (e.g., "leg curl"), with ankle weights or resistance bands, performed in standing position, sitting on a chair (e.g., "standing" or "seated leg curls") or on the floor (e.g., "hip thrust"). The choice of the appropriate exercise and load should depend on individual's mobility, personal preferences, and ability to bear the BM. Furthermore, free-body exercises are particularly suited for those elders without direct access to a gym, e.g.: those who are resident in long care home-facilities.

Some potential limitations of this study should be acknowledged: 1) our sample included people with a wide range of obesity. This means that the results are not specific for single obesity classes; 2) we did not collect metabolic measurements for providing a deeper insight about the metabolic status of our individuals that might constitute an important factor of muscle function and quality, and hence a confounder in the statistical analysis; 3) the muscle size (i.e., cross sectional area) and architecture of the quadriceps and biceps femoris were not considered in our study. Muscle force expression depends on the muscle fascicle pennation angle (i.e., sarcomeres placed in parallel) and fascicle length (i.e., sarcomeres placed in series). The adults with obesity typically show greater pennation angles in the quadriceps muscle compared to the normal weight peers. This might affect muscle performance during the isokinetic contractions, highlighting the differences between obese and non-obese participants.

Conclusion

To prevent the loss of lower limbs torque associated with aging, it seems appropriate to prescribe exercises that can preserve both KE and KF muscles and their balance. This is of particular interest for older subjects with obesity.

CHAPTER 3: THE USE OF HANDGRIP AS SURROGATE MEASURE OF MUSCLE FUNCTION IN OLDER ADULTS WITH OBESITY: STRENGTH AND LIMITATIONS

LITERATURE RESEARCH: STUDY 3

Exploring the association between handgrip, lower limb muscle strength, and physical function in older adults: a narrative review

Toni Tatangelo[a]*, Valentina Muollo[b]*, Laura Ghiotto[a], Federico Schena[a], Andrea P Rossi[c]

*First authors – contributed equally to this work

[a] Department of Neuroscience, Biomedicine and Movement, University of Verona, Verona, Italy
[b] Department of Medicine, University of Verona, Verona, Italy
[c] Department of Medicine, Section of Geriatrics, Treviso, Italy

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Abstract

Widely used in daily practice, handgrip strength (HGS) is a low cost, easy-to-use, and portable test to assess overall muscle and physical function. It can be used as a stand-alone or a first-line tool for evaluating muscle weakness, though controversy surrounds its use for assessing global or lower limb muscle function. Lower limb mobility and physical activity are reduced with advancing age. This decline is difficult to quantify with isokinetic or isometric devices in routine settings (hospital and nursing home). For this narrative review we explored and summarized the findings of studies that investigated the association between HGS, lower limb muscle strength, and physical performance in older adults. The review also provides directions for future research.

We noted contrasting findings for an association between HGS, lower limb strength, and physical performance. We found insufficient evidence for endorsing the handgrip dynamometer as a definitive tool for measuring overall muscle strength and physical function. More evidence is needed from comparable studies involving larger samples of men and women and investigating other areas such as lifestyle, daily physical activity levels, and health-related disorders.

Introduction

Aging is a natural process of progressive decline in muscle mass, strength (Keller and Engelhardt, 2019), and physical function (Doherty et al., 1993; Vandervoort, 2002). The loss of muscle mass is between 15% and 25% before age 70 and more than 40% after age 80 (Baumgartner et al., 1998) and it is associated with a reduction in global muscle strength (Surakka, 2005). Aging-related changes in muscle mass and strength are small between age 30 and age 50 (Deschenes, 2004; Proctor et al., 1998), after which become more pronounced, with an estimated 15% loss in muscle strength per decade (Baumgartner et al., 1999; Buonocore et al., n.d.; Deschenes, 2004; Proctor et al., 1998; Surakka, 2005; von Haehling et al., 2010). The decline in muscle strength precedes that of muscle mass and results in reduced activities of daily living (e.g., eating, dressing, bathing, transferring, ambulating) (Taekema et al., 2010), cognitive dysfunction (Alfaro-Acha et al., 2006), and mortality (Cooper et al., 2010; Ling et al., 2010). Early identification of reduced muscle strength could help prevent and counteract the loss of independence in carrying out daily tasks.

The handgrip dynamometer is the most widely used tool for evaluating muscle strength in clinical and research applications (O. Bruyère et al., 2016). Lower HGS is negatively associated with cardiometabolic diseases (Peterson et al., 2017), disability (Rantanen, 1999), morbidity, and early mortality (McGrath et al., 2017; Peterson et al., 2016). Since muscle strength is considered a better marker than muscle mass in predicting adverse outcomes (Lauretani et al., 2003), lower HGS test scores indicate changes in health-related fitness. Accordingly, the HGS test has been recommended in the past for defining sarcopenia (EWGSOP) (A. J. Cruz-Jentoft et al., 2010), Foundation of the National Institute of Health (FNIH) (Studenski et al., 2014)) and recently it has been included as a first-line screening test by the revised guidelines of the EWGSOP (EWGSOP2) (Cruz-Jentoft et al., 2019).

Widely used in research, the isokinetic dynamometer is considered the gold standard for evaluating muscle strength (Parraca et al., 2022) with a good to excellent reliability in measuring lower extremity muscle strength in the older population (Hartmann et al., 2009a; Parraca et al., 2022). However, the methodology requires expensive equipment and trained operators, two barriers to its implementation in clinical practice. The handgrip dynamometer is frequently used in research and clinical applications because of its low cost, ease of use, and portability (A. J. Cruz-Jentoft et al., 2010). With advancing age, the combined effect of diminished limb mobility and reduced physical activity leads to a greater decline in muscle size and strength in the lower than in the upper extremities (Janssen et al., 2000). This makes it important to quantify and assess the decline in lower limb strength in combination with HGS to monitor and design appropriate intervention strategies. To date, controversy surrounds the use of HGS as a substitute for measuring lower limb muscle strength and physical function. Hence, with this narrative review we wanted to: 1) summarize evidence for the association between HGS and lower limb muscle strength and between HGS and physical performance; 2) indicate areas of focus to determine whether the HGS test is sufficient for evaluating overall muscle strength when screening muscle weakness or if specific tools are needed to accurately measure lower limb strength in clinical practice.

Methods

The Google Scholar and PubMed databases were queried between July 2021 and September 2021 for studies on the association between HGS and lower extremity muscle strength and for peer-reviewed physical performance studies. The literature search was conducted using the search terms: “handgrip strength”, “knee flexors AND extensors”, AND “correlation OR association OR relationship” AND “physical performance OR physical function OR functional ability”, “older adults OR elderly”, “sarcopenia”. Inclusion criteria were: publication in the last 10 years in English, with an evaluation of HGS, lower extremity muscle strength, and physical performance. For consistency, the associations were classified as: weak ($R<0.4$), moderate (from 0.4 to 0.6) and strong (>0.6) (James D. Evans, 1996).

Association between handgrip strength and lower limb muscle function

Controversy surrounds use of the handgrip dynamometer for assessing general muscle strength. The assumption that a reduction in HGS is accompanied by a reduction in lower limb strength, KE strength (KES), and/or KF strength (KFS) is unclear (**Table 3. 1**). Previous studies observed an association between lower extremity strength and HGS (Alonso et al., 2018a; Bohannon, 2012; Bohannon et al., 2012; Fragala et al., 2016a; Porto et al., 2019a; Samuel and Rowe, 2012; Strandkvist et al., 2021). In a cross-sectional study involving 110 women (age>60 years) (Alonso et al., 2018a), after adjusting for age and BMI, the researchers observed a moderate association between HGS and KES but not KFS performed at 60°/s. In detail, there was a moderate association for KES of the dominant and the non-dominant limb (R 0.43, and R 0.35; both p<0.001) but no significant difference in KFS (R 0.13 and R 0.10; both p>0.05). An earlier study involving 164 participants showed a strong association between HGS and KES of both limbs (R 0.77 to 0.81; p<0.001) (Bohannon et al., 2012).

In a sample of 150 autonomous Brazilian adults of both sexes (age range 60-80 years), Porto and colleagues found a strong association between HGS, KES (R 0.62; p<0.05) and KFS (R 0.68; p <0.05) performed at a speed of 60°/s (Porto et al., 2019a). Fragala et al. suggested that HGS and KES appear to be suitable for screening muscle weakness in older adults (age range 67-93 years) of both sexes (Fragala et al., 2016a). In their study, they evaluated the association between HGS and KES in isometric (at 60°) and isokinetic (at 60°/s) modalities and investigated in two different cohort's studies that participated in the FNIH Sarcopenia Project the variables that could better explain variance in gait speed. For the AGES-REYKJAVIK group there was a significant and stronger association between HGS and isometric (60°) KES in both sexes (men R 0.57; women R 0.51; all p<0.001), in line with previous studies (Cawthon et al., 2008; Lauretani et al., 2003; Martin et al., 2006); whereas, for the Health Aging and Body Composition group the HGS showed an association between isokinetic (60°/s) KES (R 0.40 and R 0.44, respectively, in men and women; all p<0.001).

Samuel and Rowe (2012) investigated the relationship between HGS and lower limb strength in 82 older adults (age range 60-82 years) by means of HGS, isometric hip (extensor and flexor at 0°, 30°, 45°) and knee (KES and KFS at 20°- 60°- 90°) strength, hip abduction and adduction in neutral position. Comparison between the older (age>80 years) and the younger adults (age 60 years) showed a decrease in strength with advancing age: HGS was reduced by 14.3% and hip abductor by 27%, with a significant association between lower limb strength and HGS (R 0.56-0.78; p<0.001) (Samuel and Rowe, 2012). In their study, Bohannon evaluated the relationship between HGS and isometric KES in both sides at 90° in 34 older adults (age range 61-93 years) and reported an association between HGS and KES (R 0.55-0.89; p<0.001), concluding that both HGS and KES were valuable for assessing lower limb strength. For its simplicity, the handgrip dynamometer was preferable to the isokinetic devices (Bohannon, 2012).

In their cross-sectional study, Strandkvist and colleagues investigated the association between HGS and lower limb muscle strength in 45 older adults (age range 70-89 years) by means of isometric KES and KFS at 30°, hip extension with the knee flexed at 90°, hip abduction with the hip and the knee at 0°, and ankle flexion and extension at 0°. The study shared the observation by Bohannon of an association between HGS and lower limb strength. All muscle groups were significantly correlated, except for ankle flexor-extensor muscles (Strandkvist et al., 2021).

In contrast, other studies showed no association between HGS and lower limb strength (Felicio et al., 2014a; M. Harris-Love et al., 2018; Ostolin et al., 2021; A. Rodacki et al., 2020; Samuel et al., 2012a; Yeung et al., 2018a). Yeung and colleagues reported a low-to-moderate association between isometric KES and HGS in their study involving older 163 men and women (age>60 years) evaluated for HGS and lower limb strength in an isometric position in both sides. The authors suggested that KES should be included in comprehensive geriatric assessment since health fitness characteristics were more closely aligned with KES than with HGS (R 0.54; p<0.05). They went on to state that HGS alone would be insufficient as a measure of overall muscle strength in clinical practice (Yeung et al., 2018a).

Rodacki et al. obtained similar results in a sample of older Brazilian women. They evaluated isometric (at 60°) and isokinetic knee strength (at 60°/s and 180°/s) in 199 women (age range 60-86 years). Correlation analysis between HGS, isometric and isokinetic strength showed a weak association with isokinetic lower limb strength (R<0.40) that was not significant in most cases (A. Rodacki et al., 2020). In their cross-sectional study supporting these results, Felicio and colleagues investigated the association between HGS, KES, and KFS, expressed in absolute units and adjusted for BM, in a sample of 221 older women (age>60 years) (Felicio et al., 2014a). They measured total work, average power, and ratio between agonists and antagonists at 60°/s and 180°/s and found no association between HGS and lower limb strength (p>0.05). The most significant results were only peak KFS at 60°/s (R 0.16; p=0.017), peak KES at 180°/s (R 0.15; p=0.025) in total work (R 0.13; p=0.039) and in knee extension power (R 0.24; p<0.001). The authors advised caution when considering HGS as a predictor of overall muscle strength in a sample of older women.

In their study involving 38 adults (age range 20-82 years), Samuel et al. divided the sample into four groups by age and sex and measured muscle strength in the dominant limb by HGS and isometric KES (at 90°). As expected, they found a reduction in strength with ageing but a differential association for the young and the older adults: a strong and a moderate association between HGS and KES for young women (R=0.83) and men (R=0.63), respectively, and a weak association for older women (R=0.05) and men (R=0.35). Comparison of HGS and KES showed a decline in strength between the upper and the lower limbs. The association between HGS and KES was related to age changes and similar for the age-matched men and women. Furthermore, age was negatively associated with KES compared to HGS (Samuel et al., 2012a). This observation of a differential reduction in muscle strength with aging corroborated previous studies (N. A. Lynch et al., 1999). Comparison of upper and lower limb strength may provide a sensitive method to better identify the differences between young and old adults.

Previous studies (Alonso et al., 2018a; Bohannon, 2012; Bohannon et al., 2012; Strandkvist et al., 2021) have recognized that the HGS can be an indicator of lower limb strength, but its correlation with major muscle groups still needs to be established in different populations. In their recent study, Ostolin and colleagues investigated the association between HGS and muscle function in elbow, KF and KE muscles (Ostolin et al., 2021). The study sample was 780 adults (age range 18-

80 years) tested before intervention and then at 1 year follow-up. The study protocol entailed isometric (at 60°) and isokinetic (at 60°/s and 300°/s) lower limb contraction. The main results revealed a moderate to strong association (R 0.41-0.76; p <0.01) between HGS and isokinetic muscle function at baseline. However, at 1 year follow-up (smaller sample of 62 men and 180 women) these associations were weak (R 0.26-0.34; p<0.01). The authors reported that the changes in HGS were unable to explain the changes in lower limb strength and suggested that HGS was not a suitable tool to assess strength changes in different body regions. A randomized controlled trial involving 764 older (>75 years) tested the association between HGS and isometric (at 90°) KES and found a weak association between HGS and KES (R^2 0.17; p<0.001) adjusted for sex and age (Chan et al., 2014).

In one of the few studies that recruited a group of 30 veteran men (age range 45-85 years), Harris-Love and colleagues found that HGS was not associated with KES or KFS performed at 60°/s and 180°/s (p>0.05). However, KES (at 60°/s) was associated with all functional outcome measures (e.g., rapid gait speed, normal gait speed, sitting-to-standing walking time, physical performance tests; p<0.05) (M. Harris-Love et al., 2018). The authors concluded that assessment of lower limb strength may be useful in the clinical management of disorders such as sarcopenia.

Table 3. 1: Association between handgrip strength and lower limb muscle function in older

Article	Participants	Assessment	Key Finding
Samuel and Rowe, 2012	82 older adults (42 men and 40 women, mean age 73 ± 7)	HGS Isometric (20°-60°-90°) KES and KFS contraction Isometric (0°-30°-45°) hip extensor and flexor muscles Isometric hip abduction and adduction at neutral position	Association between lower limb strength and HGS (R 0.56-0.78; p<0.001)
Samuel et al., 2012 (Samuel et al., 2012a)	38 adults (age range 20-82), 20 young (10 men mean age 24 ± 4 and 10 women mean age 24 ± 3); 18 older adults (9 men mean age 71 ± 7; 9 women mean age 72 ± 8)	HGS Isometric KES at 90°	Association between HGS and KES (young women, R 0.83; men, R 0.63); association in older adults (women, R 0.05) and (men, R 0.35)

Bohannon et al., 2012	164 adults (58 men and 106 women, mean age 49 ± 22)	HGS Isometric KES and KFS at 90°	Association between left and right HGS (R 0.95; p<0.001) Association between left and right KES (R 0.95; p<0.001) Association between HGS and KES of both sides (R 0.77-0.81; p<0.001)
Bohannon, 2012	34 older adults, mean age 80 ± 8	HGS Isometric KES at 90°	Association between HGS and KES (R 0.55-0.89; p<0.001)
Chan et al., 2014	764 older adults (243 men and 521 women, age range 79-87)	HGS Isometric KES at 90°	Association between HGS and KES (R^2 0.17; p<0.001) adjusted for sex and age

Felicio et al., 2014	221 women, mean age 71 ± 5	HGS Isokinetic strength of ankle, knee and hip flexor and extensor muscles at 60°/s and 180°/s	No association between HGS and lower limb strength (p>0.05); Association between peak KFS at 60°/s (R 0.16; p=0.017) and peak KES at 180°/S (R 0.15; p=0.025)
Fragala et al., 2016	6766 adults (3001 men and 3765 women, age range 67-93) AGES -*REYKJAVIK* group (4853 men and women, age range 67-93); Health ABC group (1913 men and women, age range 76-85)	HGS KES with isometric (60°) and isokinetic (60°/s) protocols	AGES group HGS: association with isometric (60°) KES in men (R 0.57; p<0.001) and women (R 0.51; p<0.001); Health ABC group: association with HGS KES isokinetic (60°/s) in men (R 0.40; p<0.001) and women (R 0.44; p<0.001)
Harris Love et al., 2018	30 veteran men, mean age 63 ± 9	HGS Isokinetic KES and KFS at 60°/s and 180°/s	HGS not significantly associated with KES at 60°/s and 180°/s (R 0.28, R 0.06; p<0.001); KFS at 60°/s and 180°/s (R 0.27, R 0.19; p<0.001)

Alonso et al., 2018	110 women, mean age 67 ± 6	HGS Isokinetic KES and KFS at 60°/s	KES of the dominant limb (R 0.43; p<0.001); KES of the non-dominant limb (R 0.35; p<0.001); KFS of the dominant limb (R 0.13; p<0.21); KFS of the non-dominant limb (R 0.10; p<0.36)
Yeung et al. 2018	163 men and women, mean age 82 ± 7	HGS Isometric KES at 90°	KES strength included in comprehensive geriatric assessment; correlation between KES and HGS (R 0.54; p<0.05)
Porto et al., 2019	150 adults (28 men and 122 women, mean age 69 ± 5)	HGS Isokinetic KES and KFS at 60°	HGS associated with KES (R 0.62; p<0.05) and KFS (R 0.68; p<0.05)

Rodacki et al., 2020	199 women, mean age 70 ± 5, (old mean age 66 ± 2; very old (vod) mean age 74 ± 4)	HGS Isokinetic and isometric strength of ankle, knee, and hip flexor and extensor muscles at 60°/s and 180°/s	KES old (R 0.13; p>0.05) and vod (R 0.53; p<0.001), KFS old (R 0.28; p>0.05) and vod (R 0.26; p>0.05), KES at 60°/s old (R -0.05; p>0.05) and vod (R 0.38; p<0.001), KFS at 60°/s old (R -0.031; p>0.05) and vod (R 0.36; p<0.001), KES at 180°/s old (R-0.009; p>0.05) and vod (R 0.33; p<0.001), KFS at 180°/s old (R -0.08; p>0.05) and vod (R 0.19; p >0.05)

Strandikist et al., 2021	45 older adults (18 men and 27 women, mean age 76 ± 4)	HGS Isometric KES and KFS at 30° Hip extension with knee flexed at 90 ° Hip abduction with hip and knee at 0° Ankle flexion and extension at 0°	Association between HGS and lower limb strength. All muscle groups were significantly associated with HGS, except for ankle flexor-extensor muscles
Ostolin et al., 2021	780 adults, mean age 44 ± 14 Follow-up sample (242 adults, mean age 46 ± 14)	HGS Isometric KES at 60° Isokinetic KES at 60°/s and 300°/s	Association between HGS and isokinetic muscle function (R 0.41-0.76; p<0.01); association at 1 year follow-up (R 0.26-0.34; p< 0.01)

Abbreviations: AGES-REYKJAVIK: Age Gene/Environment Susceptibility—Reykjavik Study; Health ABC: Aging and Body Composition; HGS: Handgrip Strength; KES: Knee Extensor Strength; KFS: Knee Flexors Strength; vod: very old.

Association between handgrip strength and physical performance

One of the main factors contributing to the risk of living with physical disability is physical inactivity (Murray, 2013). Maintenance of physical activity levels is central to preventing early disability and mortality in older adults (Studenski, 2011). Limited mobility, defined as the capacity to move independently (e.g., overcome physical barriers to walking, getting up from a chair or climbing a flight of stairs) is estimated to affect 30-40% of adults aged 65 or older (Musich et al., 2018; Vásquez et al., 2020), with increased risk of falls, chronic disease, institutionalization, and mortality (J. M. Guralnik et al., 1994). Intervention programs that promote physical activity are essential to counteract motor disabilities and to maintain quality of life in advanced age.

The data on the association between HGS and physical performance are contradictory (**Table 3. 2**). Stevens et al. observed that HGS was significantly associated with physical performance in a group of 629 older adults (age range 63-73 years), as measured with an adaptation of the Guralnik SPPB test (Stevens et al., 2012a): a 1-kg increase in HGS was associated with a decrease of 0.07 s on the 6 meter Timed Up and Go test, a 0.02-s decrease in walking time of 3 meters, and a decrease of 1% in chair rise time for the men (all $p<0.001$). Among the women, a 1-kg increase in HGS was associated with a 0.13-s decrease on the 6-meter TUG, a 0.03-s decrease in 3-meter walking time, and a 1% decrease in chair rise time (all $p<0.001$). Similarly, Harris-Love et al., observed an association between HGS and fast gait speed (R 0.42; $p=0.021$) (M. Harris-Love et al., 2018). Martien et al. found a positive association between HGS and KES ($p<0.05$) and functional performance in 947 adults (age>60 years) of both sexes residing in communities, nursing homes or assisted living facilities (Martien et al., 2015a). They used HGS and isometric KES (at 90°) to evaluate muscle strength and the 6-minute walking test (6MWT) plus the modified Physical Performance Test for physical performance. Martien and colleagues observed a stronger association between lower limb strength and functional performance than HGS, especially in assisted living facility residents. There was a positive association between HGS, and isometric KES adjusted for body mass and functional performance across settings. Both strength variables contributed equally to functional performance in the community and the nursing home residents, whereas KES was a better predictor (R^2 0.39-0.35) of functional performance compared to HGS (R^2 0.15-0.12), respectively, on the 6MWT and the modified Physical Performance Test in the assisted living facility residents.

In their cross-sectional study, Wiśniowska-Szurlej et al. found a positive association between HGS, dynamic balance, and lower and upper limb mobility in nursing home residents of both sexes (age range 65-85 years) (Wiśniowska-Szurlej et al., 2019). The authors evaluated HGS, lower limb muscle function (with the 5-Chair Stand test), dynamic balance with Timed Up and Go test and Timed Up and Go Cognitive test, and other variables related to flexibility. They found a negative association between HGS and age (R -0.23; p<0.001), Timed Up and Go test (R -0.18; p=0.008), Timed Up and Go Cognitive test (R -0.17; p=0.014), Chair STS (R -0.27; p<0.001) and a positive association between Gait Speed and HGS (R 0.24; p<0.001). They concluded that HGS can be used for early diagnosis and scheduling appropriate interventions to prevent disability and mortality in long-term care facility residents.

Alonso and colleagues reported an association between HGS and dynamic balance, and KFS and KES as well (Alonso et al., 2018a). HGS was used to measure the strength of the dominant and the non-dominant upper limb, while the Timed Up and Go test with and without cognitive task was used to evaluate dynamic balance. They found a weak, negative association between HGS of the dominant hand and Timed Up and Go test (R -0.20; p = 0.03) and the non-dominant hand (R -0.20; p = 0.03) and between HGS and Timed Up and Go Cognitive test of the dominant (R -0.21; p = 0.02) and the non-dominant hand (R -0.28; p = 0.04). Lower HGS scores were significantly associated with worse performance on the dynamic postural balance and on the Timed Up and Go test. However, no correlation was found between HGS and static balance.

In their study of 290 adult men and women (age > 60), Jiménez-García and colleagues investigated the relationship between HGS, lower limb reaction time (via an optoacoustic, acoustic and an optic electric detection device), and functional mobility (with the Timed Up and Go test). They reported a negative, weak association between lower limb reaction time and HGS (optoacoustic electric detection device: R -0.172, p < 0.05; optic electric detection device: R -0.071, p >

0.05; acoustic electric detection device, R -0.140; $p < 0.05$). The subjects with greater HGS had a lower limb reaction time, indicating better neuromuscular activation to cope with functional abilities such as walking and climbing stairs (Jiménez-García et al., 2021). Wieczorek et al. investigated the association between HGS and physical performance in 36 non-institutionalized older people (age > 60 years). Two questionnaires, the Mini Mental State Examination and the IPAQ short form, were administered to assess cognitive function and physical activity, respectively. Strength, physical performance, and aerobic capacity were measured by means of HGS, the Timed Up and Go test, and the 6MWT. The authors found a weak but significant association between HGS and Timed Up and Go test (R -0.385; $p = 0.027$) and the 6MWT (R 0.324; $p < 0.05$) and that HGS should be used with caution in the older people community (Wieczorek et al., 2020). Similarly, Rodacki et al. evaluated the association between HGS and physical performance by means of the Timed Up and Go test, the 6MWT, and the 5-STS test. The association between HGS and performance tests ranged from negligible (R 0.0-0.3) to low (R 0.3-0.5) and HGS was unable to explain variations in the Timed Up and Go test (A. Rodacki et al., 2020). In their cross-sectional study involving 3498 adults (age range 40-84 years) Johansson et al. investigated the differences between upper and lower limbs testing to detect muscle weakness (i.e., “probable” sarcopenia) or sarcopenia according to EWGSOP2 guidelines (Cruz-Jentoft et al., 2019b) They observed a higher prevalence of sarcopenia in the group examined with the 5-STS (4.4%) compared to the HGS (1.3%) test, which had a very low level of agreement in identifying and confirming sarcopenia. Other discrepancies were showed in terms of anthropometric and body composition parameters when HGS (e.g., individuals with probable sarcopenia were shorter in height and waist circumference, leaner with lower percentage body fat compared to their non-sarcopenic peers) or 5-STS tests (e.g., individuals typically had excess weight or obesity) were used for sarcopenia screening (Johansson et al., 2020). Johansson and colleagues found that the 5-STS and the HGS test should not be used interchangeably. Instead, the choice of protocol should be based on an individual’s characteristics (anthropometric and body composition parameters) and both evaluations might be useful especially for the identification of “probable” sarcopenia (Johansson et al., 2020).

Table 3. 2: Association between handgrip strength and physical performance tests

Article	Participants	Assessment	Key Finding
Stevens et al., 2012	629 adults (349 men and 280 women, mean age 68 ±3)	HGS SPPB TUG	1 kg increase in HGS associated with decrease of 0.07s on 6m TUG, 0.002 s decrease in walking time of 3m, and 1% decrease in chair rise time for men (all $p<0.001$); 1-kg increase in HGS associated with 0.13 s decrease on 6m TUG, 0.03 s decrease in 3m walking time, and 1% decrease in chair rise time for women (all $p<0.001$)

Martien et al., 2015	947 older adults (247 men and 523 women, mean age 73 ± 8)	HGS 6MWT PPT-7 Isometric KES at 90°	Positive association between HGS and KES adjusted for body weight and functional performance across settings ($p<0.05$). Association between KES and 6MWT (R^2 0.39) and PPT-7 (R^2 0.35), association between HGS and 6MWT (R^2 0.15) and PPT-7 (R^2 0.12) in assisted living facility residents
Harris- Love et al., 2018	30 veteran men, mean age 63 ± 9	HGS Gait Speed	Association between HGS and Gait Speed (R 0.42; p=0.021)
Alonso et al., 2018	110 women, mean age 67 ± 6	HGS TUG TUGC	Negative association between HGS and TUG on the dominant (R -0.20; p=0.03) and the non-dominant hand (R -0.20; p=0.03) and between HGS and TUGC on the dominant (R -0.21; p = 0.02) and non-dominant hand (R -0.28; p=0.04)

Wisniowska-Szurlej et al., 2019	209 older adults (94 men and 115 women, mean age 75 ± 8)	HGS Gait Speed 5-Chair Stand test TUG TUGC	Negative association between HGS and age (R -0.23; p <0.001), TUG (R -0.18; p=0.008), TUGC (R -0.17; p=0.014), Chair Stand (R -0.27; p<0.001), positive association between Gait Speed and HGS (R 0.24; p<0.001)
Wieczorek et al., 2020	36 adults, mean age 67 ± 5	HGS 6MWT TUG	Association between HGS and physical ability, TUG (R -0.385; p=0.027) and 6MWT (R 0.324; p<0.05)
Johansson et al., 2020	3498 adults (1451 men and 2047 women, mean age 66 ± 9)	HGS 5-Chair Stand TUG 4MWT	Higher prevalence of sarcopenia found with the 5-Chair Stand (4.4%) than with the HGS test (1.3%)

Jiménez-Garcia et al., 2021	290 older adults (51 men and 239 women, mean age 69 ± 6)	HGS Gait Speed TUG Reaction time of lower limbs (OALLRT: via optoacoustic electric detection device, OLLRT: via optic electric detection device, ALLRT: via acoustic electric detection device)	Negative association between reaction time of lower limbs and HGS (OALLRT R -0.172; p<0.05; OLLRT R -0.071; p>0.05; ALLRT R -0.140; p<0.05)

Abbreviations: ALLRT: via an acoustic electric detection device; HGS: Handgrip Strength; KES: Knee Extensors Strength; OALLRT: via an optoacoustic electric detection device; OLLRT: via an optic electric detection device; PPT-7: Physical Performance test; SPPB: Short Physical Performance Battery; TUG: Time-Up-and-Go test; TUGC: Time-Up-and-Go-Cognitive test; 4MWT: Four-Meter Walk Speed test; 6MWT: Six-Minute Walking test.

Discussion and future directions

To the best of our knowledge, this is the first narrative review to update evidence for an association between HGS, lower limb strength, and physical performance. Beyond the international guidelines for sarcopenia, there is insufficient evidence to conclude that HGS can adequately replace specific tools or tests for measuring lower limb muscle strength and physical performance. The debate among researchers remains open and further study in large populations of all ages is needed to achieve consensus on HGS as a tool for evaluating global muscle physical function.

The accelerated decline in lower limb muscle strength during aging (Kozicka and Kostka, 2016; Samuel et al., 2012a) results from musculoskeletal disorders and lifestyle conditions. Muscle mass and strength are lower in sedentary individuals compared to their non-sedentary, active peers. The differential strength loss depends on the muscle district evaluated and individual lifestyle. Some studies analyzed samples of nursing home or assisted living facility residents with highly reduced daily physical activity. The studies that found an association between lower and upper limb strength could have been influenced by the study participants' levels of physical activity and independence (e.g., smaller differences between nursing home residents than between older adults living independently at home).

Another point is the sex-related differences. Few studies to date have investigated the relationship between HGS, lower limb strength, and physical performance in men and women separately. Upper and lower limb strength is usually greater in men than in women, though the decline with aging can differ. A previous study (Hiroshi Akima et al., 2001) reported greater absolute muscle strength and a greater decline in lower extremity muscle quality in men than in women. In contrast, other studies (N. Lynch et al., 1999; Samuel et al., 2012a) found that women experienced a marked loss in lower limb muscle strength and quality with aging, whereas the rate of decline was similar for men. Reduced physical activity (e.g., duration, intensity, number of daily steps) may contribute to a loss of lower limb muscle strength (Ikenaga et al., 2014; Rantanen et al., 1997). In particular, the major involvement of the upper body in daily activities can help to better maintain upper than lower limb muscle strength in older individuals (Nogueira et al., 2013).

Previous research has shown that older men have fewer barriers (e.g., lack of opportunity and transport) (Moschny et al., 2011) and are more engaged in regular physical activity than women (Lee, 2005), possibly explaining the rapid decline in muscle strength in the women. Despite conflicting results, aging can affect men and women differently and several physiological (e.g., neural impairment, muscle architecture, connective tissue, and changes in contractile properties) and lifestyle factors (e.g., sedentary behavior) may better explain these discrepancies (Hiroshi Akima et al., 2001; Nogueira et al., 2013). Future cross-sectional studies should consider such factors when interpreting the association between HGS and lower limb muscle strength and physical function.

The differences in association across studies could also stem from the disparate populations studied. It may be advantageous to have study samples that include people with excess body weight. In individuals with obesity, the added weight on the lower limbs places greater demand on the knee muscles to perform activities of daily living (Bollinger, 2017b). Previous studies (M Hulens et al., 2001; Dennis T. Villareal et al., 2004) reported that strength and power are higher in KE compared to KF muscles in overweight older adults because the excess abdominal fat shifts body weight anteriorly. As a consequence, KE torque increases with greater body weight, becoming disproportionally stronger than the knee flexors or upper limbs. This might create discrepancies in the association between the upper and the lower extremities, especially in overweight adults. Future studies should include protocols for the evaluation of lower limb muscle function in larger samples of men and women, while taking into account confounding factors such as lifestyle, nutritional status, physical activity, and metabolic diseases (i.e., diabetes and obesity rarely reported in the literature).

Maintenance of adequate lower limb muscle function has a central role in ensuring autonomy in performing motor tasks. Muscle power (defined by the combination of velocity and strength) provides a better indicator of muscle function loss compared to muscle strength alone (Winger et al., 2020). The latter study employed a multilinear modelling approach to investigate the association between lower limbs muscle power and strength (countermovement jump test on force plates) and HGS with physical performance tests (i.e., 400m walk test, 6m usual gait speed, 5-STS)

(Winger et al., 2020). The researchers found that the peak power was ~2-fold more associated with all physical performance test outcomes compared to the jump strength and HGS tests. Of note, a reduction in one standard deviation in peak power was associated with a reduction of almost half of the standard deviation in walk time in 400m, gait speed in 6m, and chair stand speed.

Data on dynamic muscle strength and power obtained with laboratory devices (e.g., isokinetic dynamometer, force plates, leg power rig) can yield useful information about physical impairment in the older population. In clinical practice or in a specific environment (i.e., assisted living facility or home), which requires recruitment of a large cohort, there may be barriers to implementing them, discouraging clinicians to carry out evaluation. In addition, advanced, easy-to-use technologies for measuring muscle function are not on the near horizon. Recently, the STS test (i.e., 30s STS, 10 or 5 STS repetition) (Buckinx and Aubertin-Leheudre, 2021) has attracted interest owing to the few equipment and the relatively simple equations needed to calculate or estimate lower limb muscle power (Alcazar et al., 2018a; Takai et al., 2009). A future area of focus could be to investigate the association between muscle power and HGS via simple and less expensive tests when clinical settings present barriers. On the other hand, this kind of association (particularly in older populations with different comorbidities and grades of frailty) can be effectively evaluated in research settings where access to other expensive devices for muscle power assessment may be available.

As with other narrative reviews, there are several limitations to the present one: it was not designed as an all-encompassing review, since no systematic procedure was performed; studies utilizing various procedures (e.g., non-standardized modalities for measuring lower limb muscle function, disparate cut-offs to report associations) and different age populations were included, which makes it difficult to compare the studies reviewed. Other factors, including physical activity, nutritional status, and obesity in particular, may have influenced the relationship between HGS and lower limb muscle function. Every effort was made to report the results of published studies equally; nonetheless, the conclusion may be limited in scope.

Conclusion

The current evidence is insufficient to support the use of HGS as a surrogate measure of muscle strength in relation to lower limb strength and physical performance. Further studies are needed to establish the handgrip dynamometer as a tool of overall muscle and physical function.

EXPERIMENTAL RESEARCH: STUDY 4

Is handgrip strength a marker of muscle and physical function of the lower limbs? Sex differences in older adults with obesity

Valentina Muollo[a], Toni Tatangelo[b], Laura Ghiotto[b], Valentina Cavedon[b], Chiara Milanese[b], Mauro Zamboni[c], Federico Schena[b], Andrea P Rossi[d]

[a] Department of Medicine, University of Verona, Verona, Italy
[b] Department of Neuroscience, Biomedicine and Movement, University of Verona, Verona, Italy
[c] Department of Medicine, Section of Geriatrics, Healthy Aging Center Verona, Italy
[d] Section of Geriatrics, Department of Medicine, Treviso, Italy

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Abstract

Background and Aims: In this cross-sectional study we investigate the association between HGS and muscle function of the lower limbs and the predictors of the ALMI in older adults with obesity of both sexes.

Methods: Eighty-four older (67±5 years) men (N=44) and women (N=40) with obesity (BMI: 33±4 kg/m^2) performed: the HGS, isokinetic KES and KFS and power and SPPB. The correlation between HGS and lower limbs muscle function was evaluated, and four multiple hierarchical linear models were built to assess the contribution of each ALMI predictor (i.e., HGS, BMI, SPPB, muscle strength and power).

Results: In men, HGS was weakly-to-moderately associated ($p<0.05$) with KE, KF muscle function and physical performance. In women, HGS showed a weak association ($p<0.05$) with KE muscle function. The significant predictors of ALMI were only the BMI in women, whereas in the group of men BMI, KE maximal strength and power better explain the variance in ALMI than HGS alone.

Conclusion: Our results suggest that HGS should not be used alone as a marker of lower muscle nor physical function. Sex differences exist with the BMI that is a contributor of ALMI both in men and women. However, at least in the group of men, markers related to strength and power of the lower limbs can better describe variations in ALMI compared to HGS in this kind of population.

Introduction

With aging, the gradual loss of muscle mass, strength, or performance, is referred as sarcopenia (Cruz-Jentoft et al., 2019a) that, accompanied by obesity (Donini et al., 2020) accelerates muscle quality degradation and frailty (Donini et al., 2020). Sarcopenic obesity has been extensively investigated, but a broadly accepted diagnostic criteria is not established yet (Donini et al., 2020). Some investigative groups (e.g., the revised EWGSOP2 or the FNIH) make use of the strength and the muscle mass to define a sarcopenic condition. To assess muscle strength, the handgrip dynamometer constitutes the most simple and inexpensive tool (Günther et al., 2008) and HGS cutoffs are adopted in the screening of sarcopenia (EWGSOP2 use a cutoff of 27 and 16 kg in men and women (Cruz-Jentoft et al., 2019a), whilst for FNIH cutoffs are set to 26 and 16 kg for men and women) (Dam et al., 2014b)). The diagnosis with HGS needs confirmation with either the evaluation of the low ALMI or adjusted by BMI. In clinical practice, the ALMI and the HGS are the most common markers for the screening of sarcopenia (Donini et al., 2020).

Given that an isometric contraction of the forearm muscles is required to measure HGS, this tool might not be appropriate to assess individuals with weight excess (Schlüssel et al., 2008). For example, it has been reported (Schlüssel et al., 2008) that adults with obesity can score on average 3-8 kg more in HGS than the lean counterparts and this disparity was not observed in lower limb strength (Tallis et al., 2018). Compared to the lean peers, higher absolute muscle strength of lower extremities has been found in obese young adults (+10-30%) but not in the older adults. For the young adults, the excess body fat can represent a natural overload and may act as a training stimulus for the quadriceps muscles. However, in the older population with obesity, absolute strength of lower limbs seems to be reduced (Tallis et al., 2018) or similar (Muollo et al., 2021) compared to the normal weight peers. This might be due to the insufficient ability of older muscles to adapt to the weight excess (Tallis et al., 2018).

It has been suggested that a dynamic evaluation of the lower limb muscle strength can be more reflective of an individual’s autonomy during daily living tasks (Macaluso and De Vito, 2004). In particular, muscle power is highly associated with physical performance and risk of falling and therefore it might bring key information of muscle function loss than muscle strength alone (Reid and Fielding, 2012). Lower limb muscle power assessment however typically requires expensive isokinetic dynamometers and highly demanding testing protocols, leading clinicians to favour HGS for sarcopenia screening (Buckinx and Aubertin-Leheudre, 2021). However, whilst some studies conducted in healthy older samples reported that HGS might be a representative marker of overall and limb muscle strength (Alonso et al., 2018b; Fragala et al., 2016b; Porto et al., 2019b), other works (Felicio et al., 2014b; M. O. Harris-Love et al., 2018; Yeung et al., 2018b) reported negligible or poor correlations. These contradictory results suggest that measuring HGS alone might not provide a sufficient resolution for the screening of sarcopenia where the use of multiple tests (e.g., involving both upper and lower limbs) might be warranted. Nevertheless, the costs associated with the execution of multiple tests represent a barrier for their implementation in clinical routine.

In addition to HGS and ALMI, the EWGSOP2 group classifies sarcopenia as “severe” in adults with poor physical function assessed with the SPPB test (Jack M Guralnik et al., 1994; Pavasini et al., 2016). To the extent of our knowledge, only one study investigated the association between HGS and SPPB, highlighting the need to expand the results to other older population (e.g., adults with obesity and poor mobility) (Stevens et al., 2012b). Furthermore, very little is known about the predictors that better describe muscle loss. A previous study (Iannuzzi-Sucich et al., 2002) investigated the predictors of ALMI considering only the lower limbs muscle strength and power. However, a direct comparison between upper and lower limbs muscle function in predicting ALMI is still lacking.

Given the paucity of studies in older men and women with obesity, the purposes of our research were: *i)* to examine the association between HGS, lower limbs muscle function metrics evaluated with an isokinetic dynamometer (i.e., strength and power of KE and flexors at different velocities of contraction) and physical performance assessed with the SPPB test; *ii*) to determine which tests also included in the EWGSOP2 flow chart are more predictive of ALMI. We believe that, in older men and women with obesity, HGS is a poor descriptor of isokinetic strength, power or physical performance. Also, we hypothesised that adding lower limb muscle strength or power measurements could better predict the ALMI compared to HGS alone.

Methods

Study population

Eighty-four older (60-80 years) men (N=44) and women (N=40) with obesity (i.e., body mass index, BMI≥30 $kg\cdot m^{-2}$) and resident in Verona (Italy) participated in this cross-sectional study. Individuals who reported recent musculoskeletal diseases (e.g., acute injuries, chronic symptomatic conditions, joint instability, prosthesis<6 months, or pain) in the lower limbs and any neurological or cardiovascular diseases that could contraindicate physical effort were excluded. This study was approved by the Ethics board of the University of Verona (Prog number 739CESC, prot. n 79152 December 12th, 2018) and participants gave their written informed consent.

Anthropometric and body composition

In the morning, in a fasted state, body mass was taken with an electronic scale (Tanita electronic scale BWB-800 MA) and stature was measured with a Harpenden stadiometer (Holtain Ltd., Crymych, Pembs. UK); BMI was calculated as weight (kg)/height $(m)^2$ (Visser et al., 1999). Thereafter, total and regional body composition were evaluated by means of dual-energy X-ray absorptiometry (DEXA) using a total body scanner (QDR Horizon W, Hologic, MA, USA; fan-bean technology, software for Windows XP version 12.4.2) according to the manufacturer's procedures. Furthermore, the ALMI was also calculated (Dam et al., 2014b).

Physical performance

On the same day, the SPPB test was used to assess functional performance of the lower extremities (Jack M Guralnik et al., 1994). Each participant performed: 4 m at usual customary gait speed, a five repeated chair-stands test and three standing balance tests (side by side, semi-tandem and tandem). Before starting each trial, the experimenter gave a demonstration to the participants. For each test, the experimenter recorded the time with a stopwatch and gave a score (between 0-4 points) according to the recommended cut-offs (Jack M Guralnik et al., 1994). At the end, the maximum score (from 0 to 12 points) represented by summing the category scores of each test was collected.

Handgrip strength

A digital dynamometer (CAMRY, Digital Hand Dynamometer model: EH101) was used to assess HGS and all measurements were conducted by the same operator. Before starting, participants observed a demonstration of the test procedure and engaged in two practice attempts. After five minutes of familiarisation, participants were standing upright with a neutral position of arm, forearm, and wrist (Günther et al., 2008) and instructed to apply the maximum possible handgrip pressure for 5 seconds. The test was performed three times with the dominant arm interspersed by 1-minute rest between trials. The highest peak was used for the statistical analysis (Günther et al., 2008).

Knee muscle strength measurements and analysis

An isokinetic dynamometer (CMSi Cybex Humac Norm Dynamometer, Lumex, Ronkokoma, NY, USA) was used to assess the isokinetic strength of knee flexors and extensors muscles. The device was calibrated, and the gravity correction executed according to the manufacturer procedures and all the measurements were conducted by the same operator. A full description of the protocol is reported in Study 1 and Study 2. Briefly, after familiarisation and preliminary identification of the individual full range of motion, the participants were seated on the dynamometer chair (90° at the hip) with the mid-thigh, hip and trunk secured with straps and the knee-joint aligned with the rotational axis of the dynamometer and the tibia fixed with a length-adjustable lever arm.

Maximal isokinetic knee extension-flexion tests were performed in a randomised sequence at 60, 90, 150, 180 and $210°\cdot s^{-1}$. Trials consisted in three knee extension-flexion movements with 60 s-recovery. The maximal strength of knee extensors muscle was calculated with the Hill's hyperbolic function (Hill, 1938). The isokinetic knee extension-flexion power was calculated as the product between strength and velocity. Finally, for knee extensors, maximal muscle power expressed in Watt, was calculated from the power-velocity curve (Ferri et al., 2003).

Statistical analysis

Data are presented as means ±SD. Data analysis for men and women was conducted separately. The baseline characteristics between men and women were compared by using an unpaired t-test. To check the normal distribution of variables, Shapiro-Wilk normality test was used. The Chi-square (χ^2) probability distribution was performed for categorical variables. To express the association between HGS, isokinetic strength, power and physical performance variables, Pearson's, or Spearman's correlation coefficients (R) were used according to the assumption of normality. The results of correlation coefficient R were reported according to the following criteria: <0.4 weak, 0.4-0.6 moderate, >0.6 strong (James D Evans, 1996).

Multiple linear regression analysis was performed both, in men and women, to investigate the parameters that can better predict the ALMI, considering the contribution of simple measurements used in clinical fields (i.e., BMI, HGS and SPPB test) and the contribution of laboratory tests for assessing lower limbs muscle function (i.e., maximal strength and power). The ALMI was chosen as dependent variable because it was recognised as the most representative outcome for sarcopenia screening (Cruz-Jentoft et al., 2019a). Notably, four multi-linear regression models of increasing complexity were evaluated. The Model 1 included only BMI and HGS as predictors. Starting from Model 1, additional predictors were included with a hierarchical order based on theoretical rationale, and authors' opinion and observations. In model 2, BMI, HGS and SPPB predictors were included since these are commonly used in clinical fields (Cruz-Jentoft et al., 2019a). In model 3A, the predictor lower limbs maximal strength was added compared to model 2, whereas in model 3B the predictor maximal power was added (excluded variable maximal strength). In model 4, all variables (i.e., BMI, HGS, SPPB, lower limbs maximal strength and maximal power) were included. To compare whether a model was significantly bigger than the previous one, the explained variance (R^2) changes between models were analysed using F-ratio (Stevens, 2002). Since R^2 changes can be highly sensitive to correlation between predictors, results from the correlation analysis were used to check for multi-collinearity.

All analyses were conducted with SPSS statistics software (Version 22.0, Chicago, IL, USA) and $p < 0.05$ was set for statistical significance. Furthermore, the software G*Power 3.1.9.4 was used to calculate the statistical power.

Results

Subject characteristics

The summary characteristics of study population are shown in **Table 3. 3**. Women presented a higher fat mass, lower total, and compartmental lean mass than men ($p<0.05$). In particular, the relationship between upper and lower limbs was significantly ($p<0.001$) lower in women compared to men (0.31 and 0.36, respectively). Regarding comorbidities (**Table 3. 3**), the most prevalent health condition was hypertension, followed by hypercholesterolemia, diabetes mellitus, orthopedic issues in spinal column and history of previous knee surgery, with no significant differences between the two groups ($p>0.05$). Furthermore, women were weaker than men in both KE, KF and presented lower HGS values (all $p<0.05$). However, physical performance did not differ between the two groups ($p>0.05$).

Table 3. 3: Descriptive characteristics of older men and women

Outcomes	**Men (n = 44)**	**Women (n = 40)**	
Anthropometric and body composition	**mean ± SD**	**mean ± SD**	**p value**
Age (years)	67.0 ± 5.5	67.7 ± 4.3	p = 0.499
Height (m)	1.7 ± 0.1	1.6 ± 0.1	p < 0.001
Body weight (kg)	98.3 ± 15.8	82.7 ± 9.5	p < 0.001
BMI (kg/m^2)	32.8 ± 3.8	33.3 ± 3.3	p = 0.555
Fat mass (%)	36.0 ± 5.4	46.8 ± 4.4	p < 0.001
Lean mass (kg)	59.3 ± 7.3	41.4 ± 5.3	p < 0.001
Arm lean mass (kg)	6.8 ± 1.2	4.0 ± 0.8	p < 0.001
Leg lean mass (kg)	19.0 ± 2.6	12.9 ± 1.7	p < 0.001
ALMI (kg/m^2)	8.6 ± 0.8	6.8 ± 0.8	p < 0.001
Presence of comorbidities n (%)			
Diabetes mellitus	3 (7%)	0 (0%)	p = 0.080
Hypertension	16 (36%)	14 (35%)	p = 0.090
Hypercholesterolemia	9 (20%)	10 (25%)	p = 0.433
Spinal column (arthrosis and hernia)	1 (2%)	3 (8%)	p = 0.361
Knee surgery (> 6 months)	1 (3%)	2 (5%)	p = 0.559

Strength/power of upper and lower limbs			
Handgrip (kg)	42.1 ± 6.5	26.2 ± 4.3	$p < 0.001$
KE 60°/s (Nm)	163.2 ± 35.1	100.5 ± 16.3	$p < 0.001$
KF 60°/s (Nm)	71.1 ± 22.0	40.9 ± 12.3	$p < 0.001$
KE 90°/s (Nm)	147.6 ± 33.8	89.3 ± 14.3	$p < 0.001$
KF 90°/s (Nm)	63.9 ± 19.5	35.1 ± 12.9	$p < 0.001$
KE 150°/s (Nm)	122.2 ± 26.3	72.6 ± 12.7	$p < 0.001$
KF 150°/s (Nm)	50.6 ± 17.8	28.8 ± 8.9	$p < 0.001$
KE 180°/s (Nm)	111.8 ± 29.0	65.6 ± 11.0	$p < 0.001$
KF 180°/s (Nm)	46.9 ± 14.0	26.8 ± 7.3	$p < 0.001$
KE 210°/s (Nm)	97.9 ± 25.7	58.0 ± 10.3	$p < 0.001$
KF 210°/s (Nm)	42.7 ± 14.1	25.0 ± 6.0	$p < 0.001$
Tmax (Nm)	208.8 ± 39.4	134.4 ± 18.9	$p < 0.001$
Pmax (W)	367.6 ± 107.6	200.6 ± 36.3	$p < 0.001$
Physical performance			
Side by side (s)	10.0 ± 0.0	10.0 ± 0.0	-
Semi tandem (s)	10.0 ± 0.0	9.9 ± 0.8	$p = 0.323$
Tandem (s)	9.6 ± 1.3	9.0 ± 2.2	$p = 0.117$
Gait Speed (s)	3.9 ± 1.1	3.9 ± 1.1	$p = 0.840$
Chair Stand (s)	11.1 ± 2.7	10.8 ± 2.2	$p = 0.608$
SPPB score (0-12)	11.2 ± 1.0	11.0 ± 1.1	$p = 0.360$

Abbreviations: BMI: Body Mass Index; ALMI: Appendicular Lean Mass Index; KE: knee extensors; KF: knee flexors; Tmax: maximal strength; Pmax: maximal power; SPPB: Short Physical Performance battery

Relationship between handgrip strength and isokinetic outcomes

The results of the correlation analyses between HGS and lower limbs muscle function are reported in **Table 3. 4**. The HGS showed a significant moderate correlation with KE strength and power across all speeds in men. Furthermore, maximal strength and power of knee extensors were moderately associated with HGS. Finally, HGS showed a weak association with KF strength and power at all speeds of contraction in older men, but not in women.

In women the HGS showed a weak association with KE strength at 150, 180 and 210°·s^{-1} and with power only at 90°·s^{-1}. There was no significant association between HGS and the other muscle strength outcomes in women.

Table 3. 4: Association between handgrip and isokinetic strength and power in older men and women

Outcomes		**Men (n = 44)**		**Women (n = 40)**	
Velocity	**Torque and power**	**R**	**p value**	**R**	**p value**
60 (°/s)	KE (Nm)	0.54	p < 0.001	0.27	p = 0.087
	KF (Nm)	0.37	p = 0.014	0.02	p = 0.906
90 (°/s)	KE (Nm)	0.47	p = 0.001	0.29	p = 0.071
	KF (Nm)	0.44	p = 0.003	0.08	p = 0.622
150 (°/s)	KE (Nm)	0.59	p < 0.001	0.34	p = 0.034
	KF (Nm)	0.42	p = 0.004	0.08	p = 0.608
180 (°/s)	KE (Nm)	0.47	p = 0.001	0.37	p = 0.019
	KF (Nm)	0.43	p = 0.004	0.09	p = 0.583
210 (°/s)	KE (Nm)	0.47	p = 0.001	0.35	p = 0.026
	KF (Nm)	0.36	p = 0.015	-0.22	p = 0.166
KE T_0 (Nm)		0.57	p < 0.001	0.22	p = 0.164
KE Pmax (W)		0.52	p < 0.001	0.28	p = 0.083

Abbreviations: KE: knee extensors; KF: knee flexors; T_0: maximal strength; Pmax: maximal power.

Relationship between handgrip strength and physical performance outcomes

The correlations between HGS and physical performance in both sexes are shown in **Table 3. 5**. In men, the HGS showed only a significant moderate inverse correlation with time to perform the 5-chair stand and a weak positive association with total SPPB score. In women, no significant correlation between HGS and physical performance test was observed.

Table 3. 5: Association between handgrip and physical performance in older men and women

Outcomes	Men (n = 44)		Women (n = 40)	
Physical performance	**R**	**p value**	**R**	**p value**
Side by side (s)	-	-	-	-
Semi tandem (s)	-	-	0.23	p = 0.155
Tandem (s)	-0.15	p = 0.320	-0.06	p = 0.736
Gait Speed (s)	-0.09	p = 0.548	0.23	p = 0.154
Chair Stand (s)	-0.54	p < 0.001	-0.16	p = 0.337
SPPB score	0.39	p = 0.009	0.06	p = 0.721

Abbreviations: SPPB: Short Physical Performance battery

Multi-linear regression analysis: predictors for appendicular lean mass index

Table 3. 6 showed the results of regression analysis calculated separately in both sexes. In men, multi-linear regression analysis revealed that maximal strength is the first significant predictor which better explain the variance in ALMI following by BMI, Pmax, and HGS. Model 1 revealed that HGS and BMI account for 46% of variance in ALMI, with BMI that constitutes a greater predictor than HGS (β=0.535 and β=0.272, respectively). When the new predictor, SPPB total score is included (i.e., Model 2), the model did not improve (F_{change}=0, p=0.983). Model 3A account for 66% of variance in ALMI (F_{change}=23.00, p<0.001) with BMI and maximal lower limbs strength that give the major contribution in the model (β=0.432 and β=0.574, respectively) compared to HGS. Model 3B account for 54% of variance in ALMI with BMI and Pmax that give the major contribution in the model (β=0.348 and β=0.507, respectively). By adding all variables (Model 4) the model showed no further improvements in explaining the variance in ALMI (F_{change}=0.02, p=0.889).

In women, multi-linear regression analysis revealed that only BMI had a positive association with ALMI. The HGS and BMI account for 35% of variance in ALMI (Model 1), with BMI that constitutes the significant predictor (β=0.571). When the new predictor, SPPB total score is included (Model 2), the model slightly improves but not significantly (F_{change}=2.84, p=0.101). Model 3A account for 42% of variance in ALMI (F_{change}=1.40, p=0.245) with only the BMI that give the major contribution in the model (β=0.531). Similarly, Model 3B account for 41% of variance in ALMI, but BMI is the only significant predictor (*β*=0.541). By adding all variables (Model 4), the model did not improve (F_{change}=0.468, p=0.498).

Based on the maximal number of predictors (i.e., Model 4), the statistical power was 0.99 and 1.00 respectively in the group of older women and men, indicating that the sample size was good enough to achieve a high level of power and reduce the chance of making the type 2 error.

Table 3. 6: Results of the regression analysis in older men and women

	Variables	**Unstandardised coefficient**		**Standardised coefficient**		
Men (n = 44)		**B**	**SE**	**Beta**	***t***	**p value**
Model 1 (R^2 = 0.458)	Constant	3.278	0.913		3.589	p < 0.001
	BMI	0.118	0.027	0.535	4.381	p < 0.001
	HGS	0.035	0.016	0.272	2.228	p = 0.031
Model 2 (R^2 = 0.458)	Constant	3.255	1.393		2.336	p = 0.025
	BMI	0.118	0.027	0.535	4.307	p = 0.001
	HGS	0.035	0.018	0.271	1.923	p = 0.062
	SPPB	0.003	0.118	0.003	0.021	p = 0.983
Model 3A (R^2 = 0.659)	Constant	4.030	1.131		3.564	p = 0.001
	BMI	0.095	0.023	0.432	4.232	p < 0.001
	HGS	0.005	0.016	0.042	0.344	p = 0.733
	SPPB	-0.117	0.098	-0.132	-1.200	p = 0.238
	T_0	0.012	0.003	0.574	4.794	p < 0.001
Model 3B (R^2 = 0.543)	Constant	3.823	1.313		2.912	p = 0.006
	BMI	0.112	0.026	0.507	4.370	p < 0.001
	HGS	0.016	0.018	0.126	0.892	p = 0.378
	SPPB	-0.049	0.111	-0.055	-0.442	p = 0.661
	Pmax	0.003	0.001	0.348	2.693	p = 0.010
Model 4 (R^2 = 0.659)	Constant	4.016	1.150		3.493	p = 0.001
	BMI	0.095	0.023	0.431	4.157	p < 0.001
	HGS	0.006	0.016	0.045	0.358	p = 0.723
	SPPB	-0.117	0.099	-0.132	-1.185	p = 0.243
	T_0	0.013	0.003	0.589	3.599	p = 0.001
	Pmax	0.000	0.001	-0.021	-0.140	p = 0.889
Women (n = 40)	**Variables**	**B**	**SE**	**Beta**	***t***	**p value**
Model 1 (R^2 = 0.347)	Constant	1.264	1.304		0.970	p = 0.338
	BMI	0.146	0.034	0.571	4.299	p < 0.001

	HGS	0.025	0.026	0.129	0.968	p = 0.339
Model 2 ($R^2 = 0.395$)	Constant	3.409	1.800		0.759	p = 0.066
	BMI	0.136	0.034	0.534	4.341	p < 0.001
	HGS	0.027	0.025	0.137	1.061	p = 0.300
	SPPB	-0.170	0.101	-0.222	-1.685	p = 0.101
Model 3A ($R^2 = 0.418$)	Constant	2.768	1.870		1.480	p = 0.148
	BMI	0.135	0.033	0.531	4.057	p < 0.001
	HG	0.023	0.025	0.116	0.891	p = 0.379
	SPPB	-0.185	0.101	-0.241	-1.829	p = 0.076
	T_0	0.007	0.006	0.155	1.184	p = 0.245
Model 3B ($R^2 = 0.408$)	Constant	3.035	1.857		1.634	p = 0.111
	BMI	0.138	0.034	0.541	4.087	p < 0.001
	HG	0.020	0.027	0.104	0.766	p = 0.449
	SPPB	-0.176	0.101	-0.230	-1.737	p = 0.091
	Pmax	0.003	0.003	0.118	0.866	p = 0.392
Model 4 ($R^2 = 0.426$)	Constant	2.608	1.899		1.373	p = 0.179
	BMI	0.130	0.035	0.510	3.768	p = 0.001
	HG	0.031	0.028	0.158	1.092	p = 0.283
	SPPB	-0.194	0.103	-0.254	-1.89	p = 0.067
	T_0	0.018	0.017	0.402	1,047	p = 0.302
	Pmax	-0.006	0.009	-0.27	-0.684	p = 0.498

Abbreviations: ALMI: Appendicular lean mass index; HGS: Handgrip Strength; T_0: Maximal Strength; Pmax: Maximal Power; SPPB: Short Physical Performance Battery

Discussion

This study presents novel data on the relationship between HGS and lower limb muscle function in older adults with obesity. Our results showed that HGS was associated with lower limb muscle function (from low to moderate effect) in men, whereas the HGS exhibited a poor or no association in women. Furthermore, in men, ALMI was highly associated with simple and inexpensive measurements (i.e., BMI and HGS), but by adding more sophisticated functional measurements related to the lower extremities, it is possible to explain a larger portion of the variance in the ALMI. The picture seems to be different in older women, since both muscle function of upper, lower limbs and physical performance, accounts for a relatively small portion of the total variance, suggesting that ALMI might be explained by other contributing factors in this group.

The association between handgrip strength and lower limbs muscle function

To the best of our knowledge, this is the first study which fully investigates the relationship between HGS, dynamic knee extensors/flexors performed at different speeds of contraction and physical performance. Notably, most of previous research accounted only for a sample of women, hence the sex differences within the same kind of population have been poorly investigated. Contrary to our hypothesis, in older men, HGS was significantly associated with knee extensors and flexors strength at all velocities and with maximal power. Harris et al. (M. O. Harris-Love et al., 2018) did not found any correlation between HGS, knee extensors and flexors strength at 60 and 180°$\cdot$s^{-1} in a group of Veterans men. The discrepancies could be attributed to the different populations studied. In the case of Harris and colleagues (M. O. Harris-Love et al., 2018), the participants were younger (63±9 yrs vs 67±5 yrs) and showed lower percentage of body fat (28±7 vs 33±4), as compared to our study sample. Moreover, their older group showed higher HGS values (17%), but lower strength both in knee extensors (~68%) and flexors (~64%).

In our sample a poor association between HGS and lower limbs muscle function was found in women. This is in line with previous studies which reported a weak association (i.e., $R<0.4$) between HGS, knee extensors/flexors strength (Alonso et al., 2018b; Felicio et al., 2014b; A. L. F. Rodacki et al., 2020) and power (Felicio et al., 2014b). Furthermore, it is well-known that muscle strength and power decline with ageing, with a faster loss in lower than upper extremities (Keller and Engelhardt, 2013). The different sex association between HGS and lower limbs muscle function observed in our population was somehow unexpected. In our sample, women presented 41% and 32% less muscle mass than man, in upper and lower limbs. This is close to what is reported in previous findings (Janssen et al., 2000). However, with age, muscle mass and strength do not decrease at the same rate (Hayashida et al., 2014). In fact, muscle strength declines much faster than muscle mass, particularly in women (lower limbs). For instance, Samuel et al. (Samuel et al., 2012b) observed a rapid decrease in muscle strength after the age of 55 years in women with an unbalanced strength loss between knee extensors (~40%) and HGS (~28%), whereas in the group of men the amount of muscle strength loss appeared to be gradual and similar between knee extensors (~23%)

and HGS (~17%). In our sample a weak to moderate relationship ($R \leq 0.43$) between arm lean mass and HGS was found in both groups (see **Supplementary Figure 3. 1**), but the association between leg lean mass and strength/power of the knee extensors was observed only in the group of men ($R \geq 0.6$, $p<0.05$). This might be due to the higher impairments in the neural components with aging in women vs men (Hayashida et al., 2014) and might partially explain the distinct rate of loss in muscle strength of lower and upper limbs that can differ between sexes (Barbat-Artigas et al., 2013).

Physical performance was evaluated with the SPPB test, commonly used in clinical settings for sarcopenia diagnosis (Cruz-Jentoft et al., 2019a). To the extent of our knowledge, only the study of Stevens and colleagues (Stevens et al., 2012b) have previously investigated the relationship between HGS and SPPB test. The authors reported an association between physical performance and HGS, concluding that handgrip dynamometer is preferred in some clinical settings compared to SPPB test. In contrast, looking at the SPPB total score, our results revealed a significant but weak association in the group of men and any association in the group of women. Using different functional tests (e.g., Time Up and Go and Physical Performance Test), previous studies (Martien et al., 2015b; A. L. F. Rodacki et al., 2020) have reported a low ability from HGS to predict physical performance in older people with different functional skills. Our findings corroborated these results and highlighted the need to evaluate separately physical performance and muscle strength. Furthermore, we observed a different response according to sex in the association between HGS, lower limb's function assessed by isokinetic dynamometer and SPPB test. This notion was reinforced considering the predictors related to ALMI.

The variables clinically relevant in appendicular lean muscle mass index

Our second aim was to detect the factors which could better explain the variation in ALMI, an important "hallmark" for sarcopenia diagnosis but less affordable in clinical practice. The method of hierarchical multi-linear modelling was adopted. It is important to highlight that the order in which the predictors were added could have substantial influence on the statistical outcomes (i.e., R^2 and r) of the models especially if multi-collinearity is found between predictors. Indeed, predictors were included with a specific order in mind: from those who required less effort and limited costs for the collection to those which require expensive instrumentation and considerable expertise. Muscle strength assessed via handgrip dynamometer is used as the first step to identify sarcopenia which is confirmed with lower values in ALMI, according to the EWGSOP2 (Cruz-Jentoft et al., 2019a) and FNIH guidelines (Dam et al., 2014b). Our hypothesis was that muscle strength and power of the lower limbs could better predict the ALMI compared to HGS (Cruz-Jentoft et al., 2019a). In the group of men, Model 1 explained around 46% of the variance of ALMI, where BMI was a more important predictor compared to HGS (Cruz-Jentoft et al., 2019a) (β=0.535 and β=0.272, respectively). However, the new predictor SPPB total score (Model 2), usually measured for evaluating physical performance and for classifying the severity stage of sarcopenia, did not emerge as a better predictor of ALMI. With aging occurs a reduction in muscle strength and power of the lower limbs (SKELTON et al., 1994) which impaired the ability to perform activities of daily living. Muscle power is mostly recognised as an earlier marker of age-related muscle function loss compared to strength (Keller and Engelhardt, 2013). However, as described in Model 3A, the inclusion of lower limbs strength explained the 66% of the variance of ALMI (increasing the R^2 by 0.458 to 0.659 with a F-ratio change of 23.00, $p<0.001$). Therefore, in our group of men, the inclusion of KE muscle strength might be clinically relevant since it was the predictor that much explains the variance in ALMI followed by the BMI (β=0.574 and β=0.432, respectively). Whereas Pmax seemed to have a significant but lower clinical impact (β=0.348), explaining the 54% of the variance of ALMI (Model 3B). As suggested by previous research (Valenzuela et al., 2020), maximal strength rather than power plays an important role in explaining the changes in muscle mass, whereas other physiological components (e.g., fibre types and motor unit’s recruitment) are involved with power expression.

In the women sample, only the BMI was the significant predictor which better explains the variation in ALMI. In support of our results, in a cross-sectional study conducted by Rolland et al. (Rolland et al., 2003) a lower correlation (R=0.24) was found between ALMI and HGS in older women. In addition, close to our findings previous research (Iannuzzi-Sucich et al., 2002) found that BMI, strength, and power of the lower limbs were markers for sarcopenia screening in men (explaining respectively 50%, 10% and 4% of the variance in ALMI) but not in women (only the BMI was able to explain the 48% of the variance in ALMI). It might be hypothesised that in women, there are other components responsible for the muscle mass decline. Due to the menopause phase which occur between 45-55 years, hormonal status changes with a concomitant reduction of different anabolic hormones (e.g., androgen, estrogen, growth hormone) following by an increase in catabolic factors (e.g., cytokines implicated in inflammatory process) (Abe et al., 2014) that might be involved in ALMI changes. Taken together, our findings highlighted that HGS alone seems not enough for explaining muscle mass loss. The BMI in both groups along with the assessment of maximal strength or power of the lower limbs in the older men, might help more in the evaluation of sarcopenia diagnosis. However, future studies are needed to confirm our results, extending these measurements in a large and a more heterogeneous sample of individuals with obesity.

This study is innovative in several aspects. Firstly, the results are provided for both sexes, highlighting the differences that may exist between men and women with obesity compared to the previous literature. Secondly, the SPPB test was used to measure physical performance which has been included in EWGSOP2 revised criteria for sarcopenia (Cruz-Jentoft et al., 2019a). Finally, the evaluation of muscle function in this sample of subjects with obesity was evaluated at a wide range of speeds which have not been considered in previous works.

The present study had some limitations, therefore these results should be treated with caution. Firstly, the sample analysed included a small group of community dwelling older adults with obesity able to move independently. This could have led to different results compared to previous studies which commonly investigated older adults living in long-term care facilities. Hence, the results are limited to independent subjects with obesity and may not be generalisable to other populations, age groups or different obesity classes. Furthermore, it would be interesting to compare our results with other kinds of tests performed not only in a seated position. For instance, previous studies (Winger et al., 2021) have shown that performing these tests with or without weight bearing can influence at a different rate the association with physical performance. Therefore, it could be reasonably expected that assessing maximal strength or power of the lower limbs with tests involving total body (i.e., countermovement jump, sit-to-stand muscle power test (Alcazar et al., 2021; Winger et al., 2021)), might better predict the ALMI. Lastly, data on both sides of the body as well as data regarding the reproducibility were not included, possibly limiting the interpretation of our results. To maximize reproducibility, we conducted a familiarization with all trials that were performed three times for both the upper and lower extremities. Regarding the isokinetic protocol, several speeds proposed in a random sequence were also conducted to minimize every potential systematic bias. However, the protocol used for assessing lower limbs muscle function has been well investigated (Raj et al., 2010), showing a good within-day and across-days reliabilities (ICC: 0.72-0.99; ICC: 0.92-0.93) at similar speeds (60-90°$\cdot$s^{-1}) in knee extensors (Hartmann et al., 2009b; Lanza et al., 2003) and flexors (Hartmann et al., 2009b)).

Conclusion

In conclusion, our findings showed that in a sample of older adults with obesity, muscle strength of upper and lower limbs with the physical performance should be evaluated in a separate way, considering the different sex response. We observed that in both groups the BMI is an important factor to consider in predicting ALMI loss. However, at least in older men the evaluation of lower limbs strength and power might help clinicians to identify the early decline in muscle mass and add relevant information to the HGS.

CHAPTER 4: STRATEGIES TO IMPROVE MUSCLE FUNCTION AND BODY COMPOSITION IN OLDER ADULTS WITH OBESITY

EXPERIMENTAL RESEARCH: STUDY 5

The efficacy of five months of hypocaloric diet combined with resistance training alone or amino acids supplementation in dynapenic or sarcopenic obese older adults: A randomized double blind controlled trial. Preliminary results.

Valentina Muollo[a], Andrea P Rossi[b], Laura Ghiotto[c], Toni Tatangelo[c], Chiara Milanese[c], Valentina Cavedon[c], Federico Schena[c], Mauro Zamboni[d], Elena Zoico[d]
(The list of the authors has yet to be established)

[a] Department of Medicine, University of Verona, Verona, Italy
[b] Department of Medicine, Section of Geriatrics, Treviso, Italy
[c] Department of Neuroscience, Biomedicine and Movement, University of Verona, Verona, Italy
[d] Department of Medicine, Section of Geriatrics, Healthy Aging Center Verona, Verona, Italy

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Abstract

Background and Aims: Exercise and nutrition may be useful strategies in dynapenic and sarcopenic obesity management, but identification of treatment modalities aimed at improving this condition is still lacking. We investigated if 5 months of a hypocaloric diet combined with RT alone or EAA supplementation enhance body composition, physical performance, muscle strength and function in dynapenic and sarcopenic obese older adults.

Methods: 61 older (>60 years) men and women participated in a supervised whole-body RT exercise (70-80% of 1-RM), 3 times/wk, 60 min-session and followed a hypocaloric diet (<500 kcal). Participants were randomly assigned into three double-blind groups with different dosages of oral EAA: placebo ((RT+PL) n=20), low ((RT+LOW EAA) 4 g/day, n=9) and high (RT+HIGH EAA) 8 g/day, n=18). Before and after intervention, we examined: weight and body composition with DEXA scan, physical performance with SPPB test, upper muscle strength via HGS, monthly 1-RM at lat machine, chest press and leg press. The torque-length, torque-velocity and power-velocity relationships were further assessed via isokinetic dynamometer.

Results: Over time, RT+PL and RT+HIGH EAA groups significantly decreased body weight (from -3.4 to -4%) and total fat mass (from -8.6% to -9.2%). The three groups significantly reduced leg fat mass (from -6% to -9%, p<0.05), whereas only the RT+LOW EAA and RT+HIGH EAA reduced arm fat mass (from -4% to -5.5%). Conversely, no changes were found in total and ALM in the three groups (p>0.05). Only the RT+PL group improved in HGS (+2.3 kg), SPPB score (+0.8 points) (both p<0.001) and an increasing trend in the 4m gait speed (-0.3s, p=0.056) was observed. Although the time in performing the 5-STS decrease in all groups (p<0.05), only the participants in the RT+PL group reached a substantial meaningful change (-3.1s). Over time the 1-RM increase (p<0.001) in the three groups at lat machine, chest press and leg press (from 33 to 56%). In isometric strength, the major improvements were observed when values were adjusted by BM. While looking at the torque-velocity and power-velocity curves, significant changes were shown in T_0 (per unit of BM).

Conclusion: After 5 months of intervention based on hypocaloric diet combined with RT alone or EAA, similar beneficial effects on body composition, physical performance and muscle strength/function were observed in all groups, independently of EAA intake supplementation. Further longitudinal studies with higher levels of EAA (>8g/day) are needed to investigate the potential effects of supplementation in this population.

Introduction

In the research community, sarcopenia and obesity are two topics of interest due to the large epidemiological burden of aging and overweight. Particularly, the combination of high body fat and low muscle strength (i.e., dynapenic obesity) or muscle mass (i.e., sarcopenic obesity) are associated with poor physical function, lower mobility, higher risk in developing metabolic and musculoskeletal disorders (Cruz-Jentoft et al., 2019b; Donini et al., 2020).

To date, there are no approved medications for the treatment of sarcopenic obesity, but the most common proposed strategies embed a multidisciplinary approach where exercise and nutrition appear to be the major players (Bouchonville and Villareal, 2013). Indeed, in these individuals the real challenge is to promote the loss of body fat without affecting the muscle mass and leading to a long-term enhancement of physical and muscle function. These factors constitute crucial elements to ensure a high quality of life and a successful aging.

In healthy older adults, RT has been recognised as a promising intervention to slow down the loss and atrophy of type II fibres as well as to counteract the reduction of lean muscle mass, therefore ameliorating the onset of sarcopenia (Hurst et al., 2022). Beside RT, protein or amino acids supplements have been identified as adequate approaches especially when it is required to preserve lean muscle mass during weight loss (Gielen et al., 2021). The RT and amino acids supplementation seem two powerful stimuli capable to induce the muscle protein synthesis (Argilés et al., 2016), although other studies (Moro et al., 2016) revealed a blunted protein anabolic response that can be overcome only with the ingestion of a high amount of amino acids or protein supplementation.

Regarding the older adults with sarcopenic obesity, a huge effort has been made to find the best approach for treatment; however, no consensus has been yet found to draw up guidelines in this population, especially when outcomes like body composition, muscle strength and physical function are investigated. Discrepancies have been found in previous meta-analysis which focused the attention on the role of exercise alone or combined with supplementation in individuals with sarcopenic obesity. For instance, one review (Hita-Contreras et al., 2018) concluded that exercise alone or combine with protein supplementation increases muscle mass and has beneficial effects on upper muscle strength and walking speed, whereas another work (Hsu et al., 2019) did not find any additional effects from the supplementation. Recently, another meta-analysis (Yin et al., 2020) identified exercise as the most effective tool to improve muscle strength and performance, but the additional role of nutrition required further investigation, particularly on muscle strength and muscle mass outcomes.

In the previous randomized control trial conducted in this population, muscle quantity has been fully explored, whereas muscle strength has been mainly evaluated via handgrip dynamometer. To the best of our knowledge, none of the previous works investigated the changes following different interventions on isometric or isokinetic maximal strength and power. In particular, the torque-velocity and power-velocity profiles mirror the physiological and functional adaptations that occur in the skeletal muscle following the natural aging process. Compared to young population, the older individuals often display a downward and leftward shift of these curves, mainly due to the progressive atrophy of type II muscle fibres (Narici and Maffulli, 2010). This means that with aging there is a loss of the ability to produce adequate force levels across different speeds of contraction that might constitute a real barrier in performing several daily tasks or in avoiding the risk of falling (Raj et al., 2010). For these reasons, it appears interesting to evaluate if following a multidisciplinary intervention focused on exercise alone or combined with supplementation, this kind of population may find benefits on the force-velocity profile outcomes. The few known studies (Ferri et al., 2003; Raj et al., 2010) that investigated the changes in torque-velocity relationship after a RT program were conducted only in healthy older populations. In these trials, the older adults typically showed gains in isometric strength or isokinetic strength from slow to medium speeds of contractions and in maximal power (Raj et al., 2010), with an overall improvement in the force-velocity curve.

To maximize the effects on body composition, physical and muscle function, the combination of RT and nutritional supplementation seems the successful strategy. From our point of view, the few studies proposed a combination of RT and aerobic modality (Kim et al., 2016) or investigated the role of proteins (Nabuco et al., 2019) instead of amino acids. In light of these considerations, the purpose of this study was to investigate the effects of a hypocaloric diet combined with RT alone or with different amounts of amino acids supplementation on anthropometric and body composition, muscle strength of upper and lower limbs and physical performance in older men and women with dyanapenic or sarcopenic obesity. Our hypothesis was that RT combined with amino acid supplementation would improve body composition, muscle strength and physical performance in this population.

Methods

Study design and population

In this double-blind randomised control trial, older men and women resident in Verona (Italy) were selected from the Nutritional Clinic of the Borgo Trento Hospital or were contacted by telephone. A specific medical screening was initially programmed to verify the criteria of recruitment. Participants were included in the study based on the following inclusion criteria:

- Older men and women between 60-80 years
- BMI ≥ 27 kg·m^{-2}
- HGS adjusted for BM $\leq 50^{th}$ percentile from the NHANES population according to the sex and age specific cut offs (Peterson and Krishnan, 2015)
- Resident in Verona (Italy)
- Stable weight in the previous 2 months
- Previously sedentary (less than one hour of exercise per week in the last 6 months)
- Signing of the informed consent for participation in the study

Participants were excluded if they presented one of the following conditions:

- Unstable angina or recent myocardial infarction
- Malignant or unstable arrhythmias
- Heart failure NYHA class > II
- Severe respiratory failure
- Severe heart valve disease (i.e., severe aortic stenosis)
- Abdominal and/or thoracic aneurysm
- Recent intracerebral or subdural haemorrhage
- Poorly controlled arterial hypertension

- Presence of pacemakers or metal prostheses
- Severe chronic renal failure
- Symptomatic musculoskeletal pathology
- Symptomatic disc herniation, arthrosis, acute joint, tendon and ligamentous injuries, hip and/or knee prostheses recently placed (<6 months) or with joint instability, symptomatic or large inguinal or abdominal hernia
- Acute retinal detachment or bleeding
- Recent eye surgery (laser, cataract, retinal surgery, glaucoma surgery)
- History of malignant cancer within the previous 5 years
- Diagnosis of dementia
- Eating disorders

A total of 111 men and women were screened for this study. After the first visit, sixty-one participants were randomly allocated to one of the three groups. The complete flow chart of our study is presented in **Figure 4. 1.**

The study was approved by the Ethics board of the University of Verona (Prog number 1956 CESC, prot n 76121 November 21th, 2018).

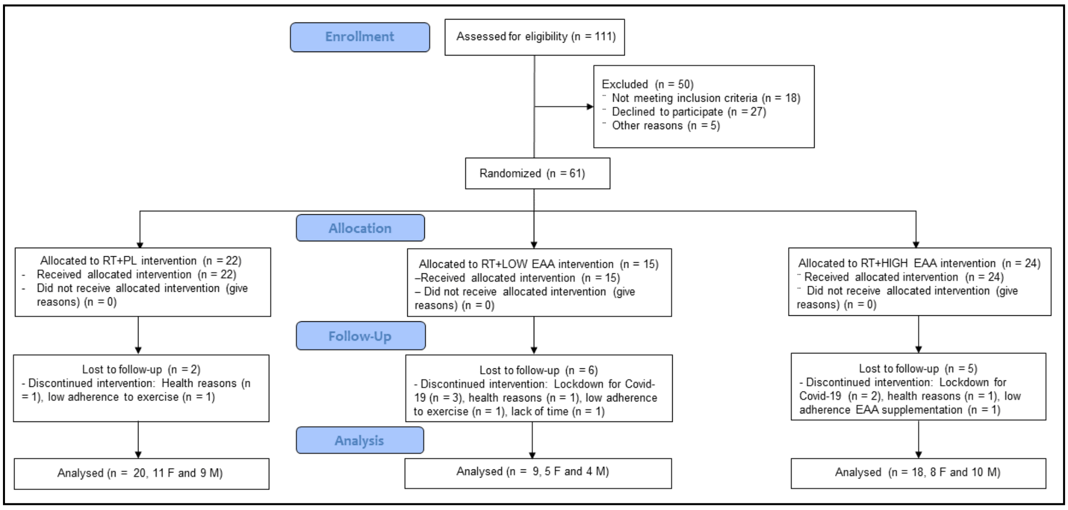

Figure 4. 1: Flow chart of the intervention. Abbreviations: RT: Resistance Training; PL: Placebo; EAA: Essential Amino Acids, F: Female; M: Male.

Progressive resistance training protocol

All the participants performed 5 months of progressive RT, three times per week, 1 hour per session, supervised by an accredited exercise physiologist. Each participant performed the same strength training protocol, starting with 3 sets of 8-10 repetitions at 70% of 1-RM (month 1), with a progressive increase of intensity at 75% of 1-RM (month 2 and month 3), and 80% 1-RM that was maintained for the rest period of intervention.

Each training session consisted in 10 min of warm-up (i.e., 5-min of aerobic, mobility, balance exercises), 40 min of central phase (i.e., whole body exercises specifically performed on isotonic machines, free body weight exercises or with elastic bands), 10 min of cool down and stretching exercises of the main muscle groups. In the central phase, the isotonic machines included: leg press, leg extension, lat machine, chest press, triceps pushdown and vertical traction. For each exercise, participants were instructed to perform the concentric and eccentric phases in 2-3 seconds with 1-2 minutes of rest between sets.

Compliance defined as number of performed exercise sessions was monitored on an individual bases and this number was expressed in % of the target value. At the end of the intervention, each participant had to reach an attendance above the 70% to be included in the analysis.

Nutritional intervention and amino acids supplementation

Participants followed a moderately low-calorie diet aimed at obtaining a weight loss of 5% compared to the initial weight. The caloric restriction was of 500 Kcal below the resting energy expenditure calculated by indirect calorimetry and multiplied by a physical activity level of 1.4 (Rossi et al., 2012). Each participant received nutritional indications capable of providing 60% carbohydrates, 25% fat, 15% protein and 20 g of fiber, divided into three meals and two snacks; furthermore, to guarantee 1 g of protein per kg of ideal body weight, the share protein content has been further calculated.

Participants were randomized into three double-blind groups who received different amount of an oral mixed EAA supplementation (Amino-Ther, Professional Dietetics, Milan, Italy). In detail, one group received an isocaloric product containing maltodextrins instead of amino acids (PL), one group received 4 g/day of amino acids (LOW EAA) and one group received 8 g/day of amino acids (HIGH EAA). Each packet of EAA comprised 4 g of EAA divided as follows: L-Leucine 1.25 g, L-Lysine 0.650 g, L-Isoleucine 0.625 g, L-Valine 0.625 g, L-Threonine

0.350 g, L-Cysteine 0.150 g, L-Histidine 0.150 g, L-Phenylalanine 0.100 g, L-Methionine 0.050 g, L-Tyrosine 0.030 g, L-Tryptophan 0.020 g (Aquilani et al., 2011).

Each participant was instructed to ingest one packet of amino acid in the morning (i.e., 0 g, 4 g, and 4 g respectively for PL, LOW EAA and HIGH EAA) and one in the afternoon (i.e., 0 g, 0 g, and 4 g respectively for PL, LOW EAA and HIGH EAA) dissolved in half a glass of water far from meals. Instead, during the day of exercise, participants ingested the content of amino acids 1 hour before the start of the training session. This amount was selected according to previous works (Aquilani et al., 2011).

Every month, the dietician assisted each patient during the intake of placebo or EAAs to be certain about patient compliance; the patients every month had to return the packets empty, and the dietician numbered the packets.

Outcomes measures

Anthropometric and body composition assessments

The BMI, the total and regional body composition (lean mass and body fat) were evaluated by DEXA using a total body scanner (QDR Horizon W, Hologic, MA, USA; fan-bean technology, software for Windows XP version 12.4.2). To determine the prevalence of sarcopenia in our sample of men and women, the ALM was also calculated and adjusted by BMI, according to the FNIH cut-offs (Studenski et al., 2014).

1-RM assessment

Before starting training intervention, participants performed three sessions of familiarization with the resistance isotonic machines. During the familiarization phase, correct lifting and breathing technique were taught and practiced using submaximal and near-maximal loads. After this phase, the 1-RM was evaluated every four weeks: at baseline, before the first training sessions of each month of training and after a 5-months of intervention.

The 1-RM protocol included ten minutes of whole-body warm-up, one set of eight repetitions at a light load that served as a specific warm-up. Then, the load was gradually increased until failure after 3-6 repetitions that was proved to be suitable in subjects without strength training experience (Moro et al., 2017; Reeves et al., 2004). A proper lifting technique, without compensatory movements or assistance, was imposed. Using the results of strength testing, 1-RM was estimated with Brzycki formula (Brzycki, 1993). For each participant, the heaviest successful lift was determined with maximum five attempts interspersed by 2-minutes rest to ensure recovery.

The initial estimated 1-RM was assessed for six different exercises: chest press, leg press, lat machine, triceps pushdown, leg extension and vertical traction machine. The estimated 1-RM were monitored every month of training for chest press, leg press and lat machine.

Handgrip strength and physical performance assessments

Upper body strength was measured with a handgrip dynamometer (CAMRY, Digital Hand Dynamometer model: EH101) as reported in Study 4. After five minutes of familiarisation, HGS was recorded while standing upright with a neutral position of arm, forearm, and wrist (Günther et al., 2008) and instructed to apply the maximum possible handgrip pressure for 5 seconds. Three attempts with the dominant arm were made interspersed by 1-minute of rest. The best trial expressed in absolute values (in kilograms) and adjusted by BM (Peterson and Krishnan, 2015) were used for the statistical analysis.

The SPPB test was used to assess physical performance of the lower extremities (Jack M Guralnik et al., 1994). For each test, the experimenter recorded the time with a stopwatch and gave a score ranging between 0-4 points according to the recommended cut-offs (Veronese et al., 2014), resulting in a total of 12 points maximum.

Knee extensors muscle torque measurements and analysis

The isokinetic dynamometer (CMSi Cybex Humac Norm Dynamometer, Lumex, Ronkokoma, NY, USA) was used to evaluate the maximal isometric and isokinetic torque of the knee extensors. Following a period of familiarisation, three maximal isometric trials were performed at for knee angles: 30°, 60°, 75° and 90° interspersed by 60 s-recovery. The highest isometric peak was used for the analysis at each tested angle. Additionally, the Tmax and optimal angle was calculated (See Methods section of Study 1 (Muollo et al., 2021)).

After 10 minutes of recovery, maximal isokinetic knee extension-flexion torque was also performed in a randomised sequence at these velocities: 60, 90, 150, 180 and $210°·s^{-1}$. For each tested speed, three knee extension-flexion movements were performed. The values of maximal isokinetic knee-extensor torque at different velocities were fitted with the Hill's hyperbolic function (Hill, 1938) to assess the maximal torque at velocity equal to zero (T_0). The Pmax, Vmax, Topt and Vopt were further calculated according to our previous study (See Methods section of Study 1 (Muollo et al., 2021)).

Statistical analysis

All statistical analyses were performed with SPSS, version 28 statistical package (IBM SPSS, Chicago, IL, USA) and data are presented as mean ± 95% confidence interval, unless otherwise stated. At baseline, the characteristics, and comorbidities between the three groups were compared by using a one-way ANOVA and a chi-square tests, respectively.

To examine the differences between the three groups in anthropometric, body composition, muscle strength and physical function of the extremities, and physical performance outcomes, an analysis of covariance (ANCOVA) was used taking the baseline values. The Bonferroni method for pairwise comparison tests was also used to perform the post hoc analysis. Paired t-tests were used to investigate the changes within groups. Regarding the 1-RM, a two-way ANOVA for repeated measures was used to determine the time x group interactions; in the case of significant main effects or interactions, the Bonferroni post hoc test was performed. For all the variables the normal distribution (as assessed by Shapiro-Wilk's test), homogeneity of variances (as assessed by Leven's test) and Mauchly's sphericity (for the 1-RM parameters) was checked ($p>0.05$). Finally, the effect size with Cohen *d* was used to interpret the magnitude of the effects according to the following criteria: 0.20 is considered small, 0.50 is considered medium, 0.80 is considered large, 1.3 is considered very large (Maher et al., 2013). The level of significance was set at $p\leq0.05$.

Results

Characteristics of participants and training compliance

The anthropometric and clinical characteristics of participants in the three groups are presented in **Table 4. 1**. The three groups were similar at baseline (p>0.05). Additionally, the 53% of the total sample was classified as sarcopenic (See **Table 4. 1**).

Table 4. 1: Baseline characteristics of participants

Outcomes	RT+PL (n=20)	RT+LOW EAA (n=9)	RT+HIGH EAA (n=18)	p value
Men (n, %)	9 (45.0%)	4 (44.4%)	10 (55.6%)	0.525
Age (years)	66.1 ± 4.0	68.3 ± 4.0	68.1 ± 4.9	0.288
Height (m)	1.65 ±0.08	1.65 ±0.07	1.65 ±0.09	0.993
BMI (kg/m^2)	33.8 ± 4.1	32.0 ± 1.3	32.0 ± 4.0	0.277
Comorbidities				
Diabetes mellitus (n, %)	2 (10.0%)	1 (11.1%)	1 (5.6%)	0.678
Hypertension (n, %)	13 (65.0%)	3 (33.3%)	10 (55.6%)	0.684
Myocardial infarction (n, %)	1 (5.0%)	0 (0.0%)	1 (5.6%)	0.912
Hypercholesterolemia (n, %)	9 (45.0%)	4 (44.4%)	5 (27%)	0.285
Sarcopenia				
Prevalence (n, %)	8 (40%)	8 (89%)	9 (50%)	0.506

Abbreviations: BMI: Body Mass Index; RT: Resistance training; PL: Placebo; EAA: Essential Amino Acids

During the intervention, there were 13 dropouts (**Figure 4. 1**), and the main reasons were: health issues (n=3), lack of time (n=2), low adherence to training or supplementation (n=2), lockdown for Covid-19 (n=6). However, the participants who completed the intervention showed a high adherence with an average rate of 86% (RT+PL: 51.4±5.1; RT+LOW EAA: 52.1±5.6, RT+HIGH EAA: 52.3±4.7) with no differences between the three groups (p=0.826).

Changes in anthropometric and body composition

After adjustment for baseline values, no significant differences (p>0.05) between interventions were showed in anthropometric, total, and compartmental body composition variables (**Table 4. 2**). Compared to baseline, arm fat mass decreased only in RT+LOW EAA and RT+HIGH EAA (-5.5% and -4%, respectively), whereas all the three groups observed a loss in leg fat mass (RT+PL: -6%, RT+LOW EAA: -7%, RT+HIGH EAA: -9%). Furthermore, after intervention total fat mass showed a reduction, although the total and compartmental lean mass remained well-preserved in all the three groups. Finally, the ANCOVA reported a significant difference in ALM adjusted by BMI between the three groups (p<0.05). The post hoc analysis revealed that ALM/BMI was statistically significantly improved in favour of RT+PL *vs* RT+LOW EAA group. Compared to baseline only the RT+PL and RT+HIGH EAA showed a significant increase in ALM/BMI (5.5% and 4%, respectively).

Changes of 1-RM in the isotonic machines

Figure 4. 2 illustrates the improvements of isotonic machines tested every month before training sessions. Compared to baseline, the percentage variations showed a significant improvement (all p<0.001) in lat machine (RT+PL: 33.1%, RT+LOW EAA: 35.8%, RT+HIGH EAA: 39.9%), chest press (RT+PL: 45%, RT+LOW EAA: 39.3%, RT+HIGH EAA: 44.7%) and leg press (RT+PL: 38.4%, RT+LOW EAA: 40.7%, RT+HIGH EAA: 56.1%). No significant interactions were found between groups in the three 1-RM isotonic machines (p>0.05).

Changes in handgrip strength and physical performance

After adjustment for baseline values, there were no significant differences (p>0.05) between the three groups in HGS and physical performance (**Table 4. 3**). Compared to baseline, the 5-STS significantly decreased in RT+PL (-25%), RT+LOW EAA (-12.5%) and RT+HIGH EAA (-13.7%). Furthermore, only the RT+PL showed a trend in improving gait speed (-8.6%), with a significant increase in SPPB total score (7%), HGS in absolute values (7%). Whereas an increase in HGS adjusted for BM was observed both in RT+PL (11.8%) and RT+HIGH EAA (9.8%).

Table 4. 2: Anthropometric and body composition are reported in the three groups after the 5-months of intervention.

	RT+PL (n=20)			**RT+LOW EAA (n=9)**			**RT+HIGH EAA (n=18)**			**Between group**	
Outcome	**Baseline**	**Mean change (95% CI)**	**ES**	**Baseline**	**Mean change (95% CI)**	**ES**	**Baseline**	**Mean change (95% CI)**	**ES**	**p value**	**ES**
BM (kg)	92.4 ± 12.2	-3.6*** (-5.1 to -2.1)	-1.106	87.2 ± 5.2	-1.0 (-2.8 to 0.8)	-0.415	87.5 ± 13.7	-3.0** (-5.0 to -0.9)	-0.712	0.271	0.059
Arm FM (kg)	4.7 ± 1.6	-0.2 (-0.4 to 0.0)	-0.395	4.6 ± 1.4	-0.3* (-0.6 to -0.1)	-0.991	4.6 ± 1.6	-0.5** (-0.8 to -0.2)	-0.794	0.184	0.076
Leg FM (kg)	10.7 ± 2.9	-0.6* (-1.1 to -0.1)	-0.599	10.9 ± 3.4	-0.8* (-1.5 to -0.1)	-0.892	9.9 ± 3.7	-0.9*** (-1.4 to -0.5)	-1.018	0.396	0.042
Arm LM (kg)	5.4 ± 1.6	-0.1 (0.0 to 0.3)	0.342	4.9 ± 1.4	0.1 (-0.1 to 0.3)	0.534	5.4 ± 1.7	0.1 (0.0 to 0.3)	0.364	0.990	0.000
Leg LM (kg)	16.0 ± 3.1	-0.1 (-0.3 to 0.6)	0.120	14.9 ± 3.2	-0.4 (-1.1 to 0.3)	-0.450	15.8 ± 3.6	0.1 (-0.3 to 0.4)	0.074	0.268	0.059
Total LM (kg)	51.5 ± 9.3	-0.12 (-1.02 to 0.78)	-0.063	47.1 ± 8.9	0.39 (-1.12 to 1.91)	0.200	49.4 ± 10.1	0.55 (-0.51 to 1.61)	0.259	0.615	0.022
Total FM (kg)	37.1 ± 8.2	-3.15*** (-4.20 to -2.10)	-1.406	36.8 ± 5.5	-1.16 (-2.52 to 0.20)	-0.657	34.7 ± 9.4	-3.24*** (-4.96 to -1.53)	-0.940	0.102	0.101
Total FM (%)	40.7 ± 7.7	-2.2*** (-3.1 to -1.3)	-1.158	43.0 ± 8.0	-0.96 (-2.1 to 0.1)	-0.667	40.1 ± 8.2	-2.4*** (-3.5 to -1.4)	-1.155	0.185	0.075
ALM (kg)	21.4 ± 4.6	0.2 (-0.3 to 0.8)	0.218	19.7 ± 4.4	-0.3 (-1.1 to 0.6)	-0.238	21.2 ± 5.3	0.2 (-0.3 to 0.6)	0.188	0.395	0.042
ALM/BMI (m)	0.641 ± 0.154	0.035 †*** (0.022 to 0.047)	1.304	0.620 ± 0.155	-0.001 (-0.022 to 0.020)	-0.031	0.671 ± 0.180	0.029** (0.011 to 0.046)	0.827	0.020	0.167

† $p<0.05$, indicates a significant difference in RT+PL vs RT+LOW EAA; * $p<0.05$, ** $p<0.01$, $p<0.001$ indicate a significant difference compared with baseline.

Abbreviations: BM: Body Mass; FM: Fat Mass; LM: Lean Mass RT: Resistance training; PL: Placebo; EAA: Essential Amino Acids, ES: Effect Size

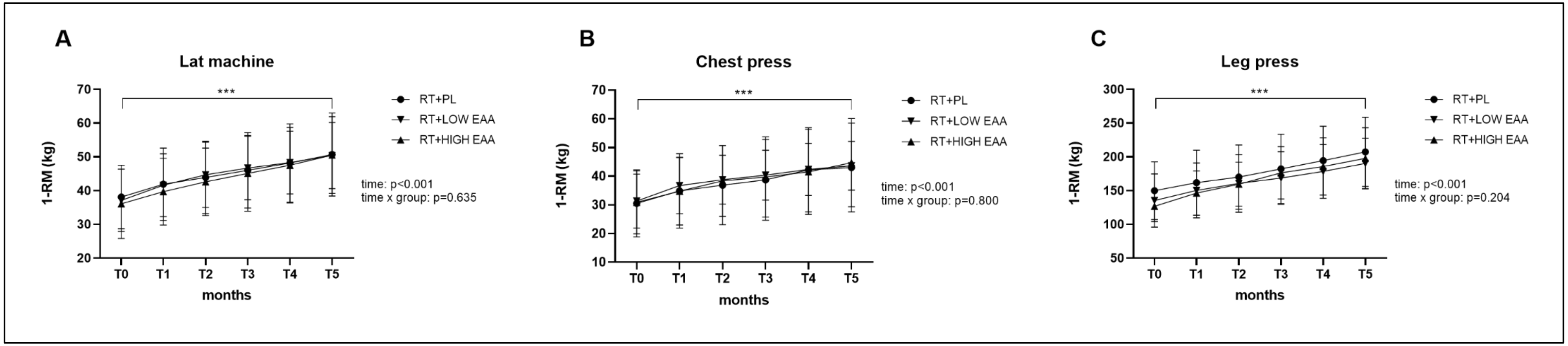

Figure 4. 2: Changes over time of the estimated one repetition maximum tested every month in Lat machine (Panel A), Chest press (Panel B) and Leg press (Panel C). ***p<0.001 indicates a significant difference compared with baseline.

Abbreviations: RT: Resistance Training; PL: Placebo; EAA: Essential Amino Acids, 1-RM: One Repetition Maximum.

Table 4. 3: Physical performance and handgrip strength are reported in the three groups after the 5-months of intervention.

	RT+PL (n=20)			RT+LOW EAA (n=9)			RT+HIGH EAA (n=18)			Between group	
Outcome	**Baseline**	**Mean change (95% CI)**	**ES**	**Baseline**	**Mean change (95% CI)**	**ES**	**Baseline**	**Mean change (95% CI)**	**ES**	**p value**	**ES**
Gait speed (s)	4.0 ± 1.2	-0.3 (-0.7 to 0.0)	-0.455	3.99 ± 1.23	-0.5 (-1.2 to 0.2)	-0.556	4.1 ± 1.1	-0.3 (-0.8 to 0.179)	-0.317	0.625	0.022
Chair stand (s)	12.3 ± 2.9	-3.1*** (-4.2 to -2.0)	-1.377	9.9 ± 2.0	-1.2** (-2.1 to -0.4)	-1.110	10.8 ± 2.4	-1.5** (-2.4 to -0.617)	-0.850	0.194	0.074
SPPB (score)	10.9 ± 0.9	0.8*** (0.4 to 1.1)	0.882	11.1 ± 1.4	0.4 (-0.5 to 1.4)	0.360	11.2 ± 1.1	0.4 (-0.1 to 0.9)	0.375	0.777	0.012
Peak HGS (kg)	31.9 ± 8.0	2.3** (0.96 to 3.55)	0.814	36.4 ± 7.5	1.5 (-1.2 to 4.3)	0.434	32.9 ± 8.8	1.9 (-0.8 to 4.5)	0.348	0.892	0.005
Peak HGS/BM	0.347 ± 0.082	0.041*** (0.023 to 0.058)	1.104	0.416 ± 0.071	0.022 (-0.011 to 0.055)	0.511	0.375 ± 0.079	0.034* (-0.000 to 0.069)	0.496	0.722	0.015

***** p<0.01, *** p<0.001 indicate a significant difference compared with baseline. Abbreviations: GS: SPPB: Short Physical Performance Battery; HGS: Handgrip Strength; BM: Body Mass; RT: Resistance training; PL: Placebo; EAA: Essential Amino Acids; ES: Effect Size***

Changes in knee extensors isometric torque at different angles

The torque-angle relationship of the knee extensors after the intervention in the three groups are plotted in **Figure 4. 3**.

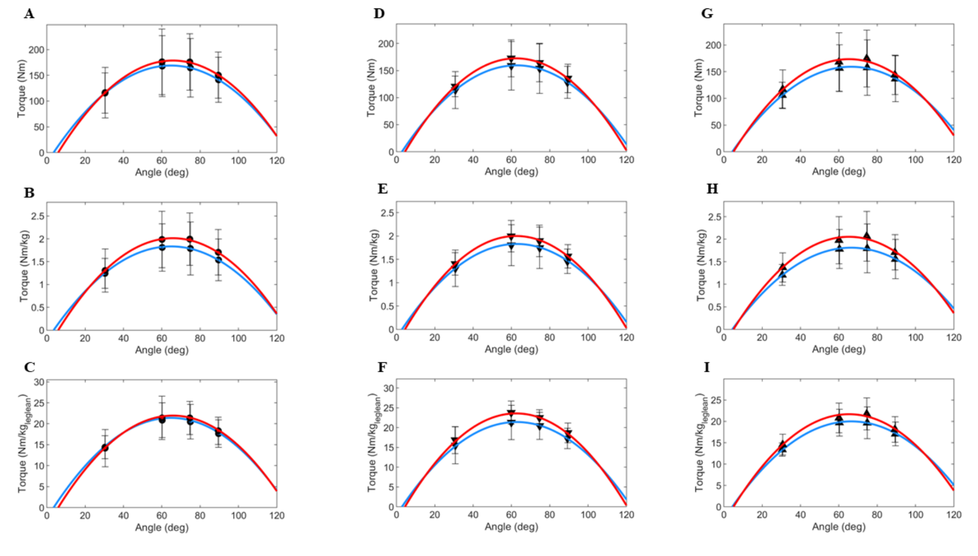

Figure 4. 3: Pre (Blue lines) and post (Red lines) isometric knee extensors strength at different knee angles of the RT+PL group (black circle), RT+LOW EAA group (black-down triangle) and RT+HIGH EAA (black-up triangle). The values are expressed in absolute units (Panel A, D, G), normalized for body mass (Panel B, E, H) and normalized for leg lean mass (Panel C, F, I).

After 5-months of intervention, the ANCOVA showed no differences between groups in the Tmax expression (**Table 4. 4**). Furthermore, no shift in the optimal angle were observed in the three groups (p=0.560) (**Table 4. 4**).

Compared to baseline, Tmax significantly increased only in the RT+PL (8.3%). Whereas, when normalised for BM and leg lean mass maximal isometric torque improved similarly in RT+PL and RT+HIGH EAA (both ~11% and ~7%, respectively).

Looking at the torque expressed in absolute values, normalised by BM and leg lean mass, no significant differences were observed between groups at all the tested angles (p>0.05). Compared to baseline, the greatest isometric torque was showed at 75° of contractions (in absolute values, normalised by BM and leg lean mass), only in the RT+HIGH EAA group (**Table 4. 4**).

Table 4. 4: Maximal isometric torque at different knee angles is reported in the three groups after the 5-months of intervention.

	RT+PL (n=20)			RT+LOW EAA (n=9)			RT+HIGH EAA (n=18)			Between group	
Outcome	**Baseline**	**Mean change (95% CI)**	**ES**	**Baseline**	**Mean change (95% CI)**	**ES**	**Baseline**	**Mean change (95% CI)**	**ES**	**p value**	**ES**
Absolute values											
30° MVC (Nm)	111.6 ± 34.9	5.0 (-9.3 to 19.3)	0.163	114.1 ± 34.2	6.6 (-16.3 to 29.4)	0.220	105.8 ± 24.2	11.2* (1.7 to 20.6)	0.588	0.788	0.011
60° MVC (Nm)	167.3 ± 55.7	9.2 (-3.8 to 22.1)	0.331	158.7 ± 44.9	13.9 (-15.2 to 43.0)	0.367	156.7 ± 44.2	11.4 (-2.1 to 24.8)	0.421	0.934	0.003
75° MVC (Nm)	167.2 ± 59.5	8.9 (-1.1 to 18.9)	0.415	153.7 ± 46.1	10.7 (-5.5 to 26.8)	0.508	159.3 ± 51.5	15.4* (0.3 to 30.5)	0.508	0.758	0.013
90° MVC (Nm)	143.4 ± 47.6	7.0 (-1.5 to 15.5)	0.385	127.7 ± 29.5	7.6 (-11.0 to 26.2)	0.312	137.6 ± 42.5	8.7 (-6.0 to 23.3)	0.294	0.930	0.003
Tmax (Nm)	171.5 ± 57.9	14.2** (4.8 to 23.6)	0.706	161.4 ± 44.7	11.7 (-11.5 to 34.9)	0.389	161.4 ± 47.5	12.3 (-1.7 to 26.4)	0.438	0.924	0.004
Normalised for BM											
30° MVC (Nm/kg)	1.2 ± 0.3	0.1 (-0.1 to 0.3)	0.304	1.3 ± 0.4	0.1 (-0.2 to 0.4)	0.290	1.2 ± 0.2	0.2** (0.1 to 0.3)	0.740	0.825	0.009
60° MVC (Nm/kg)	1.8 ± 0.5	0.2* (0.0 to 0.3)	0.536	1.8 ± 0.4	0.2 (-0.1 to 0.5)	0.476	1.8 ± 0.4	0.2* (0.0 to 0.3)	0.554	0.997	0.000
75° MVC (Nm/kg)	1.8 ± 0.6	0.2** (0.1 to 0.3)	0.721	1.7 ± 0.4	0.2 (0.0 to 0.3)	0.696	1.8 ± 0.5	0.2* (0.1 to 0.4)	0.676	0.646	0.020
90° MVC (Nm/kg)	1.5 ± 0.5	0.2*** (0.1 to 0.2)	0.839	1.5 ± 0.3	0.1 (-0.1 to 0.3)	0.430	1.6 ± 0.4	0.2 (0.0 to 0.3)	0.488	0.788	0.011
Tmax (Nm/Kg)	1.9 ± 7.0	0.2*** (0.1 to 0.4)	1.006	1.8 ± 0.4	0.2 (-0.1 to 0.4)	0.522	1.8 ± 0.5	0.2* (0.0 to 0.4)	0.608	0.795	0.011
Normalised for LLM											

30° MVC (Nm/kg)	13.7 ± 2.6	0.5 (-1.2 to 2.2)	0.140	15.5 ± 4.6	1.4 (-1.5 to 4.2)	0.365	13.3 ± 1.6	1.2* (0.1 to 2.4)	0.544	0.517	0.030
60° MVC (Nm/kg)	20.4 ± 3.8	1.0 (-0.8 to 2.8)	0.269	21.3 ± 4.3	2.5 (-1.1 to 6.1)	0.530	19.6 ± 2.9	1.2 (-0.1 to 2.6)	0.451	0.404	0.041
75° MVC (Nm/kg)	20.3 ± 4.1	1.1 (-0.2 to 2.4)	0.390	20.4 ± 3.4	2.1* (0.0 to 4.1)	0.770	19.8 ± 3.6	2.0 * (0.3 to 3.7)	0.578	0.588	0.024
90° MVC (Nm/kg)	17.4 ± 3.2	0.9 (-0.2 to 2.0)	0.382	17.2 ± 2.5	1.5 (-0.8 to 3.7)	0.493	17.1 ± 2.7	1.3 (-0.3 to 2.9)	0.411	0.893	0.005
Tmax (Nm/kg)	21.1 ± 4.0	1.4* (0.1 to 2.8)	0.488	21.6 ± 3.9	2.2 (-0.6 to 5.0)	0.595	20.1 ± 3.1	1.5* (0.1 to 3.0)	0.526	0.598	0.024
Angle Opt (°)	67.4 ± 7.0	2.1 (-5.2 to 9.3)	0.136	61.5 ± 10.3	1.4 (-5.4 to 8.2)	0.161	65.8 ± 7.7	2.6 (-3.4 to 8.7)	0.224	0.510	0.032

**** p<0.05, ** p<0.01, *** p<0.001 indicate a significant difference compared with baseline. Abbreviations: MVC: Maximal Voluntary Contraction; BM: Body Mass; LLM: Leg Lean Mass, Opt: Optimal Angle; Tmax: Maximal Force at knee angle; RT: Resistance training; PL: Placebo; EAA: Essential Amino Acids; ES: Effect Size***

Changes in knee extensors force-velocity and power-velocity relationships

After the intervention, the torque-velocity and power-velocity curves of the knee extensors are plotted in **Figure 4. 4**.

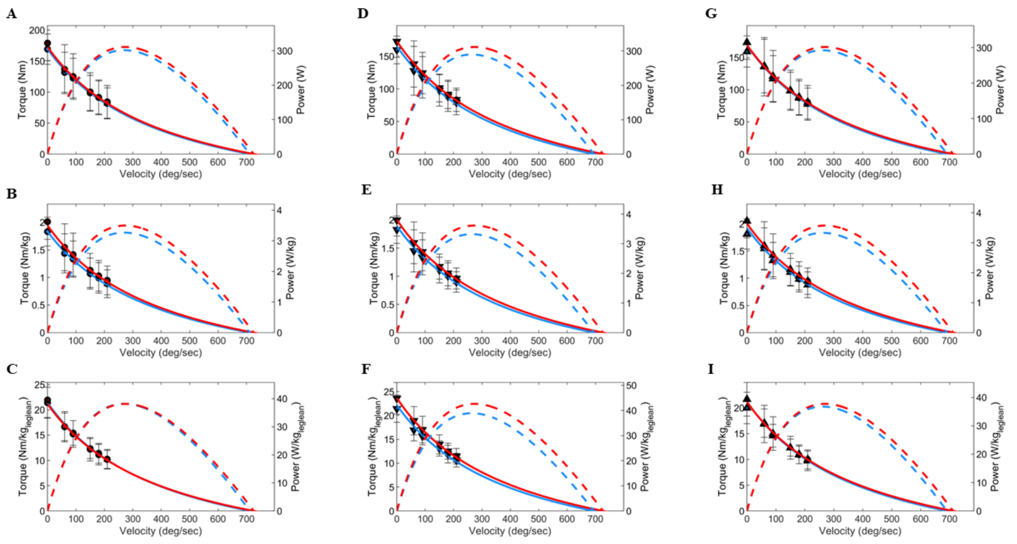

Figure 4. 4: Pre (Blue lines) and post (Red lines) knee extensors force-velocity and power-velocity relationships of the RT+PL group (black circle), RT+LOW EAA group (black-down triangle) and RT+HIGH EAA (black up-pointing triangle). The values are expressed in absolute units (Panel A, D, G), normalized for body mass (Panel B, E, H), and normalized for leg lean mass (Panel C, F, I).

After adjustment for baseline values, no significant differences ($p > 0.05$) between groups were found in torque-velocity and power-velocity relationships (**Table 4. 5**). Compared to baseline, RT+PL significantly increased T_0 (6%, p=0.013) and Topt (6%, p=0.032), with a trend in Pmax (6.5%, p=0.055), when values where normalised by BM. For each speed of contraction, RT+PL showed greater gains in maximal strength normalised for BM at 60°/s (8%, p=0.014), 90°/s (7%, p=0.017) and 210°/s (13%, p=0.050).

The RT+LOW EAA significantly increased T_0 normalised for leg lean mass (8%, p=0.041). Improvements were also observed in Pmax in absolute units (7%, p=0.037), normalised by BM (10%, p=0.013) and leg lean mass (10%, p=0.010). For each speed of contraction, RT+LOW EAA showed greater gains in maximal strength at 60°/s (in absolute units: 10%, p=0.043; normalised by leg lean mass: 11.4%, p=0.028), 90°/s (normalised by leg lean mass: 10%, p=0.020), 150°/s (normalised by BM: 9%, p=0.018; normalised by leg lean mass: 7%, p=0.023), 180°/s (normalised by BM: 4.5%, p=0.044) and 210°/s (in absolute units: 8%, p=0.006; normalised by BM: 12.5%, p=0.002; normalised by leg lean mass: 10%, p=0.007). Compared to baseline, RT+HIGH EAA showed no significant changes (p>0.05).

Table 4. 5: Maximal torque and power at velocity of contractions are reported in the three groups after the 5-months of intervention.

	RT+PL (n=20)			RT+LOW EAA (n=9)			RT+HIGH EAA (n=18)			Between group	
Outcome	**Baseline**	**Mean change (95% CI)**	**ES**	**Baseline**	**Mean change (95% CI)**	**ES**	**Baseline**	**Mean change (95% CI)**	**ES**	**p value**	**ES**
Absolute values											
60 deg/s max peak (Nm)	130.1 ± 32.5	5.0 (-2.5 to 12.4)	0.309	124.8 ± 37.8	9.7 (-1.4 to 20.8)	0.669	136.6 ± 43.3	-2.278 (-10.1 to 5.6)	-0.145	0.166	0.080
90 deg/s max peak (Nm)	120.8 ± 31.7	3.0 (-2.9 to 8.8)	0.236	113.4 ± 31.5	8.111 (-2.4 to 18.6)	0.595	116.3 ± 37.1	3.278 (-5.4 to 12.0)	0.187	0.668	0.019
150 deg/s max peak (Nm)	95.9 ± 27.8	2.3 (-4.8 to 9.3)	0.149	93.2 ± 22.8	4.4 (-0.7 to 9.6)	0.662	97.3 ± 30.2	-0.2 (-5.5 to 5.1)	-0.021	0.661	0.019
180 deg/s max peak (Nm)	88.1 ± 26.3	1.0 (-4.9 to 6.8)	0.076	84.2 ± 21.5	2.9 (-0.7 to 6.5)	0.611	85.9 ± 27.7	1.0 (-5.3 to 7.3)	0.079	0.925	0.004
210 deg/s max peak (Nm)	78.3 ± 25.6	2.6 (-3.0 to 8.2)	0.218	74.0 ± 17.4	5.7** (2.1 to 9.2)	1.229	75.6 ± 26.1	2.8 (-6.2 to 11.7)	0.154	0.881	0.006
T_0 (Nm)	169.7 ± 39.4	5.3 (-3.0 to 13.6)	0.298	166.6 ± 42.5	9.3 (-2.7 to 21.4)	0.593	176.5 ± 51.7	-1.1 (-10.8 to 8.6)	-0.057	0.353	0.047
Pmax (W)	289.0 ± 99.9	10.6 (-11.2 to 32.4)	0.228	266.0 ± 79.9	17.9* (1.4 to 34.4)	0.836	280.7 ± 108.0	1.9 (-23.0 to 26.9)	0.038	0.678	0.018
Topt (Nm)	65.1 ± 13.4	0.6 (-2.1 to 3.4)	0.108	63.8 ± 14.1	2.8 (-1.8 to 7.5)	0.473	67.6 ± 18.7	-0.97 (-4.7 to 2.8)	-0.129	0.436	0.038
Normalized for BM											
60 deg/s max peak (Nm/kg)	1.4 ± 0.3	0.1* (0.0 to 0.2)	0.604	1.4 ± 0.4	0.1* (0.0 to 0.3)	0.800	1.6 ± 0.4	0.030 (-0.1 to 0.1)	0.173	0.227	0.067
90 deg/s max peak (Nm/kg)	1.3 ± 0.3	0.1* (0.0 to 0.2)	0.585	1.3 ± 0.3	0.113 (0.0 to 0.2)	0.702	1.3 ± 0.3	0.085 (0.0 to 0.2)	0.432	0.912	0.004

150 deg/s max peak (Nm/kg)	1.0 ± 0.3	0.1 (0.0 to 0.2)	0.395	1.1 ± 0.2	0.1* (0.0 to 0.1)	0.989	1.1 ± 0.3	0.0 (0.0 to 0.1)	0.335	0.795	0.011
180 deg/s max peak (Nm/kg)	1.0 ± 0.3	0.0 (0.0 to 0.1)	0.331	1.0 ± 0.2	0.0* (0.0 to 0.1)	0.797	1.0 ± 0.2	0.0 (0.0 to 0.1)	0.346	0.997	0.000
210 deg/s max peak (Nm/kg)	0.8 ± 0.3	0.1* (0.0 to 0.1)	0.469	0.8 ± 0.2	0.1** (0.0 to 0.1)	1.567	0.9 ± 0.2	0.1 (0.0 to 0.2)	0.306	0.973	0.001
T_0 (Nm/kg)	1.8 ± 0.4	0.1* (0.0 to 0.3)	0.612	1.9 ± 0.4	0.1 (0.0 to 0.3)	0.719	2.0 ± 0.5	0.1 (0.0 to 0.2)	0.294	0.420	0.040
Pmax (W/kg)	3.1 ± 1.0	0.2 (0.0 to 0.5)	0.458	3.0 ± 0.8	0.3* (0.1 to 0.4)	1.065	3.2 ± 1.0	0.1 (-0.1 to 0.4)	0.259	0.787	0.011
Topt (Nm/kg)	0.7 ± 0.1	0.0* (0.0 to 0.1)	0.519	0.7 ± 0.1	0.0 (0.0 to 0.1)	0.619	0.8 ± 0.2	0.0 (0.0 to 0.1)	0.257	0.624	0.022
Normalized for LLM											
60 deg/s max peak (Nm/kg)	16.1 ± 2.3	0.4 (-0.6 to 1.4)	0.195	16.5 ± 2.2	1.9*† (0.3 to 3.5)	0.891	16.9 ± 2.9	-0.2 (-1.2 to 0.7)	-0.136	**0.049**	0.131
90 deg/s max peak (Nm/kg)	14.9 ± 2.1	0.2 (-0.7 to 1.1)	0.103	15.1 ± 1.8	1.5* (0.3 to 2.8)	0.965	14.4 ± 2.4	0.443 (-0.7 to 1.6)	0.194	0.242	0.064
150 deg/s max peak (Nm/kg)	11.7 ± 1.6	0.3 (-0.7 to 1.2)	0.125	12.5 ± 1.5	0.9* (0.2 to 1.7)	0.933	12.0 ± 1.8	0.0 (-0.8 to 0.8)	-0.004	0.314	0.052
180 deg/s max peak (Nm/kg)	10.8 ± 1.8	0.1 (-0.7 to 0.8)	0.037	11.3 ± 1.8	0.6 (0.0 to 1.2)	0.731	10.6 ± 1.8	0.1 (-0.7 to 0.9)	0.073	0.401	0.042
210 deg/s max peak (Nm/kg)	9.5 ± 1.7	0.3 (-0.5 to 1.1)	0.197	10.0 ± 1.4	1.0** (0.4 to 1.6)	1.213	9.4 ± 2.0	0.3 (-0.8 to 1.4)	0.142	0.257	0.061
T_0 (Nm/kg)	21.2 ± 2.8	0.3 (-1.1 to 1.7)	0.109	22.3 ± 2.4	1.8* (0.1 to 3.5)	0.810	22.0 ± 3.4	-0.1 (-1.2 to 1.0)	-0.037	0.187	0.075
Pmax (W/kg)	35.3 ± 7.3	0.6 (-2.4 to 3.6)	0.096	35.4 ± 5.6	3.5** (1.1 to 5.9)	1.120	34.4 ± 7.5	0.3 (-2.9 to 3.5)	0.044	0.317	0.052

Topt (Nm/kg)	8.2 ± 1.1	0.0 (-0.6 to 0.5)	-0.041	8.6 ± 0.8	0.6 (0.0 to 1.2)	0.715	8.5 ± 6.0	-0.1 (-0.5 to 0.3)	-0.094	0.137	0.088
Vmax (deg/s)	650.6 ± 149.9	22.6 (-15.1 to 60.2)	0.280	613.8 ± 97.4	26.9 (-23.1 to 76.9)	0.413	617.0 ± 163.2	5.4 (-60.7 to 71.6)	0.041	0.627	0.021
Vopt (deg/s)	248.8 ± 46.3	4.3 (-7.0 to 15.7)	0.180	235.8 ± 30.5	7.8 (-10.6 to 26.1)	0.326	235.1 ± 50.8	1.7 (-16.9 to 20.2)	0.045	0.688	0.017

†***p<0.05 indicates a significant difference between RT+LOW EAA vs RT+PL and RT+HIGH EAA; * p<0.05, ** p<0.01 indicate a significant difference compared with baseline. Abbreviations:*** T_0***: Maximal torque at velocity equal to zero; Pmax: Maximal Power; Topt: Optimal torque; Vmax: Maximal Velocity of Contraction; Vopt: Optimal Velocity of Contraction; BM: Body Mass; LLM: Leg Lean Mass; RT: Resistance training; PL: Placebo; EAA: Essential Amino Acids; ES: Effect Size***

Discussion

In this randomized control trial, the goal was to investigate if a hypocaloric control diet combined with RT program plus different amounts of EAA supplementation could give additional effects on body composition, muscle strength, muscle function and physical performance in older adults with dynapenic or sarcopenic obesity. In contrast to our first hypothesis, we found that this multidisciplinary intervention had similar beneficial effects in the three groups on body weight, fat mass loss and some parameters related to lower limbs muscle strength and physical performance. Therefore, our findings cannot confirm the additive effects of the combination of RT and EAA supplements, at least at these prescribed doses. To the best of our knowledge, this is the first study which tried to investigate the combination of the three common recommended approaches for the management of sarcopenic obesity. Furthermore, for the first time the intervention was focused on the separate evaluation of one form of exercise (i.e., RT program) with the nutrition that only included the EAA supplementation.

Weight loss constitutes the cornerstone of therapy for people with obesity (Cava et al., 2017) since it ameliorates the metabolic profile (e.g., lipid profile and insulin sensitivity) and the physical mobility in functional activities. Weight loss is defined clinically significant when the weight reduction is equal to the 5% of the baseline weight (Swift et al., 2016). Although the three groups did not reach this goal, compared to the baseline, both RT+PL and RT+HIGH EAA groups showed a significant weight loss (from -3.4% to -4%), accompanied by a decrease in total fat mass (from -5% to -6%). These findings are close to the conclusion reported in a recent meta-analysis (Hsu et al., 2019). Indeed, in this work they found a weight loss of 4 kg with exercise, whereas RT intervention led to a reduction in whole body fat close to 3%. Alongside the fat reduction, total and compartmental lean mass was preserved; this may confirm that during hypocaloric diet, RT alone or combined with EAA supplementations can attenuate or even prevent the loss in muscle mass (Frimel et al., 2008). However, contrary to our first hypothesis, in our older adults who received the supplement, no significant improvements were shown in muscle mass, nor in ALM. Among the few trials available, one study (Zhou et al., 2018) conducted in older sarcopenic obese men, the group that received a combination of electrical acupuncture with 10g/day of mixed EAA showed improvements in body fat mass and lean mass in a shorter period of time (12 weeks) compared to the group which only received the same quantity of EAA. A possible explanation for our results might be because the total amount of EAA prescribed was not sufficient to induce an adequate response in muscle protein synthesis. In fact, other studies which prescribed similar protein supplementation, with a content of 7g of EAA (Maltais et al., 2016) or 3g of EAA (Kim et al., 2016), did not show any additional effects on body composition, probably because older adults are not responsive to the ingestion of this amount of EAA (7g), with a content in leucine of ~1.7g (Nabuco et al., 2019). Other studies (Moore et al., 2015; Moro et al., 2018) supported the idea that to stimulate muscle protein anabolism, the older population should have an intake of ~0.04 g/kg body weight. Considering these recommendations, the RT+LOW EAA and RT +HIGH EAA had respectively on average 0.01 g/kg and 0.03 g/kg body weight that might be quite lower to promote the protein synthesis inside the muscle. These findings indicate that providing 8g/day of EAA might be adequate to prevent the risk of losing muscle mass but might not be enough to enhance its growth.

Regarding physical performance, no differences were found between the three groups after the intervention. Surprisingly, over time only the RT+PL group showed a significant increase of +0.8 point in the total SPPB score with a large effect size. In the SPPB an increase of 0.5 points indicates a small change and 1 point indicates a substantial meaningful change (Buckinx and Aubertin-Leheudre, 2021); this latter result was almost achieved by the RT+PL group. Furthermore, looking at the single item of the SPPB, after intervention all the three groups significantly improved their score, reducing the time in performing the 5-STS. Notably, the RT+PL group showed a difference of -3s which reflects a substantial and clinically relevant difference (2.3 s) compared to baseline (Buckinx and Aubertin-Leheudre, 2021). By contrast, the 4-m gait speed remained unchanged following intervention, although a small improvement of 0.08 m/s close to the significance was observed in the RT+PL group. Previous meta-analysis (Hita-Contreras et al., 2018; Yin et al., 2020) concluded that exercise alone or with nutrition can lead to similar gains in physical performance. Furthermore, another study which proposed a RT and aerobic protocol alone or in combination with amino acids, found similar findings (Kim et al., 2016), suggesting that an intervention based on RT is sufficient to improve physical function in this kind of population.

The HGS is the most common outcome used to evaluate muscle strength (Harris-Love et al., 2018). Similar to the trend observed for physical performance, the HGS improved following the intervention only in the RT+PL group, with no differences between treatments. The absolute increment in HGS observed in this group was 2.3 kg, therefore lower compared to the results shown in the meta-analysis of Hsu and colleagues (Hsu et al., 2019). However, it should be highlighted that HGS cannot necessarily reflect the changes in general strength after a period of exercise intervention (Harris-Love et al., 2018) and that to obtain a meaningful difference the improvements should be between 5-6.5 kg (Bohannon, 2019b), hence values that are much higher compared to our results.

Differently, upper, and lower body strength represented monthly by 1-RM showed significant gains in all the three groups. In a meta-analysis (Liao et al., 2017b) conducted in older adults, the authors found an overall increase in 1-RM in the lower limbs in favour of individuals with sarcopenic obesity who received the protein supplementation, likely because the high quality of proteins induce myofibrillar proteins synthesis in muscles under resting period. Even though statistical analysis has not reported differences in respect to the treatment, the groups that received the supplementation had the highest changes in the three tested machines. To the best of our knowledge, few studies (Balachandran et al., 2014; Nabuco et al., 2019) conducted in a population with sarcopenic obesity have previously used the 1-RM as outcome for evaluating the maximal strength gains. For instance, the 1-RM in chest press and leg extension monitored in the study of Nabuco and colleagues showed no differences between the group that received 12-week of exercise plus whey protein supplements compared to the placebo group. The improvements in 1-RM observed in their study were lower than our results, probably due to the different exercise program prescribed to increase muscle strength and the different time of intervention.

The improvements observed in the 1-RM were much higher than those observed in performing the isometric and isokinetic protocols. Our findings are in line with previous studies (Ferri et al., 2003; Van Roie et al., 2013) conducted in healthy older adults, indicating that the neuromuscular adaptations occur specifically with the type of training and/or the trained movement. Indeed, in our study, the protocol was focused on a whole-body exercise, therefore not specific for the lower limbs. A characterisation of the torque-length, torque-power-velocity profiles were explored after the intervention. Notably, some parameters (i.e., Vmax, Vopt, Topt) associated with muscle fibres contractions were extrapolated in this population for the first time. Some evidence (Thompson et al., 2018) suggested that with aging there was a larger strength decline in the short (20°) and long muscle length (90°). In contrast, other works (Maffiuletti et al., 2013, 2008) found that compared to normal weight people, the individuals with obesity expressed more strength at short angles (40° of knee flexion) but not at long (80° of knee flexion) muscle length; the explanation was that, due to the excess body weight, these people try to avoid all those activities where is required a deep knee flexion that can potentially increase the articular joint's stress surfaces. Based on these considerations, we decided to explore the changes of torque-length profile in individuals with dynapenic or sarcopenic obesity, prescribing an exercise program able to train lower limbs muscle across the entire range of motion. After the intervention, the optimal angle of the exerted isometric maximal force did not statistically change. The absolute isometric maximal strength increased only in the RT+PL group, whereas a general increment was found when values were normalised for BM and leg lean mass in the RT+PL and in RT+HIGH EAA group. Looking at the different tested angles, greater improvements were observed at 60°, 75° and 90°, suggesting the ability of these elders to easily adapt following the prescribed exercise.

Compared to baseline, less consistent changes were instead observed in the torque-velocity and power-velocity profile in the three groups. The major improvements were shown in the RT+PL group when the values were expressed by BM. This suggests that the improvements might be associated with torque rather than shortening velocity; indeed, the Vopt and Vmax remained unmodified, likely because our participants were trained at high load (70-80% 1-RM) and controlled speed of movement. Therefore, our present findings may also suggest that according to the type of training prescribed, different adaptations will occur inside the muscle and clinical physiologists should target the exercise prescription focusing on hypertrophy or speed of contractions based on the individual's deficits. In our previous study (Muollo et al., 2021) the older men and women with obesity (grade I as average of BMI) had a lower strength/power per unit of BM (i.e., useful strength/power), whereas the values were similar per unit of leg lean mass (i.e., specific strength/power). These typically constitute respectively good indicators of mobility and muscle deterioration (i.e., muscle quality). Surprisingly, in the present study, the groups that received the supplements did not show any additional improvements compared to the RT+PL group, reinforcing the idea that the amino acids prescribed at these doses cannot augment the effects compared to the RT alone. However, due to the novel of these data and the lack of existing literature in this population, more studies are warranted to expand and to draw solid conclusions.

Some limitations should be raised from our preliminary study. Firstly, since this are preliminary data, specific indications of the content of the hypocaloric diet or compliance to diet and supplementations were not analysed yet. Secondly, due to the rate of drop out the sample size used to interpret the results was quite small especially in the RT+LOW EAA group. Thirdly, our sample size was not large enough to make a sub-analysis for sex, BMI, or age classification, hence limiting the generalisability of these results in other sample of older individuals.

Conclusion

After 5 months of intervention based on hypocaloric diet combined with RT alone or EAA, similar beneficial effects on body composition, strength and performance were observed in people with sarcopenic obesity. In the future, longitudinal studies with higher levels of EAA (>8g/day) are needed to investigate the potential additional effects of supplementation in subjects with sarcopenic obesity. Finally, reporting outcomes related to muscle function (i.e., torque-length, torque-velocity, and power-velocity relationships) and muscle quality are strongly encouraged for evaluating the improvements inside skeletal muscle.

CHAPTER 5: FINAL CONSIDERATIONS

Overall discussion and conclusion

Aging is a natural and progressive process that involves each individual and causes changes including the reduction of muscle mass and a more pronounced reduction in muscle strength and muscle power. On the other side, obesity in the older population is an alarming factor as well and is gradually increasing all over the world. The factors contributing to the reduction of disability are mainly focused on the cardiovascular, metabolic, and musculoskeletal components. Surprisingly, in the past less attention was dedicated to the skeletal muscle component.

Older individuals with obesity commonly show low muscle mass and muscle strength which increase the risk of frailty, leading to a long-term loss of independence. Particularly, the lower limbs are more compromised due to aging and a sedentary lifestyle. Muscle strength deteriorates with negative consequences that impact the mechanics of walking, balance, and several tasks of daily living. Therefore, one of the purposes of this thesis was to enhance the knowledge about muscle strength and muscle function of the lower limbs in older adults with obesity. In the second chapter two cross-sectional studies were conducted to investigate if in a sample of older individuals of both sexes, obesity could impair the ability of skeletal muscles to express sufficient force levels. Two different protocols on knee extensors and knee flexors muscles via isometric and isokinetic protocols. In the first two papers we provided reference values of maximal strength performed at different knee joint angles and maximal isokinetic strength performed at different speeds of contraction. Furthermore, regarding the knee extensors, a characterization of the torque-velocity and power-velocity curves was analysed since they have been recognised as useful for describing the quantitative and qualitative information on muscle function. In addition, recently this has been established as a novel tool to target the exercise prescription.

The first two studies can be summarised as follows:

Study 1: In our cross-sectional study, a detailed picture of the impact of sex and obesity on isometric and isokinetic strength and power during ageing was shown. In absolute values, the ability to express isometric, isokinetic maximal strength and power changed with different muscle lengths and speeds of contraction. However, a similar profile of these curves was reported in both men and women with or without obesity. Unexpectedly, absolute values of strength, power and speeds were not different among BMI groups. By contrast, our sample of individuals with obesity showed lower values of strength and power adjusted by BM. This variable that we define as “useful” strength/power is clinically important since it can be used as an indicator of physical mobility when it is required to move the body into space. However, contrary to previous findings conducted in participants with higher levels of obesity (i.e., on average class II or III) the overall intrinsic skeletal muscle’s ability of producing strength and power, defined as “specific force/power” (i.e., muscle quality) was well-preserved in our sample of older adults with obesity compared to the normal weight counterpart.

Study 2: In this cross-sectional study a characterisation of the knee flexors muscle was further provided. The main findings revealed that in the older group with obesity, muscle quality of the knee flexors was impaired. Furthermore, the ratio between knee flexors and knee extensors were lower than 0.5 in all groups. However, the group with obesity presented the lower values not because of relevant weakness of the knee flexors but because of the disproportionate strength of the knee extensors. Therefore, in clinical practice the exercise physiologists should prescribe exercises targeting to preserve in the same way knee extensors and knee flexors, also considering the balance between both muscles. This should be kept in mind especially in those adults with obesity.

After providing reference values about muscle strength of the lower limbs and their functional implications, in the third chapter we conducted a narrative review and a cross-sectional study where the goals were to clarify the role of handgrip dynamometer and its association with the lower limbs’ strength and physical performance. This was conducted to enhance the research around this topic, also considering a population less explored in the previous literature. The studies can be summarised as follows:

Study 3: Considering the previous works, in our narrative review we concluded that the evidence to use the handgrip dynamometer as surrogate of the lower limbs muscle’s function are insufficient and in some cases with discrepant results. Therefore, we suggested the need to consider larger and heterogeneous studies, with an effort in a standardization of the protocols used for strength evaluation. We also provided new direction for future studies that should also investigate how sex, lifestyle (nutritional status or sedentary behaviour) and obesity impact on these associations.

Study 4: Based on some of the conclusions highlighted in study 3, we investigated in older adults with obesity of both sexes the associations between HGS and muscle function of the lower limbs. In addition, compared to previous studies a particular attention was made in predicting the ALMI, an important index for sarcopenia. Our main findings expand previous literature, revealing that these associations were more significant in men but not in women, hence highlighting the need to apply different evaluations based on sex response. Another important key message was that the BMI impacts on the ALMI in both sexes and that the evaluation of maximal strength and power of the lower limbs are effective markers for identifying the decline in muscle mass compared to using HGS alone.

In the last chapter we presented the preliminary data of a longitudinal study which involved older adults affected by dynapenic and sarcopenic obesity. Unfortunately, the intervention was conducted during Covid-19, slowing the process in data collection, and causing different drop-outs due to the interruption of local or national lockdown (mainly in the first wave of Covid-19). Initially, the study was projected to last 9 months (with evaluation at baseline, after 5 and 9 months of intervention), but due to the several difficulties encountered along the way, we had to shorten the intervention. Although the elaboration of some outcomes is still in process, looking at the preliminary results some general conclusions can be addressed and are summarised as follow:

Study 5: A moderately hypocaloric diet with RT alone or different dosages of EAA as supplements can be useful strategies for improving some outcomes related with body composition, strength, and physical performance in older adults with sarcopenic obesity. However, the prescribed doses of supplementation (4 g/day and 8g/day) were shown not enough to promote advantages on the above-mentioned variables in our sample. These preliminary findings leave open the question if the older adults need higher amounts (>8g/day) as supplements to have additional benefits on muscle mass, muscle strength, muscle function and performance compared to exercise alone. On the other hand, we brought original data on the changes in torque-length, torque-velocity, and power-velocity profiles after the proposed intervention in such a population. However, in the future more studies are needed to consolidate and expand our results using these novel parameters to obtain a detailed picture of the improvements that can occur inside skeletal muscle.

Each study has its own limitations which have been discussed in previous chapters. Nevertheless, this dissertation covers several aspects in respect of older population with obesity and/or sarcopenia. In detail: 1) we provided normative data of the muscle strength and power of the lower limbs considering the effect of sex; 2) we highlighted the important role that the additional evaluation of lower limbs can provide compared to handgrip dynamometer alone; 3) we proposed a multidisciplinary approach which embed nutrition and exercise as potential strategies to manage and treat obesity and sarcopenia.

In the future, further studies should carry on these topics considering large sample size, recruiting older adults with different classes of obesity and frailty status, looking at longitudinal changes in muscle strength and function of upper and lower limbs. Additionally, regarding the treatment of obesity and sarcopenia, more research is needed to implement the most effective approach that might combine physical exercise and nutrition with the goals to improve muscle mass during weight loss, strength, and physical function.

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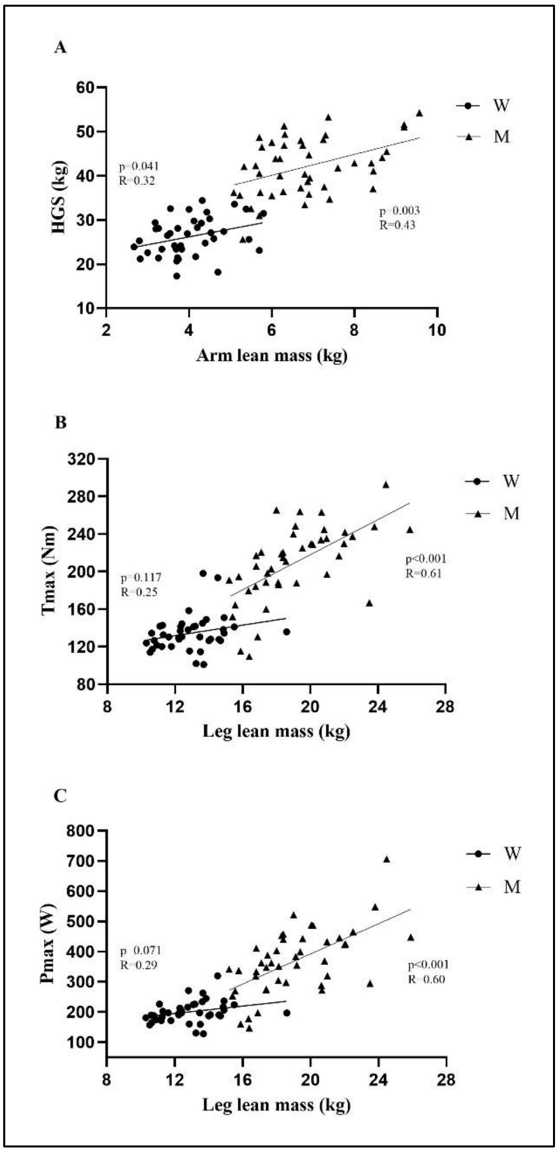
APPENDICES

APPENDIX 1



Supplementary Figure 3. 1: Association between handgrip strength vs arm lean mass (panel A), maximal knee extensor strength vs leg lean mass (panel B), maximal knee extensor power vs leg lean mass (panel C), in older men (▲) and women (●) with obesity.

Abbreviations: HGS: Handgrip Strength; Tmax: Maximal torque; Pmax: Maximal Power; W: Women; M: Men.

APPENDIX 2

Manuscripts authored and co-authored during the PhD program

- E. Calabria, **V. Muollo**, V. Cavedon, T. Capovin, L. Saccenti, F. Passarotti, L. Ghiotto, C. Milanese, M. Gelati, D. Rudi, G.L. Salvagno, G. Lippi, E. Tam, F. Schena, S. Pogliaghi, "Type 2 diabetes Related Mitochondrial Defects in Peripheral Mononucleated Blood Cells from Overweight Postmenopausal Women", 2023, *Biomedicines*, 11(1), 121
- L. Ghiotto, **V. Muollo**, T. Tatangelo, F. Schena, A.P. Rossi, "Exercise and physical performance in older adults with sarcopenic obesity: a systematic review", 2022, *Frontiers in Endocrinology,* 13, 913953
- A.P. Rossi*, **V. Muollo***, Z. Dalla Valle, S. Urbani, M. Pellegrini, M. El Ghoch (*first co-authors), "The role of body composition and nutrition in COVID-19 pandemia", 2022, *Nutrients,* Volume 14 (17), 3493.
- T. Tatangelo*, **V. Muollo***, L. Ghiotto, F. Schena, A.P. Rossi (*first co-authors), "Exploring the association between handgrip, muscle strength of the lower limbs and physical performance in older adults: a narrative review", 2022, *Experimental Gerontology,* 111902
- **V. Muollo**, T. Tatangelo, L. Ghiotto, V. Cavedon., C. Milanese, M. Zamboni, F. Schena, A.P. Rossi "Is handgrip strength a marker of muscle and physical function of the lower limbs? Sex differences in elders with obesity", 2022, *Nutrition, metabolism and Cardiovascular diseases*, Volume 31, Issue 4, Pages 1247-1256
- **V. Muollo**, A. Zignoli, L. Ghiotto, C. Milanese, M. Zamboni, F. Schena, A.P. Rossi "Knee flexor and extensor torque ratio in elderly men and women with and without obesity: a cross-sectional study", 2022, *Aging Clinical and Experimental Research*, Volume 34, Issue 1, Pages 209-214
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- **V. Muollo**, A.P. Rossi, A. Zignoli, M. Teso, C. Milanese, V. Cavedon. M. Zamboni, F. Schena, C. Capelli, S. Pogliaghi “Full characterisation of knee extensors’ function in ageing: effect of sex and obesity”, 2021, *International Journal of obesity*, 45: 895-905
- A.P. Rossi, S. Urbani, S. Gattazzo, N. Nori, F. Fantin, E. Zoico, G. Mazzali, **V. Muollo**, M. El Ghoch, M. Zamboni “The Mini Sarcopenia Risk Assessment (MSRA) Questionnaire score as a predictor of skeletal muscle mass loss”, 2021, *Aging Clinical and Experimental Research*, 1-5
- Zignoli, A. Fornasiero, P. Rota, **V. Muollo**, L. Peyrè Tartaruga, D. A. Low, F. Y. Fontana, D. Besson, M. Püronger, S. Ring-Dimitriou, L. Mourot “Oxynet: a collective intelligence that detects ventilatory thresholds in cardiopulmonary exercise tests”, 2020, *European Journal of Sport Science*, 1-38
- A.P. Rossi, S. Urbani, F. Fantin, N. Nori, P. Brandimarte, A. Martini, E. Zoico, G. Mazzali, A. Babbanini, **V. Muollo**, M. Zamboni “Worsening disability and hospitalization risk in sarcopenic obese and dynapenic abdominal obese: a 5.5 years follow-up study in elderly men and women”, 2020, *Frontiers in Endocrinology*, 11:314
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Manuscripts in preparation during the PhD program

- **V. Muollo**, V. Steinhauser, V. V. Shanbhogue, L. G Hvid, D. Caporossi, I. Dimauro, M. Andersen, C. Fantini, E. Grazioli, E. S. Strotmeyer, P.Caserotti, “Bone microarchitecture and bone strength following a 12-week high intensity progressive power training in mobility-limited older adults”, in preparation the final draft.