Sarcopenia and Low Back Pain in Older Adults

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Abstract

The risk of having a disability increases with advancing age and as the life expectancy is growing worldwide, the number of people living with disability is expected to increase, as well as the number of years lived with disability. Low back pain and sarcopenia are health problems that present a higher prevalence with aging. While low back pain is a symptom, sarcopenia is considered a geriatric syndrome. However, both issues constitute a significant health burden in older adults. Although there are many research studies investigating low back pain, the participation of older adults is often missing from these studies, preventing the generalization of the findings to this population, and leaving some questions unanswered. On the other hand, sarcopenia is a new research field with gaps to fill and flaws to correct. Questions related to low back pain management in older adults, the inclusion of this population in clinical trials, the presence of association between sarcopenia and low back pain and questions pertaining the diagnosis and measurement of sarcopenia have yet to be fully addressed by researchers. The broad aim of this thesis therefore was to contribute to a better understanding concerning low back pain and sarcopenia in older adults by performing studies in these key research areas.

Different interventions are presented in clinical practice guidelines for the treatment of low back pain. However, these recommendations are based on clinical trials investigating young and middle-aged adults and as a result, the recommendations do not encompass older adults. Therefore, a systematic review was performed with the objective of assessing the effectiveness of interventions for low back pain in older adults ≥ 60 years (Chapter 3). Eligible studies were identified via searches in Medline, EMBASE, CINAHL, LILACS,

PEDro, and Cochrane CENTRAL. A total of 18 randomized controlled trials fulfilled the eligibility criteria and the results from eight trials were pooled in a meta-analysis to test the effectiveness of complementary health approaches (i.e., manual therapy, acupuncture, mindfulness, yoga). Evidence about interventions to manage non-specific low back pain in older adults was found to be weak. Very low to moderate quality evidence showed that complementary health approaches, percutaneous electrical nerve stimulation, education, exercise, or pharmacological agents did not produce a clinically significant reduction in pain and disability at short and intermediate terms compared to sham, usual care, or minimal intervention. Interventions were often not well described and the risk of bias was moderate (average of 6.4 on the 10-point PEDro Scale (SD = 1.44)). Evidence about interventions for non-specific low back pain in older adults is limited and new studies are highly likely to change these results.

Participation of older adults in clinical trials pertaining to the management of low back pain has been limited. Usually, the exclusion of older adults from clinical trials is based solely on an arbitrary age limit. Therefore, an investigation concerning the potential increased inclusion of older adults in upcoming clinical trials was conducted (Chapter 4). Chapter four presents an analysis of the International Clinical Trial Registry Platform database from the World Health Organization performed to verify the participation of older adults in registered clinical trials. A total of 167 clinical trial protocols for low back pain with registration dates from January 2015 through November 2018 were planning to recruit participants older than 65 years. However, only five registered trials (2.99%; pooled sample = 169 participants) were designed to target this population specifically. The exclusion of older participants was not formally justified and imposed through an arbitrary upper-age

limit in 93.6% of the protocols. Most studies planning to include older adults were interested in pharmacologic interventions, devices/technology, and physical rehabilitation, and were to be carried out in developed regions. However, older adults with low back pain will continue to be under-investigated in clinical trials for low back pain in the near future.

Although a slight increase in the participation of older adults in clinical trials was observed, the improvement is small and some questions still need an answer. Therefore, a survey investigating whether researchers recognize the exclusion of older adults from clinical trials, its impact, and justifications to support this exclusion was realized (Chapter 5). All attendees of the 2017 International Back Forum were invited by email to answer an electronic survey about their opinions regarding participation of older adults in clinical trials for low back pain. Approximately 90% of those who answered the questionnaire were engaged with back research, with more than a half having done or doing a clinical trial for low back pain. Most of the respondents believed that older people are excluded from clinical trials for low back pain and that exclusion based solely on age is not justifiable. About two thirds of the respondents reported that the exclusion of older people from clinical trials can impose a barrier in offering evidence-based interventions to this population. More researchers are planning to include older adults in their current/future trials compared to their previous work. An increase in the investigation of older adults in clinical trials is expected in the future which may optimize the development of evidence-based interventions for this population.

As early evidence suggests an association between sarcopenic markers and low back pain, the association between the diagnosis of sarcopenia and low back pain still needs to be

investigated (Chapter 6). Therefore, a study investigating the association between sarcopenia using different diagnosis criteria and low back pain in older adults was performed. Data from 12,646 older adults (50.1% men, 49.9% women) ≥ 65 years of age that participated in the Canadian Longitudinal Study on Aging (CLSA) were analyzed. The prevalence of low back pain in the past 12 months as well the prevalence of sarcopenia assessed through different definitions, and the number of comorbidities and depressive symptoms were included in the analysis. Associations between sarcopenia, comorbidities and lifestyle factors with low back pain were examined using multivariate logistic regressions. Prevalence of low back pain was 16.3% and the prevalence of sarcopenia varied among sarcopenia definitions and the presence of low back pain. Participants with low back pain had higher prevalence of pre-sarcopenia and sarcopenia compared to those without low back pain based on the International Working Group on Sarcopenia ($x^2 = 20.25$, $p < 0.001$) and the Foundation National Institute of Health definitions ($x^2 = 13.83$, $p < 0.001$). The odds of having low back pain was higher among those with sarcopenia based on the Foundation National Institute of Health criterion (OR 1.28, 95%CI 1.0-1.64). These results suggest that sarcopenia may influence low back pain in older adults and future studies should consider to test whether the association between sarcopenia and low back pain is causal.

Current clinical practice guidelines recommend to divide patients with low back pain in specific subgroups to provide a targeted intervention. However, despite older adults presenting specific age-related characteristics that could classify them as a subgroup, this population has been neglected. Sarcopenia is a muscle disease affecting older adults and is diagnosed with the presence of a reduction in muscle strength and muscle quantity/quality. Although low back pain has been shown to be associated with muscle dysfunction, the role

of sarcopenia in relation to low back pain is unknown. An experiment comparing sarcopenic markers (grip strength and gait speed), muscle activity and elasticity between older adults with and without chronic low back pain was conducted (Chapter 7). The anticipatory activity of transversus abdominis muscle during the rapid arm abduction test, transversus abdominis muscle elasticity, grip strength and gait speed were collected from a group of older adults (≥ 60 years) with chronic low back pain (≥ 3 months) and the results compared with a control group of matched older adults without low back pain. Participants with chronic low back pain presented with a reduction in the sarcopenic markers compared with the controls: grip strength (mean difference (MD) = 5.3Kg, 95%CI = 1.5-9.0, p = 0.006), gait speed (MD = 0.21m/s, 95%CI = 0.10-0.31, p<0.001), as well as a delay in activation of transversus abdominis (p = 0.002). A delay in transversus abdominis muscle activation, and a reduction in muscle strength and gait speed were observed in older adults with chronic low back pain compared to subjects without back complaints. These findings show an association between muscle dysfunction and chronic low back pain in older adults.

Although the definition of sarcopenia was recently updated establishing muscle strength as the key criteria surpassing the role of muscle mass, there remains confusion regarding its diagnosis and the comparison of estimates is problematic. Therefore, a systematic review assessing how sarcopenia is measured and defined in population-based studies was performed. Chapters 8 and 9 describe the protocol of a systematic review and the full systematic review respectively. The databases Medline, EMBASE, CINAHL, Web of Science (Core Collection), and Google Scholar were searched for observational population-based studies reporting prevalence of sarcopenia in community dwelling older adults. Descriptive statistics were used to present data pertaining to sarcopenia definition and

measurement tools, and the quality-effects model for meta-analysis of pooled prevalence. Results found seven different operational definitions of sarcopenia and a variety of measurement tools applied to assess the sarcopenic markers: muscle mass, muscle strength and physical performance. The prevalence of sarcopenia varied between the definitions, with general estimates ranging from 5% based on the European Working Group on Sarcopenia in Older People (EWGSOP1) criterion to 17% with the International Working Group on Sarcopenia criterion. The use of different measurement tools to assess muscle mass, strength and physical performance resulted in variations within definitions ranging from 1 to 7%, 1 to 12% and 0 to 22%, respectively. The criteria used to define sarcopenia, as well as the measurement tools used to assess sarcopenic markers has an influence in the prevalence of sarcopenia. The establishment of a unique definition for sarcopenia, the use of methods that guarantee an accurate evaluation of muscle mass, and the standardization of measurement tools are necessary to allow a proper diagnosis and comparison of sarcopenia prevalence among populations.

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I grew up with my father telling me that knowledge is the only thing that cannot be stolen or robbed. However, with knowledge, you have the chance to achieve anything. With his words on my mind, I have been trailing my path and trying to disseminate what I've learnt to help other people.

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Paulo Roberto Carvalho do Nascimento

PhD Rehabilitation Sciences Candidate

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Publications

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Nascimento, P., Costa, L., Araujo, A. C., Poitras, S., & Bilodeau, M. (2019). Effectiveness of interventions for non-specific low back pain in older adults. A systematic review and meta-analysis. Physiotherapy, 105(2), 147–162.

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Presentations

Nascimento P, Poitras S, Bilodeau M (2015). Sarcopenia prevalence around the world: A systematic review. 8th International Conference on Cachexia, Sarcopenia and Muscle Wasting, Paris, France.

Nascimento P, Costa LOP, Imbeault P, Ramsay T, Poitras S, Bilodeau M (2017). Relationship between low back pain and sarcopenia in older adults. XV International Back and Neck Pain Research Forum. Oslo, Norway.

Nascimento P, Araujo A, Costa LOP, Poitras S, Bilodeau M (2017). Intervention strategies for management of non-specific low back pain in older adults – A systematic review XV International Back and Neck Pain Research Forum. Oslo, Norway.

Nascimento P, Poitras S, Ferreira M, Bilodeau M (2018). Recruitment of older adults in low back pain research: a survey with with attendees in the 2017 back and neck pain forum. XXII Congresso Brasileiro de Fisioterapia – COBRAF, Belo Horizonte, Brazil.

Nascimento P, Poitras S, Ferreira M, Bilodeau M (2018). Trends in the recruitment of older adults in clinical trials on low back pain: a review of the World Health Organization Trial Registry Database. XXII Congresso Brasileiro de Fisioterapia – COBRAF, Belo Horizonte, Brazil.

Preface

This thesis presents a series of 11 chapters that contain seven research papers. The work presented in this thesis involves two topics low back pain in older adults (Chapters 3 to 7) and sarcopenia (Chapters 8 and 9). This thesis is written following a paper-based format according to the recommendations established by the University of Ottawa. Chapters 3, 4, 8, and 9 are the PDF files of the published papers and Chapters 5, 6 and 7 are the submitted papers. Chapter 10 presents the discussion of the thesis results, while Chapter 11 provides the conclusion of the thesis.

In Chapter One, the thesis provides an introduction of the topic along with the thesis objectives. Chapter two presents an overview of the relevant literature about low back pain in older adults and sarcopenia. Chapter Three contains a full published systematic review. The paper is presented as published in *Physiotherapy*. The systematic review summarized the evidence about the effectiveness of interventions for non-specific low back pain in older adults. Chapter Four is a full published analysis of the inclusion of older adults in ongoing clinical trials investigating interventions for low back pain. This paper is presented as published in the *Journal of American Geriatrics Society*. Chapter five describes the results of a survey investigating the perceptions and expectations of low back pain researchers about the participation of older adults in randomized controlled trials. The paper is presented in the format required by *Spine,* where it was submitted for publication. Chapter Six is a cross-sectional analysis of the sarcopenia parameters between older adults with and without chronic low back pain. The paper is presented according to the authors' guidelines proposed by *Physical Therapy,* where it was submitted for publication. Chapter Seven is an

analysis of data from the Canadian Longitudinal Study on Aging investigating the association between Sarcopenia, comorbidities, lifestyle factors and low back pain. The paper is presented in the format required by *Journal of Medical Directors Association*, where it was submitted for publication. Chapter Eight is the full published protocol for a systematic review presented in Chapter Nine. The paper is presented as published in *Systematic Reviews*. Chapter Nine presents the results of a systematic review describing how sarcopenia has been defined and measured in epidemiological studies and its impact on prevalence values. The paper is presented as published in *Age and Ageing*.

Each chapter contains its own reference list. A combined list of the references from Chapters 1, 2, and 10 is included at the end of the thesis.

The research that forms Chapters 5, 6 and 7 presented in this thesis has received ethical approval from the Office of Research Ethics and Integrity at the University of Ottawa and the Bruyère Research Ethics Board of the Bruyère Research Institute before the beginning of recruitment. The research presented in Chapter 4 also received ethical approval from the Research Ethics Board of the Federal University of Minas Gerais (UFMG). The ethical approval of all studies is presented at the end of this thesis.

Part I

Chapter One

Introduction

1.1 Background

Life expectancy is increasing, and in 2019, there were approximately 703 millions of people ≥ 65 years old worldwide ("United Nations, Department of Economic and Social Affairs," 2019). As the population gets older, there is an increase in the number of people living with sequelae of diseases and injuries (Vos et al., 2016), which may lead to challenging and complex health issues, such as low back pain (LBP),and in turn, which leads to major health and economic burden in older people (Hoy et al., 2014).

LBP has been the leading cause of years lived with disability (YLD) for almost 30 years ("GBD 2017 Disease and Injury Incidence and Prevalence Collaborators," 2018). LBP is a disabling symptom with a point prevalence of about 9.4% in the general population (Hoy et al., 2014). Despite being considered a common symptom, in most cases the underlying cause of LBP is not identified; these cases are termed non-specific low back pain (NSLBP) (Hartvigsen et al., 2018; Maher et al., 2016). Consequently, the lack of a specific target for the rehabilitation of LBP contributes to a great number of patients developing chronic LBP (CLBP) (Koes et al., 2006).

The prognosis for LBP in older adults is often less favorable than in younger adults (Enthoven et al., 2014; Macfarlane et al., 2012), and in addition, older adults present with more severe forms of back complaints compared with young adults (Docking et al., 2011; Scheele et al., 2012). The point prevalence of LBP in older adults is about 21% (Leopoldino et al., 2016), with up to 40% of the cases presenting back complaints one year after a new episode (Scheele et al., 2012) reporting limitations in their daily function and an economic burden for health care systems (Hoy et al., 2014).

Older adults presenting with CLBP compared with pain-free individuals demonstrate significantly greater disruption in psychosocial function, greater self-reported disability, and lower scores on performance-based measures of physical capacity (Enthoven et al., 2014; Rudy et al., 2007). Furthermore, recovery rate for CLBP in older adults is low, with 23% reporting recovery in pain levels at 12 months (Rundell et al., 2015), decreasing to 3% when considering a simultaneous improvement in pain and function (Deyo et al., 2015). However, despite the impact of CLPB in older adults, this population is usually missing in clinical trials investigating interventions for LBP (Paeck et al., 2014), and the reasons to justify this unrepresentativeness are unknown.

Strategies to manage LBP are reported in several randomized trials with inconsistent and small effects (Cherkin et al., 2016; L. O. P. Costa et al., 2009; Hori et al., 2019b; Jesus-Moraleida et al., 2016; Koumantakis et al., 2005; Macedo et al., 2012; Zadro et al., 2019). In an attempt to increase the effectiveness of interventions for LBP, it has been suggested in the last decade that an ideal approach could be to divide patients with NSLBP into subgroups (Brennan et al., 2006; Delitto et al., 2012; Wand & O'Connell, 2008) and get away from the current tendency to treat patients with NSLBP as one homogenous group (Kamper et al., 2010).

Older adults can be affected by a syndrome termed ‘sarcopenia’, which was first described as an accentuated reduction in muscle mass (Rosenberg, 1997). Currently, there is a recommendation to define sarcopenia based on the association between decreased muscle strength, loss of muscle mass and decline in physical function (Cruz-Jentoft et al., 2019). The muscle impairment is claimed to occur due to reductions in the size, number, and

contractility of muscle fibers; as well as, fat tissue infiltration in the muscles (Stenholm et al., 2008; Vandervoort, 2002). These alterations have been reported to affect the muscles responsible for stabilization of the spine (Cuellar et al., 2017; Pezolato et al., 2012). Despite the growing interest on sarcopenia research after the publication of a consensus from the European Working Group on Sarcopenia in Older People (EWGSOP) (Cruz-Jentoft et al., 2010), information about the diagnosis criteria, tools and prevalence still needs to be properly summarized and clarified.

The muscular system is advocated to play a role in the motor control of the spine (Panjabi, 1992, 2003, 2006). There is, some evidence supporting the efficacy of interventions targeting the improvements of abdominal wall and spine muscles recruitment/activation in reducing disability and pain in subjects with LBP (Saragiotto Bruno et al., 2016; Yamato et al., 2015). The generalizability of these findings or their relevance to older people is, however, unknown. Thus, the muscle impairment caused by sarcopenia could be a predisposing factor for LBP, or a contributor to the recurrence of symptoms in older adults, categorizing these individuals into a specific subgroup for LBP.

1.2 Aims of the thesis

The main goal of this thesis is to contribute to a better understanding of sarcopenia and low back pain in community dwelling older adults, and to investigate their association.

The specific aims of this thesis were to:

1. Systematically review the evidence regarding interventions for low back pain in older adults.

2. Investigate the International Clinical Trial Registry Platform (ICTRP) to verify if researchers are paying more attention about the necessity of targeting older adults in clinical trials for the management of LBP.
3. Identify, through a survey with low back pain researchers, their beliefs, and expectations about the participation of older adults in randomized clinical trials.
4. Conduct a cross-sectional analysis of the baseline data from the Canadian Longitudinal Study on Aging to assess whether sarcopenia is associated with LBP.
5. Assess the feedforward response of the transversus abdominis muscle along with sarcopenia parameters (i.e., grip strength and gait speed) in older adults with and without chronic low back pain.
6. Perform a systematic review to summarize how sarcopenia has been measured and defined, and the impact of this on prevalence estimates in community-dwelling older adults.

Chapter Two

Literature Review

2.1 The growth in life expectancy

The increase in life expectancy is a global phenomenon contributing to the growth in the number of older men and women (Wang et al., 2016). By 2050, the number of people older than 65 years of age is expected to double, rising above 16% of the world population (approximately 1.5 billion) meaning that 1 in 6 people in the world will be over the age of 65, up from 1 in 11 in 2019 ("United Nations, Department of Economic and Social Affairs," 2019).

In 1980, it was expected that a man 50 years of age would live another 23.1 years. This number increased to 26.6 years in 2015, whereas a woman 50 years of age could live an additional 26.4 years in 1980 and 30.9 years in 2015 (Wang et al., 2016). Due to the increase in survival rates and longevity, in 2050, approximately 400 million people will be 80 years or older ("United Nations, Department of Economic and Social Affairs," 2019).

The decline in mortality rates has not been paralleled with a similar reduction in age-standardised YLD rates ("GBD 2015 DALYs and HALE Collaborators," 2016; Vos et al., 2016). As people are living longer, morbidity increases due to the higher chance of developing age-related health-issues, such as LBP, which ranks at the top among the leading causes of YLD ("GBD 2015 DALYs and HALE Collaborators," 2016; Hoy et al., 2014; Vos et al., 2016).

2.2 Epidemiology of low back pain

The prevalence of LBP has been exhaustively investigated among young adults and middle-aged adults of working age (Louw et al., 2007; Nascimento & Costa, 2015; Walker, 2000),

with an estimated point prevalence equal to 11.9%. However, recent evidence is showing that the prevalence and burden of LBP increase with aging (Cieza et al., 2020; "GBD 2017 Disease and Injury Incidence and Prevalence Collaborators," 2018; Hoy et al., 2014), which furthers the interest in investigating this population.

Despite such interest concerning the epidemiology of LBP in older adults in the last decade (Docking et al., 2011; Leopoldino et al., 2016; Macfarlane et al., 2012), a global pooled prevalence rate is still not available due to methodological differences between studies, mainly in the delimitation of age groups, symptoms duration, LBP definitions and the population studied with values extending from 21% to 75% (de Souza et al., 2019). For example, Docking et al. (2011) reported a prevalence rate for LBP of 23%, while Cecchi et al. (2006) found values of 31,5%. In both studies different definitions of LBP, symptoms duration, and age groups were used. Whilst the first study investigated recent episodes of LBP in participants aged 75 years or over, the second one was focused on persistent episodes in people aged 65 years or older.

The role played by age in the prognosis of LBP remains unclear (Manogharan et al., 2017) although some studies have shown a negative influence of old age (Hayden et al., 2009; Jarvik et al., 2014). However, older individuals with LBP present an increased risk of becoming chronic sufferers (Scheele et al., 2012; Van der Gaag et al., 2019), and develop greater disability (Docking et al., 2011; Macfarlane et al., 2012; Rundell et al., 2015). In addition, Hoy et al. (2014) has shown that over a time period of only 20 years (i.e., 1990-2010), the global burden of YLD due LBP in the population between 50–69 years old has

increased by about 8% (i.e., from 59% to 67%), making LBP the leading cause of disability globally, with a peak prevalence around 80 years of age.

The course of LBP has been reported to be benign in the general population with greater improvements in the first 6 weeks (Menezes Costa et al., 2012). However, in older adults the course is worse, with a high rate of persistent complaints at 3 months (i.e., up to 40%), 12 months (i.e., up to 45%) (Scheele et al., 2012), and five years (57%) (Van der Gaag et al., 2019). In a study concerning the course of new episodes of LBP (i.e., no pain in the previous 6 months) in older adults, Rundell et al. (2015); revealed that 75% of participants showed persistent symptoms at 12 months. Using the same dataset, (Deyo et al., 2015); showed that the symptoms trajectory is usually constant for pain and disability with a small group presenting significant improvements in each outcome, and only 3% recovered (i.e., at least 1 month with no pain) for both outcomes. Older adults are a common age group that visit physicians for LBP (Licciardone, 2008; Turner et al., 1998).However, they are more likely to receiving treatment options that are unnecessary and inconsistent with current guideline recommendations (Traeger et al., 2019).

2.3 Etiology of low back pain

Regardless of the high prevalence, incidence, and burden of LBP (Hoy et al., 2012; Hoy et al., 2014; Taylor et al., 2014), only a small number of cases receive a specific diagnosis (Hartvigsen et al., 2018; Maher et al., 2016). Due to the incapacity in providing a specific cause for LBP, the biopsychosocial model should be the prevailing framework to help understand LBP occurrence and chronicity (Waddell, 1987).

The biopsychosocial model suggests that LBP must be considered a symptom (i.e., a complex interaction of biological, psychological, and social factors), instead of a purely physical disease (Waddell, 1987). The biopsychosocial nature of LBP was shown in a systematic review, revealing that first-time LBP or transition to LBP from a pain-free state baseline was associated with both psychosocial and physical risk factors (Taylor et al., 2014). In addition, biopsychosocial factors such as higher pain intensity, higher body weight, carrying heavy loads at work, difficult working positions, and depression; were indicated as relevant prognostic factors for pain chronicity in LBP (Nieminen et al., 2021). Further, the relevance of the biopsychosocial framework for LBP was also shown by Steffens et al. (2015) using a case-crossover design to study the transient risk factors for a new episode of LBP. Results of this study revealed that manual tasks involving awkward posture, heavy loads, objects not close to the body, unstable or unbalanced objects and manual tasks involving people or animals (i.e., physical domain), and being distracted during a task or activity or being fatigued (i.e., psychosocial domain) were associated with a new onset of LBP in young and middle-aged adults (Steffens et al., 2015). Although this study included only young and middle-aged adults, recent evidence suggests that the influence of biopsychosocial characteristics among older adults may differ from younger individuals with contributor such as sarcopenia, depressive symptoms, reduced memory and executive function, and suboptimal medical interaction amongst others (Simon & Hicks, 2018b).

2.4 Management of low back pain in older adults

Chronic low back pain is a challenging condition to treat and the effectiveness of different exercise-based interventions such as strength or performance training (Hayden et al., 2005;

Searle et al., 2015; Van Tulder et al., 2000), motor control-based exercises (Saragiotto Bruno et al., 2016), Pilates (Hayden et al., 2021; Yamato et al., 2015), the Mackenzie Method (Garcia et al., 2018; Hayden et al., 2021; Sanchis-Sánchez et al., 2020) and a combination of different types of exercise (Koldas Dogan et al., 2008; Koumantakis et al., 2005) have been insvestigated showing small or no effect when compared to other active interventions. In addition, pharmacological interventions and spine manipulation produce small (Chaparro et al., 2013; Rubinstein et al., 2019) or no better outcomes (Saragiotto et al., 2016) when compared to placebo, and may not be worth the associated risks of harm. Furthermore, non-pharmacological treatments such as acupuncture, massage, yoga, spinal manipulation interdisciplinary treatments, and mindfulness have been pointed as second-line or adjunct interventions (Nadine E. Foster et al., 2018).

The finding of mixed results with regards to the efficacy of interventions for LBP can possibly be explained by the presence of different causal mechanisms and the failure to identify subgroups in the LBP that would benefit from different interventions (Delitto, 2005; Wand & O'Connell, 2008). Because of this, it has been suggested that an ideal approach could be to divide patients with NSLBP into treatment-based subgroups (Alrwaily et al., 2016; Brennan et al., 2006; Delitto et al., 2012), and move away from the current tendency to treat this population as one homogenous group (Kamper et al., 2010).

The differing biopsychosocial characteristics of older adults, when compared to their younger counterparts, may warrant this population to be classified as a specific subgroup for LBP treatment (Dziechciaz & Filip, 2014; Molton & Jensen, 2010; Simon & Hicks, 2018b). Reduction in muscle strength, loss of muscle mass, and impairments in functional

performance are remarkable characteristics of aging (Goodpaster et al., 2006), which in combination, are denoted under the term sarcopenia (Cruz-Jentoft et al., 2019). Based on the assumption that the musculoskeletal system plays an important role in low back health, older adults presenting with sarcopenia, could constitute a specific 'at risk' subgroup, which deserves investigation. Notably, most of the participants in clinical trials for LBP are middle-aged, which may prevent the generalizability of the results to other age groups (Paeck et al., 2014). A study reviewing the effectiveness of interventions for LBP in older adults is presented in chapter three of this thesis.

2.5 Recruitment of older adults in clinical trials for LBP

The participation/inclusion of older adults in clinical trials has been limited in different health-related disciplines (Cruz-Jentoft et al., 2013; Talarico, Chen G Fau - Pazdur, et al., 2004; Zulman et al., 2011), including LBP research (Bressler et al., 1999; Paeck et al., 2014). Common barriers in recruiting older adults for clinical trials include refusal to participate, informed consent complexity, access issues, ethnic barriers, subject fear/concerns, gatekeeper influence, morbidity and mortality (Ridda et al., 2010). Also, barriers can be related to participants, investigators and trial design (Denson & Mahipal, 2014); however, the exclusion of older adults is usually not reasonably justified, but is rather based on the establishment of an arbitrary upper age limit (Bayer & Tadd, 2000).

Although there is significant evidence reporting the need to optimize the participation of older adults from RCTs, the barriers, and possible solutions, the problem persists. (Cherubini et al., 2011). An investigation about the participation of older adults in ongoing RCTs for LBP is presented in chapter 4 of this thesis. Also, a survey on the beliefs and expectations of

LBP researchers regarding the engagement of older adults in RCT is described in chapter five.

2.6 Sarcopenia

Sarcopenia, so named by Rosenberg (1989), is considered a complex "geriatric syndrome" with a multifactorial etiology. Sarcopenia is associated with a high risk of falls, disability and is a prognostic factor for morbidity and mortality after surgery (Landi et al., 2012; Peng et al., 2012). Besides age, common risk factors for sarcopenia include early life disturbances, poor diet, a sedentary lifestyle, chronic diseases, race, and gender (Berger & Doherty, 2010; Cesari & Pahor, 2008; Fielding et al., 2011; Verlaan et al., 2017).

The specific mechanisms underlying the development of sarcopenia remain unclear and the theory that muscle atrophy plays a major role in the reported age-related muscle weakness is not supported (Goodpaster et al., 2006). Instead, current evidence advocates that age-related weakness is rather related to a combination of different factors such as increased intramuscular fat infiltration; increased muscle denervation that decreases the number of muscle fibers and motor units, and the size of muscle fiber (Deschenes, 2004; Manini, 2011; Manini et al., 2013), decreased number and proliferation capacity of satellite cells which decrease muscle fiber size and the reparation capacity from normal muscle change; decreased hormone/growth factors such as circulating testosterone and growth hormone factor which decreases muscle protein accretion (Goldspink, 2012), decreased circulating IGF-1, inflammation and increased production of interleukin-6 (IL-6) that increases the rate of muscle protein degradation (Deschenes, 2004). Furthermore, changes in central nervous system (CNS) drive (e.g., reduced neural drive to agonist muscles or increased neural drive

to antagonist muscles) (McNeil & Rice, 2018) and peripheral nerve dysfunction (i.e., reduced nerve conduction amplitude and velocity) can contribute with muscle weakness in older adults (Ward et al., 2014).

2.7 Definitions of sarcopenia

The term sarcopenia was firstly used by Rosenberg (Rosenberg, 1989) to describe the accentuated loss of muscle mass with aging. Two decades later a group of researchers from different countries in Europe founded the European Working Group on Sarcopenia in Older People (EWGSOP) that established a consensus definition and diagnosis for age-related sarcopenia (Cruz-Jentoft et al., 2010). According to the EWGSOP, the diagnosis of sarcopenia must be based on the presence of low muscle mass plus low muscle function (strength or performance), using cut-off points at two standard deviations below the normative values for healthy young adults (Cruz-Jentoft et al., 2010). Recently, the EWGSOP revised its definition generating the EWGSOP2, with muscle strength overtaking the role of low muscle mass in the diagnosis of sarcopenia (Cruz-Jentoft et al., 2019).

After the establishment of the first EWGSOP consensus, different groups of expert such as the International Working Group on Sarcopenia (IWGS) (Fielding et al., 2011) and the Asian Working Group for Sarcopenia (AWGS) (Chen et al., 2014) published definitions for sarcopenia following the same criteria proposed by the EWGSOP although with cut-off values specific for their population in an attempt to obtain reliable measures. Another criterion for sarcopenia definition was developed by the Foundation for the National Institutes of Health (FNIH) (Studenski et al., 2014), which also suggested specific cut-off values however, the FNIH proposed that muscle quantity should be based on muscle mass

adjusted by the body mass index (BMI) instead of adjusting it by height squared as in the aforementioned definitions.

2.8 Epidemiology of Sarcopenia

Estimates of the prevalence of sarcopenia vary according to the criteria definition used to diagnose it with values ranging from 9.9 to 40.4% (Mayhew et al., 2019). In their study, Mayhew et al. (2019) found that prevalence of sarcopenia was lower among the studies using the IWGS definition (9.9%), followed by the EWGSOP and AWGS criteria (12.9%), and the FNIH (18.6%), with higher prevalence estimates found when sarcopenia was defined as the loss of muscle mass alone (24.2 to 40.4%).

Divergent results in the prevalence of sarcopenia are found even within the same definition criterion and in the same sample when different tools are used to measure muscle mass and muscle strength (Beaudart et al., 2015; Cruz-Jentoft et al., 2014; Kim et al., 2016). Cruz-Jentoft et al. (2014) investigated a set of studies that measured the prevalence of sarcopenia following the recommendations of the EWGSOP and found that estimates in community-dwelling older adults varied with muscle mass measures from 1% to 29%. Similarly, Kim et al. (2016) evaluated the prevalence of sarcopenia in a sample of older Japanese and showed different estimates of prevalence within the same definition with different tools used to measure muscle mass. The reported prevalence according to the AWGS definition based on DXA measurements of muscle mass were 2.5% in men and 2.3% in women whereas estimates derived from BIA to quantify muscle mass led to a prevalence of 7.1% and 19.8% for men and women respectively (Kim et al., 2016). Further, distinct estimates in the prevalence of sarcopenia were also found in a study with older adults from Belgium when

using different tools to measure muscle mass: BIA (12.8%) and DXA (21%); as well as for muscle strength measurement: pneumatic dynamometer (22.4%) and hydraulic dynamometer (11.4%) (Beaudart et al., 2015).

The existence of different criteria definitions plus a wide range of diagnostic tools used to quantify muscle mass/function contribute to a lack of agreement among studies reporting sarcopenia. Chapters eight and nine of this thesis present a protocol of a systematic review and the full systematic review on the prevalence of sarcopenia based on definitions and measurement tools used.

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Part II

Chapter Three

Effectiveness of interventions for non-specific low back pain in older adults. A systematic review and meta-analysis

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Effectiveness of interventions for non-specific low back pain in older adults. A systematic review and meta-analysis

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Abstract

Objectives Systematically review the literature about all available interventions to manage non-specific low back pain (NSLBP) in older adults (≥60 years).

Design We searched the Medline, EMBASE, CINAHL, LILACS, PEDro, and Cochrane CENTRAL databases reference lists for randomized controlled trials (RCTs) testing interventions for NSLBP. Two independent reviewers extracted data, assessed the risk of bias and completeness of the description of interventions.

Results Eighteen (RCTs) fulfilled the eligibility criteria. Evidence about interventions to manage NSLBP in older adults is weak. Very low to moderate quality evidence showed that complementary health approach (i.e., manual therapy, acupuncture, mindfulness, yoga), percutaneous electrical nerve stimulation (PENS), education, exercise or pharmacological agents were not effective to produce a clinically significant reduction in pain and disability at short-term and intermediate-term compared to sham, usual care or minimal intervention. Interventions were moderately well-described according to the template for intervention description and replication (TIDieR) and the risk of bias was moderate 6.4 points on the 10-point PEDro Scale (SD = 1.44).

Conclusion Evidence about interventions for NSLP in older adults is limited and new studies are highly likely to change these results. This result may impact healthcare providers due to the lack of effective evidence based interventions, patients, and policy makers that will expend financial resources with interventions that provide in the best scenario a not significant improvement of the clinical symptoms. Researchers need to consider the importance of designing clinical trials targeting older adults and examine possible outcome modifiers present in this population allowing the recommendation of more efficacious evidence-based interventions.

Systematic Review Registration Number PROSPERO (CRD42016036686).
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Keywords: Aged; Aged, 80 and over; Low back pain; Therapeutics; Rehabilitation

Introduction

The 2010 global burden of disease study revealed that the prevalence and burden of low back pain (LBP) increase with age [1]. Age is also associated with lower recovery rates [2], higher risks of chronicity [3] and severe symptoms [4], which can contribute to the fact that most persons with NSLBP seeking healthcare are older adults [5].

Current recommendations to manage LBP suggest to stratify patients into specific subgroups aiming to improve health outcomes [6]. Although older adults present specific biopsy-

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chosocial changes due to aging [7–9], the investigation of older adults as a subgroup is missing and they are underrepresented in RCTs [10]. As a consequence, older adults are embracing other alternatives such as complementary health approaches (i.e., acupuncture, massage, yoga, spine manipulation, and mindfulness) [11].

To date, little is known about the effectiveness of NSLBP interventions for older adults. The development of knowledge about how to treat LBP in older people is important since this population is growing worldwide [12] and LBP contributes to more years living with disability [13] besides the indirect risk of death [14] resulted from falls associated with LBP [15]. Two previous reviews have summarized the effectiveness of "physical therapy" interventions and exercises for older adults (65 years and older) presenting NSLBP [16,17]. In contrast, the present review searched for all type of interventions and duration of symptoms, in adults 60 years and older according to the United Nations [18] definition of elderly. Therefore, our aim was to systematically review all type of interventions compared to any control to decrease pain and disability in community-dwelling older adults with NSLBP at short, intermediate and long-term follow-up.

Methods

Selection criteria

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [19].

A PICOT approach [20] was applied to formulate the research question. All existing evidence from randomized controlled trials focusing on the management of NSLBP (i.e., no known pathoanatomical cause) in community dwelling older adults were considered for inclusion, independent of language and publication date. Studies recruiting participants presenting LBP in which the pain arises from problems beyond the lumbar spine (e.g. leaking aortic aneurysm); specific disorders (e.g. epidural abscess, compression fracture, spondyloarthropathy, malignancy, cauda equine syndrome); or radicular pain, radiculopathy, or spinal canal stenosis were excluded [21]. Remaining cases were considered NSLBP. We included only papers published in peer-reviewed journals through September 2018. The protocol for this systematic review was prospectively registered on PROSPERO CRD42016036686.

Studies were included according the following inclusion criteria: (a) older adult (≥60 years) population with acute (<4 weeks), subacute (>4 weeks but <12 weeks) or chronic (>12 weeks) NSLBP, (b) randomized controlled trials, and (c) reporting at least one clinical outcome as: (1) pain intensity, (2) functional status/disability, or (3) perceived recovery. Articles reporting pilot, feasibility or preliminary studies, and data on individuals under 60 years or institutionalized subjects were not considered.

Search strategies

Electronic database searches were conducted in Medline, EMBASE, *Cumulative Index to Nursing and Allied Health Literature* (CINAHL), Latin American and Caribbean Health Sciences Literature (LILACS), Physiotherapy Evidence Database (PEDro), and Cochrane Central Register of Controlled Trials (CENTRAL). Search strategies followed the recommendations of the Cochrane Back Review Group [22]. Detailed search strategies used in each database are described in a supplement (Supplementary file 1). Additionally, the reference lists from eligible studies were screened to identify possible additional relevant trials.

Two independent reviewers (PN, AA) screened the retrieved articles for eligibility. A third reviewer was consulted in case of disagreement providing consensus through discussion or arbitration.

A standardized data extraction form was used to collect the following information: authors, year of publication, population, sample size, interventions, comparisons, follow-up, and outcomes. Self-reported outcomes for pain and disability/function were assessed in this review. Authors were contacted by email in case of insufficient data and further data were requested.

Risk of bias assessment

The risk of bias in the eligible studies was assessed using the PEDro scale [23]. The PEDro scale is an 11-item (higher scores = lower risk of bias) valid tool to measure the risk of bias and statistical reporting of clinical trials [24,25]. The PEDro score was extracted directly from the PEDro database (www.pedro.org.au) since all eligible studies were already indexed in the database, which provides a reliable rating score.

Description of interventions

Information on interventions was extracted using the Template for Intervention Description and Replication (TIDieR) [26]. The TIDieR is a checklist of 12 items that was developed aiming to improve the reporting of interventions.

Quality of evidence

We assessed the overall quality of the evidence and the strength of the recommendation for each outcome using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach, as recommended in the Cochrane Handbook for Systematic Reviews of Interventions [27]. The GRADE approach establishes the quality of evidence as high, moderate, low and very low. Five domains that are able to decrease the quality of the evidence are: study design and risk of bias; consistency of results; directness (generalizability of the findings); precision (i.e., sufficient

Table 1
Characteristics of all included studies.

Study	Population	Intervention group	Comparison group
Inoue [32]	n = 31 Low back pain (not specified the time duration) Age (yr) = exp 68 (SD 6), con 70 (SD 8)	Acupuncture – therapists inserted a stainless steel needle to a depth of 20 mm at the most painful point and stimulated the needle with the sparrow pecking method (lifting and thrusting) for 20 seconds.	Sham acupuncture – therapists tapped the end of a guide tube on the skin at the most painful point, without a needle, and then acted as if they were inserting a needle there
Giemza [33]	n = 80 Men with chronic low back pain (>3 m) Mean age of both groups, age (yr) = 70.1	Whole body cryotherapy five times per week during one week. The treatments were conducted in a Cryogenic chamber with treatment lasting 3 minutes. Participants subject spent approximately 30 s in a vestibule at a temperature of −60 °C to adapt to the cold. Next, the subject moved to the main chamber at a temperature −120 °C for 3 minutes.	Same protocol as the experimental group, however, two times per week.
Dougherty [34]	n = 136 Non-specific low back pain (≥3 months) Age (yr) = exp 76.99 (SD 6.77), con 77.04 (SD 6.81)	Spinal manipulative therapy – two times per week during 4 weeks. Participants received a high-velocity, low-amplitude spinal manipulation, and/or flexion distraction therapy and/or mobilization alone or in combination based on the clinician's judgment. In addition, participants received a brochure with stretching and strengthening exercises.	Sham "detuned ultrasound", applied over the lumbar spine for 11 minutes two times per week during 4 weeks. Participants also received the brochure with stretching and strengthening exercises.
Grant [35]	n = 60 Chronic low back pain (>6 m) Age (yr) = exp 75, con 72	Acupuncture two times per week during 20 minutes for 4 weeks. Acupuncturist selected the points for each participant as in routine clinical practice, using only points on the back. Six needles were used on average at each treatment with a minimum of two and a maximum of eight.	Home application of TENS during 30 minutes as required (maximum of 6 hours per day) using 50 Hz stimulation with the intensity adjusted according participants' tolerance. Participants also meet the physiotherapist twice per week during 20 minutes, to review the symptoms, discuss the treatment and the optimum use of the device.
Meng [36]	n = 47 Non-specific chronic low back pain (≥3 months) Age (yr) = exp 75 (SD 2), con 70 (SD 6)	Acupuncture treatments twice a week for 5 weeks. Ten to 14 needles with electrical stimulation at 4–6 Hz and pulse duration of 0.5 ms were applied in standard acupoints for 20 minutes. Standard care – participants were allowed to maintain their standard therapy prescribed by their physician. Prohibited therapies were narcotic medications, muscle relaxants, TENS, epidural steroid injections and trigger point injections.	Standard care – participants were allowed to maintain their standard therapy prescribed by their physician. Prohibited therapies were narcotic medications, muscle relaxants, TENS, epidural steroid injections and trigger point injections.
Morone [37]	n = 282 Chronic low back pain (≥3 months) age (yr) = exp 75 (SD 7.2), con 74 (SD 6.0)	Mindfulness – 8-week program. Four methods of mindfulness meditation were taught taking regular activities such as sitting, walking, and lying down and transform them into a meditation through directed breathing and mindful awareness of thoughts and sensations. The methods used included the body scan, sitting practice, walking meditation, and mindful stretching. To encourage proficiency with the meditation method after completion of the intervention, monthly 60-minute booster sessions were held.	10 keys to health aging – 8-week health education program teaching an interactive, dynamic program to older adults on key health topics relevant to healthy aging such as hypertension management. The same chair stretches taught in the intervention were taught in the control program. To ensure that the control group received an equal amount of attention and social support, they also received monthly booster classes, which met monthly for 1 hour.

follow-up. Results from continuous data are presented as mean differences (MD) and 95% confidence interval (CI). When this information was not provided, the size of the treatment effect (i.e., difference between intervention A and intervention B) and the 95% CI, was calculated using the mean value, standard deviation and the number of participants in each group through a confidence interval calculator [29]. A negative effect size indicated that the experimental intervention was more beneficial than the comparator. We evaluated the overall quality of evidence using the GRADE approach and for effect sizes we used three levels: small (mean difference (MD) <10% of the scale), moderate (MD 10% to 20% of the scale) or large (MD >20% of the scale) [30]. Furthermore, we used the size of the effect to determine whether the results were clinically relevant or not, where a reduction of 25 points (0 to 100 scale) in the MD was considered to represent the minimally clinically important change (MCIC) [31].

The Chi^2 and I^2 statistics were used to measure the heterogeneity between the eligible studies. Non-significant values in the Chi-squared test ($p > 0.05$) and I^2 scores of lower than 40% were considered unimportant [27]. Where possible, data were pooled and a meta-analysis was performed using a random effect model. All data synthesis was conducted with RevMan version 5.3.

Scale (VAS) [37,44,46,48,49], or Pain Functional Rating Index (PFRI) [45]. Low back pain disability was evaluated using the Roland Morris Disability Questionnaire (RMDQ) [36,40–43,47], Oswestry Disability Index (ODI) [34,39,44], Modified Von Korff (MVK) Scales [48], Hannover Functional Ability Questionnaire (FFbHR) [45], or the Pain Disability Assessment Scale (PDAS) [49].

Risk of bias

The risk of bias of the eligible studies is presented in Table 2. These trials were considered of moderate quality, with a mean of 6.17 points (SD = 1.3) on the 10-point PEDro Scale (range 3 to 8). The items least frequently satisfied were blind therapist one trial [38] and blind subjects 3 trials [32,34,38].

Description of the interventions

The analysis concerning the completeness of the description of the interventions (TIDieR) revealed that interventions are usually well-described including identification with a brief name or phrase, and description of materials, procedures, mode of administration, frequency and intensity

Soriano [38]	n = 85 Chronic low back pain (>3 months) age (yr) = exp 63.2, con 64.3	Laser therapy – 5 × /week × 2 weeks. Pulsed GaAs diodo laser, wavelength 904 nm, pulse frequency 10.000 Hz and pulse width 200nsec, peak power 20W, average power 40 mW, spot size 150 μm^2 in area and angle of divergence of 6°. The laser was applied using the point contact irradiation technique with a dose of approximately 4J/cm^2 per point, which were separated by 2 cm.	Sham laser – participants were irradiated with a deactivated laser system 5 × /week × 2 weeks.
Sritoomma [39]	n = 140 Chronic low back pain (>12 weeks) Age (yr) = not available	Swedish massage with ginger oil – massage combined with aromatic ginger oil using the following five basic strokes: effleurage, petrissage, friction, tapotement and vibration.	Traditional Thai massage – based on meridians energy-line theory. The massage therapist stretched the muscles, applied pressure with the palms, thumbs and elbows, all techniques addressing the energy pathway and points.
Weiner [40]	n = 34 Chronic low back pain (≥3 months) Age (yr) = exp 74.1 (SD 4.6), con 73.5 (SD 5.7)	PENS + PT – 30′, 2 × /week × 6 weeks. Application of acupuncture needles and electrical stimulation occurred at the appropriate dermatomal, myotomal, and sclerotomal levels. Stimulation frequencies ranged from 2 to 200 Hz; Intensity of the electrical stimulation was maintained below the pain threshold. PT – included modalities of manual therapy, stretching exercise and flexibility exercise, education addressing the topics of the anatomical and pathological bases for the pain condition, importance of active participation of the subject in managing the pain, and the use of flare management techniques.	Sham PENS + PT – 30′, 2 × /week × 6 weeks. Acupuncture needles were applied using a technique identical to that used in the PENS group, but no electrical stimulation was provided. PT – same program as applied in the experimental group.
Weiner [41]	n = 200 Chronic low back pain (≥3 months) Age (yr) = exp 73.9 (SD 5.2), con1 73.3 (SD 6.0), con2 74.1 (SD 5.6), con3 74.3 (SD 6.4)	PENS + exercise – 2/weeks × 6 weeks. PENS was administered for 30′ using 10 needles for each session, placed bilaterally at dermatomal, myotomal, scleratomal, and sympathetic levels corresponding to T12, L3, L5, and S2, and the motor point for the piriformis muscle. Participants also had two needles placed at the T12 level. The exercise program included both general conditioning (strength and flexibility) and acrobic components sessions lasted for 60 minutes. The program also had a home component consisting of flexibility exercises and a graded walking program performed three times a week for 6 weeks.	Sham PENS + exercise – 2/weeks × 6 weeks. PENS was administered for 30′ replicating the positioning and number of needles in the experimental group. However, electrical stimulation was applied only at the T12 dermatome. Five minutes followed the initiation of electrical stimulation, the electrostimulator unit was turned off to avoid the delivery of potentially therapeutic microcurrent.
Costantino [42]	n = 56 Chronic non-specific low back pain (>3 months) Age (yr) = exp 73.63 (SD 3.36), con 73.3 (SD 3.55).	Back school – sessions of one hour, 2 times per week during 12 weeks. Education about the anatomy of spinal column, its functioning and ergonomic position and the basis of the pain-inducing mechanism, psychological aspects and stress management (first session). Following sessions, muscle stretching (iliopsoas muscle), muscular strengthening (rectus, external and internal oblique abdominis, erector spinae, gluteal, and quadriceps muscles), and exercise for trunk flexion/extension, and pelvic tilt associated with proper breathing.	Hydrotherapy – sessions of one hour, 2 times per week during 12 weeks. During each session participants performed bilateral stretching (iliopsoas, gastrocnemius, hamstrings and posterior muscle chain) and selective muscle strengthening (abdominal, erector spinae, and hip abductor/adductor muscles).

Table 1 (*Continued*)

Study	Population	Intervention group	Comparison group
Hondras [43]	n = 225 Subacute non-specific low back pain (≥4 weeks) Age (yr) = exp1 63.0 (SD 6.0), con1 63.8 (7.6), con2 62.3 (SD 6.1)	High-velocity low amplitude spinal manipulation – max of 12 visits, up to 3 times per week for the first 2 weeks, 2 times per week for the third and fourth weeks, and once per week during weeks 5 and 6. The HVLA-SM was designed as the side-lying diversified lumbar spine "adjustment" or maneuver. Home exercise – at week 3 participants received 30 minutes of standardized instructions for a home exercise program based on 7 exercises including flutter kick, buttocks pinch, pillow squeeze, cat stretch, pelvic tilt, press up extension, and double knee to chest.	Con1 – Low-velocity variable amplitude spinal mobilization – max of 12 visits, not to exceed 3 times per week for the first 2 weeks, 2 times per week for the third and fourth weeks, and once per week during weeks 5 and 6. LVVA-SM was designed as the flexion-distraction technique or Cox Technique with the application of up to 15 slow repetitions of flexion depending on participant tolerance. Con 2 – Minimal conservative medical care – meetings with the medical provider for 3 times during the 6 weeks (weeks 1, 3, and 6) to provide, adjust and/or change medicine prescription. Home exercise – same routine as the experimental group where indicated to all controls.
Learman [44]	n = 49 Non-specific low back pain (≤4 weeks) Age (yr) = exp 63.8 (SD 10.1), con 65.0 (SD 8.2)	Spine manipulation with thrust – 2 sessions (1 to 4 days apart). Technique was not described because the intent was to use a pragmatically prescribed intervention that was adjusted by the physiotherapist according to the results of the assessment with patient feedback. Physiotherapy – After completion of the manual therapy sessions, participants were treated with strengthening exercises, movement-based methods, or other intervention, as long as the clinician felt it fit within the treatment plan of the patient. Patients were discharged once the clinician felt the patient had met their maximal improvement within the current treatment program. There was no limitation on total visits. Home exercise program – included standing hamstring stretches, cat and camel, quadruped pelvic rocking, prone press-ups, and supine lying piriformis stretches performed for 10 repetitions, 3 times daily	Spine manipulation without thrust 2 sessions (1 to 4 days apart). Maitland's concepts were applied using passive, low-velocity oscillatory movements within the available physiologic range. The techniques consisted of grade I through grade IV and included side-lying rotational techniques, unilateral or central posterior to anterior glides. Physiotherapy – based on the same principles as the experimental group Home exercises – same program as the experimental group.
Teut [45]	n = 176 Chronic low back pain (≥6 months) Age (yr) = exp1 73.0 (SD 5.6), exp2 72.4 (SD 5.7), con 72.6 (6.0)	Exp1 Yoga – 45′, 2/week × 12 weeks. Each class included physical, breathing, and concentration exercises that occurred while sitting, standing, and lying. Exp2 Qigong – 90′, 1/week × 12weeks. A standardized program of qigong ("Dantian") and Nei Yang Gong exercises from the Training System Liu Ya Fei was applied. Additionally, self-massage was part of the training.	Wait list – Participants in the control group received no additional intervention for 6 months.

Cruz-Diaz [46]	n = 97 Chronic low back pain (not defined the symptoms duration) Age (yr) = exp 72.81 (SD 3.47), con 69.58 (SD 2.21).	Physical therapy sessions plus Pilates – PT two times per week during six weeks. Each session consisted in the application of TENS with a pulse frequency of 100 Hz for 40 min, and 20 minutes of massage and stretching of the low-back zone. One hour of Pilates sessions was applied two times per week.	PT sessions only (same PT routine as in the experimental group).
Vincent [47]	n = 60 Chronic low back pain (≥6 months) Age (yr) = exp 68.6 (SD 7.3), con1 67.5 (SD 6.4), con2 68.7 (SD 7.1)	Total body exercise – 3/week × 4 months. Training sessions comprised 1 × 15 repetitions of leg press, leg curl, leg extension, chest press, seated row, overhead press, triceps dip, lumbar extension, biceps curl, calf press, abdominal curl, and lumbar extension exercise.	Con1 – Lumbar extension exercise. During the first 2 weeks, participants performed two sets of lumbar extensions once a week. From week 2 until the end of the study, participants performed one set of lumbar extensions (15 repetitions) three times a week Con2 – Standard care – normal medical care and follow-up during the 4-month study, with no resistance exercise intervention.
Haas [48]	n = 101 African or white American with chronic low back pain (≥3 months) Age (yr) = exp 78.6 (SD 7.5), con 75.5 (SD 7.5)	Chronic disease self-management program – applied through a 6-week workshop lasting 2½ hours. The course content included general principles of chronic conditions; overview of self-management principles; symptoms; care-seeking options; community resources; exercise; relaxation; nutrition; medication and side-effects; skills building; learning from others; sharing with others; goal setting; action plans; feedback; and problem-solving.	Wait list
Miki [49]	n = 127 randomized (70 completed the study) Acute low back pain (<12 weeks) **Characteristics of participants who completed the study (n = 70)** Age (yr) = exp 66.03 (SD 2.97), con1 70.17 (SD 3.03)	Acetaminophen group – participants received 600 mg acetaminophen 4 times daily for 4 weeks randomization procedure.	Loxoprofen group – participants received 60 mg loxoprofen 3 times daily for 4 weeks, which is the traditional dosage in Japan. All treatment was provided to both groups by a single orthopedist throughout study.

*Exp – experimental, Con – control, SMT – spine manipulation therapy, WBC – whole body cryotherapy, US – ultrasound, PENS – percutaneous electrical neurostimulation, PT – physical therapy.

Table 2
Methodological quality of eligible studies (n = 11), PEDro scale.

Study	Eligibility criteria[a]	Random allocation	Concealed allocation	Baseline comparability	Blind subjects	Blind therapists	Blind assessors	Adequate follow-up	Intention-to-treat analysis	Between-group comparisons	Point estimates and variability	Pedro score (0 to 10)
Inoue [32]	Y	Y	N	Y	Y	N	Y	Y	N	Y	Y	**7**
Giemza [33]	Y	Y	N	Y	N	N	N	N	N	Y	N	**3**
Dougherty [34]	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	**8**
Grant [35]	Y	Y	Y	N	N	N	Y	Y	N	N	Y	**5**
Meng [36]	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	**7**
Morone [37]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	**8**
Soriano [38]	N	Y	N	Y	Y	Y	Y	N	N	Y	Y	**7**
Sritoomma [39]	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	**7**
Weiner [40]	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	**7**
Weiner [41]	Y	Y	N	Y	N	N	Y	Y	N	Y	Y	**6**
Costantino [41]	N	Y	N	Y	N	N	N	Y	Y	Y	Y	**6**
Hondras [43]	Y	Y	Y	Y	N	N	N	N	Y	Y	Y	**6**
Learman [44]	Y	Y	N	Y	N	N	N	Y	N	Y	Y	**5**
Teut [45]	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	**7**
Cruz-Diaz [46]	N	Y	N	Y	N	N	Y	Y	N	Y	Y	**6**
Vincent [47]	Y	Y	Y	Y	N	N	Y	N	N	Y	Y	**6**
Haas [48]	Y	Y	Y	Y	N	N	N	N	Y	Y	Y	**6**
Miki [49]	Y	Y	N	Y	N	N	N	N	N	Y	Y	4
Total	**14**	**17**	**8**	**16**	**3**	**1**	**9**	**12**	**9**	**16**	**16**	

Y: yes; N: no.
[a] Does not contribute to the total score.

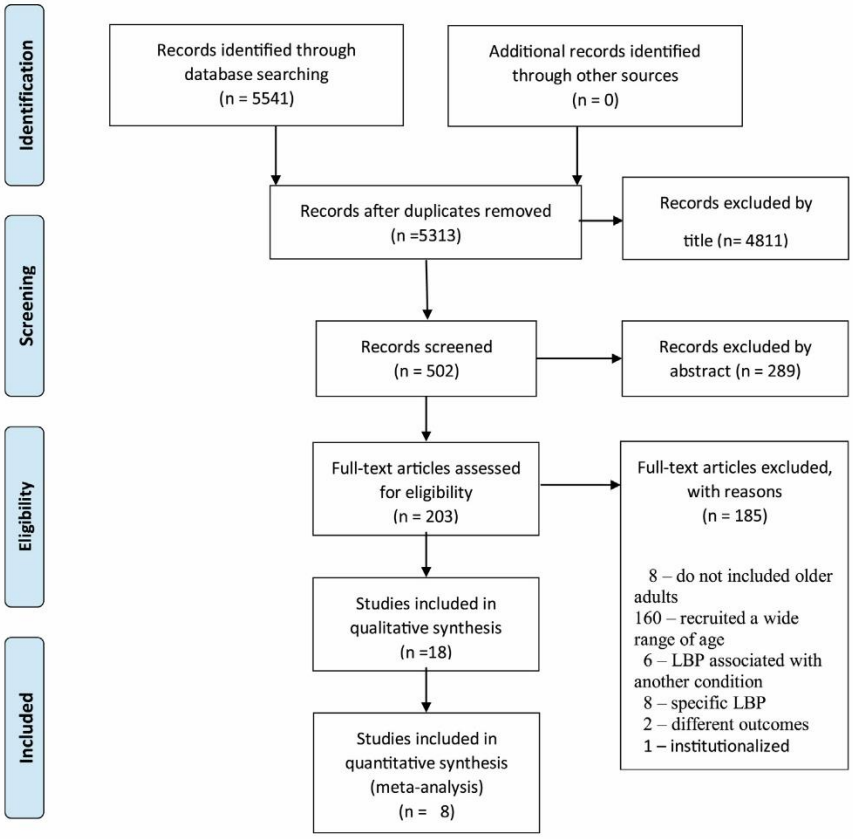

Fig. 1. Diagram flow of the eligibility assessment.

(Table 3). However, the rationale for the use of a specific intervention was described in only four studies [36,41,47,49].

Effects of interventions

Complementary health approach

Trials investigating interventions that are classified as CHA were pooled in a meta-analysis. The number of trials included in the meta-analysis varied for each comparison and outcome. We included a total of eight trials with low risk of bias in the meta-analysis for pain at short-term [32,34,35,37,39,43–45] and six trials at intermediate-term [34,35,37,39,44,45].

Outcome: pain intensity

For the outcome pain (Figs. 2 and 3), there is low quality evidence (downgraded due to inconsistence and imprecision) that there is a small, but no clinically important effect of CHA compared to minimal intervention or sham at short (MD = −2.96, 95% CI −5.87 to −0.04, eight three trials, $p = 0.05$) and intermediate-term follow-up (MD = −4.12, 95% CI = −6.35 to −1.93, six trials, $p = 0.002$).

Outcome: disability

In total, for disability (Figs. 4 and 5), we included six trials with low risk of bias [34,37,39,43–45] that provided moderate quality evidence (downgraded due to inconsistence) that there is no clinical important difference on improving disability at short-term compared to minimal or sham interventions (MD = −2.00, 95% CI −4.07 to 0.06, $p = 0.06$), and moderate quality evidence for a small but not clinically important difference at intermediate-term (MD = −2.55, 95% CI −4.64 to −0.46, $p = 0.02$).

Other interventions

Percutaneous neurostimulation (PENS)

Outcome: pain intensity. Based on two trials [36,41], there is low quality evidence of a moderate but not clinically significant effect on reducing pain for PENS plus physiotherapy (PT) compared to sham PENS plus PT [41] (MD −12.91; 95% CI −22.56 to −3.26), and small but no clinically significant effect (MD −8; 90% CI −15.28 to −2.52) in favors of PENS compared to standard care [36] at short-term. One trial [40] provided low quality evidence that there is no effect for PENS plus exercise on reducing pain at short-term (MD

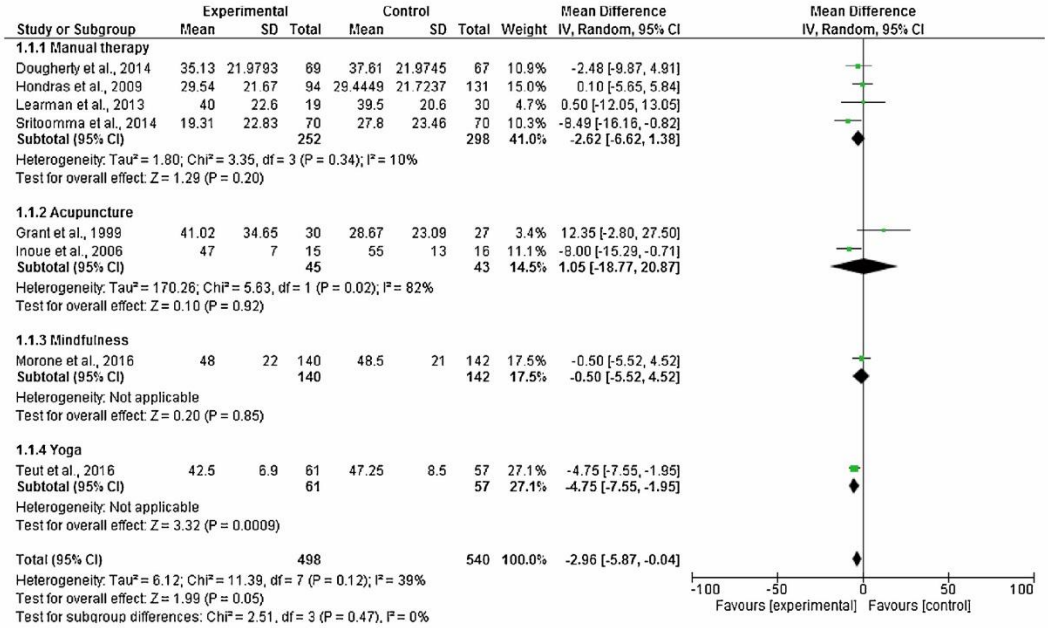

Fig. 2. Complementary health approach versus control for pain at short-term.

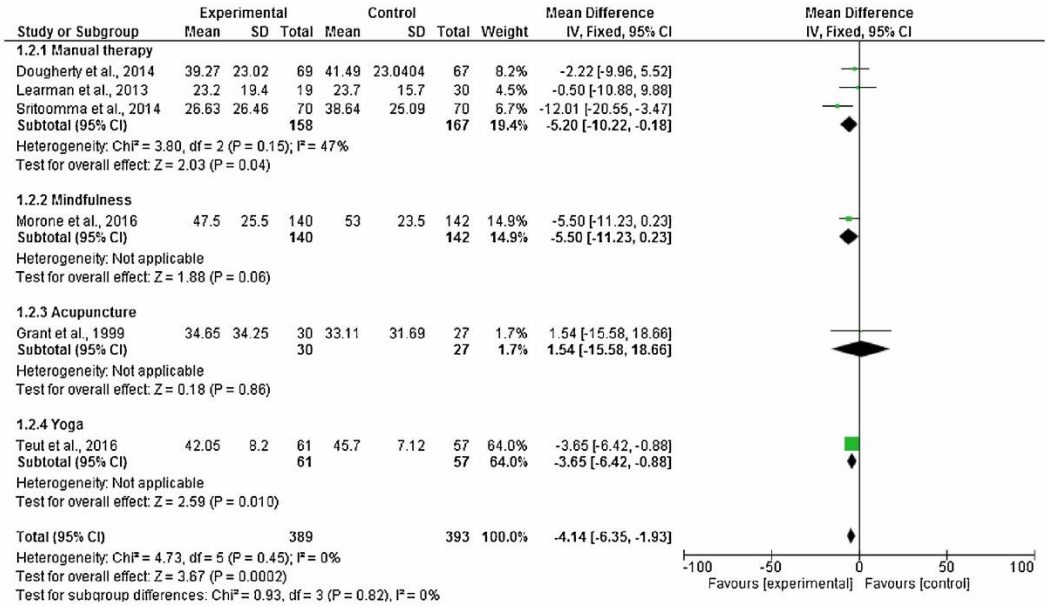

Fig. 3. Complementary health approach versus control for pain at intermediate-term.

−0.44 95% CI −3.94 to 3.05), compared to PENS, sham PENS or sham PENS plus exercise. For intermediate-term, there is low quality evidence [41] that there is a moderate but no clinically important effect on reducing pain (MD −12.51; 95% CI −21.62 to −3.40) for PENS plus PT compared to sham PENS plus PT, and no effect in pain reduction for PENS plus exercise [40] (MD = 0.21, 95% CI −4.98 to 1.84).

Outcome: disability. Results from one trial showed that there is low quality evidence that there is a large but not clinically important effect on reducing disability in favors

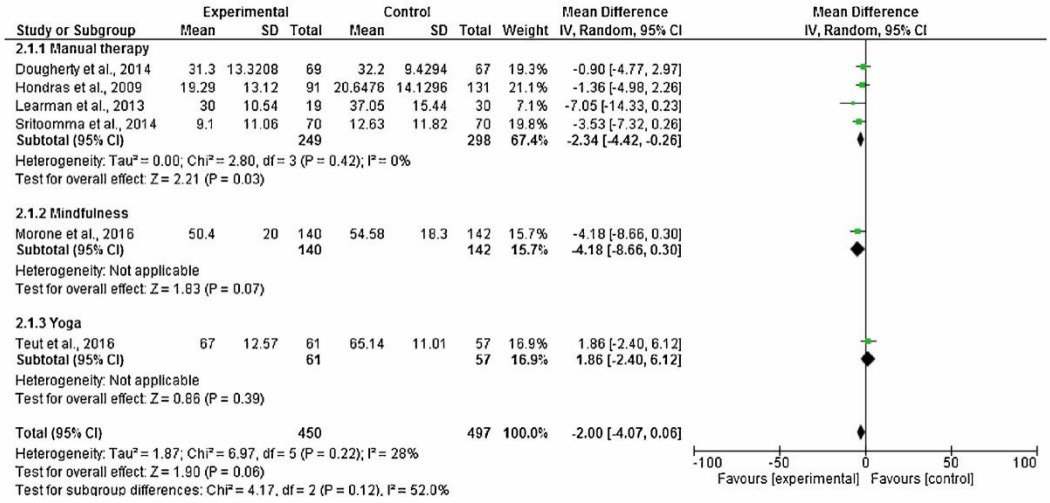

Fig. 4. Complementary health approach versus control for function at short-term.

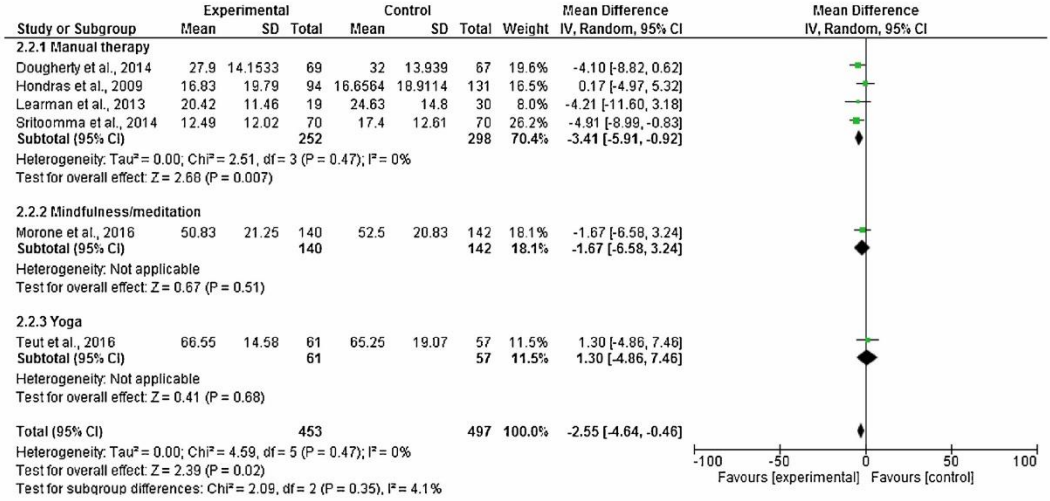

Fig. 5. Complementary health approach versus control for function at intermediate-term.

of PENS compared to usual care [36] (MD −23.59; 95% CI 34.84 to 12.34), and that there is a moderate, no clinically significant effect when comparing PENS plus PT to sham PENS plus PT [41] (MD −13.54; 95% CI −16.61 to −10.47) at short-term follow-up. There is low quality evidence that there is no clinical effect (MD = 0.80, 95% CI −5.55 to 7.16) when comparing PENS plus exercise to PENS, sham PENS, and sham PENS plus exercise. At intermediate-term follow-up, there is low quality evidence that there is a small but no clinical important effect for PENS on reducing disability when compared to usual care [36] (MD 2.62, 95 CI 0.73 to 4.51), and two trials [40,41] provided low quality evidence that there is no significant effect when comparing PENS plus PT to sham PENS plus PT (MD −12.21; 95% CI −25.37 to 0.95), and for PENS plus exercise compared to PENS, sham PENS and sham PENS plus exercise (MD −0.11; 95% CI −6.06 to 6.28).

Education

Outcome: disability

At short-term, there is low quality evidence of no difference for back school compared to hydrotherapy (MD = 4.45, 95% CI −0.72 to 9.62) [42], and when comparing self-management to no intervention (MD = −3.00, 95% CI −15.02 to 9.02) [48].

Pharmacological agents

Outcome: pain

Based on a non-inferiority trial [49], there is very low quality evidence that acetaminophen and loxoprofen are not statistically different beyond a specified non-inferiority margin (0.84 points on a 0 to 10 points numerical rating scale) for acute LBP at short-term (MD −0.51, 95% CI −1.70 to 0.67).

Outcome: disability

At short-term, there is low quality evidence [49] that there is no difference between acetaminophen and loxoprofen for older adults with acute low back pain (change from baseline for acetaminophen -4.14 ± 2.13, for loxoprofen -7.11 ± 1.94; $p = 0.621$).

Low level laser therapy

Outcome: pain intensity

Based on low quality evidence, one study [38] demonstrated that low level laser therapy (LLLT) reduces pain compared to sham deactivated laser (OR 4.53, 95 CI% 1.44 to 14.26) at short-term follow-up.

Thermotherapy

Outcome: pain intensity

There is very low quality [33] of evidence that whole body cryotherapy (WBC) using a cryogenic chamber five times a week has a large effect on reducing pain compared to WBC two times a week at short-tem follow-up (MD 21.02; 95% CI −25,68 to −6.36).

Exercise

Outcome: disability

One study [47] provided low quality evidence that total body exercise improves disability at short-term follow-up compared to lumbar extension exercise, with a moderate but not clinically significant effect (MD −25.83, 95% CI 0.79 to 25.87), and with a small not clinically important effect (−5.41, 95% CI 5.7 to 16.54) when compared to standard care (i.e., education regarding physical activity and diet). The practice of Pilates exercise combined with PT resulted in a small and not clinically important reduction in pain at short-term (MD = 1.97, 96% CI −2.05 to −1.89) compared to PT alone.

Discussion

Summary of main results

The aim of this systematic review was to examine the effectiveness of interventions to manage pain and disability in older adults with NSLBP. In total, 18 RCTs representing a variety of strategies for management of NSLBP in older adults were included in this review. The quality of evidence ranged from very low to moderate quality primarily because there are only single studies.

In general, the pooled effects of the CHA demonstrated not clinically significant reductions in pain and disability at short and intermediate-term. The lack of studies with a low-risk of bias, precludes any strong conclusions; however, the principal findings for the CHA, which are based upon low to moderate quality evidence, suggest no clinically beneficial effect compared with sham, passive modalities or any other intervention for treatment of chronic low back pain (CLBP). These results are partially supported by two previous broader reviews investigating the efficacy of CHA for LBP [50] and CNSLBP [51] showing a small statistical but not clinically significant reduction in pain and disability immediately and at short-term after the application of CHA. However, may these results cannot be extrapolated to older adults since most of the trials included in these reviews encompassed young and middle aged participants from 18 to 65 years old.

Although some criticism might be levelled at our population, to our knowledge, this is the first review examining the whole spectre of interventions for LBP in older people. Two previous systematic reviews [16,17] investigated CLBP in older adults limited to physical and active therapies. In addition, these reviews present a low methodological quality according to the AMSTAR [52] score. The review of Ehrenbrusthoff *et al*. fulfilled only four of eleven (4/11) possible AMSTAR items, while the review of Kuss *et al*. fulfilled five items (5/11).

Our results showed that PENS combined with PT [41] is statistically but not clinically relevant to reduce pain at short and intermediate-term follow-up than sham PENS plus PT. This result is partly in concordance with a crossover RCT [53] that showed better results for PENS when compared to sham PENS for pain outcomes at short-term but not in subsequent follow-ups in subjects with CLBP. Our review also showed, a not clinically relevant effect on reducing pain in favors of PENS compared to usual care at short-term follow-up [36]. In contrast, a previous study [54] showed a higher effectiveness of PENS to decrease pain compared to TENS at short-term follow-up. For function, studies comparing PENS to sham PENS [41] or usual care [36] revealed that PENS improved function at short-term follow-up whilst previous evidence [53] revealed similar results at short-term favorable to PENS in comparison to TENS. However, the NICE guidelines [55] does not recommend offering PENS for patients over 16 years with LBP.

We found two studies [42,48] that provided very low-quality evidence that educational strategies are not efficient to reduce disability related to LBP. These results are in accordance with two recent systematic reviews that revealed that the effect of back school for LBP is insufficient [56] with a dubious benefit [57]. Whilst a review of self-management

strategies [58] showed only small, no clinically significant effects.

A single study investigating LLLT provided very-low quality evidence of a clinical important effect favouring LLLT compared to sham laser to reduce pain at short-term follow-up. The positive effect of LLLT compared to sham for NSLBP were also available in a previous systematic reviews [59]. However, more robust evidence [60] showed that studies with LLLT are methodologically weak, present small sample size and the control groups are in general no active interventions.

The use of continuous sessions of cryotherapy led to a large but no clinically significant reduction on pain when compared to intermittent applications at short-term However, results of three previous reviews [61–63] found a lack of sufficient evidence to evaluate the effects of cryotherapy for LBP.

We found very-low quality evidence [49] that the administration of acetaminophen or loxoprofen for a short-term was unable to provide clinically significant improvements on pain and disability symptoms for acute LBP at short-term. A recent Cochrane review [64] concluded based on high-quality evidence that paracetamol is no better than placebo for relieving acute LBP in either the short or longer term. Furthermore, there is guideline recommendation [55] to not offer paracetamol alone for managing LBP. Although there was a previous recommendation for using nonsteroidal anti-inflammatory drugs (NSAIDs) [55] for LBP, the recent published Danish guideline [65] presents a weak recommendation against paracetamol and NSAIDs based on moderate and low quality evidence respectively.

A short-term not clinically improvement in functional status was observed after the implementation of a total body exercise program compared to lumbar exercise alone and standard care. Results of a Cochrane review [66] showed that exercise is better than other interventions to improve function at short-term. However, a meta regression [67] concluded that exercises provide similar results to other forms of conservative treatments at short-term follow-up. In addition, a previous review targeting older adults [17] showed a low quality evidence for active therapies in providing small-to-moderate reduction in pain and small improvement in function.

Strengths and weaknesses of the study

In this review, we used a systematic approach with two independent reviewers processing the articles for eligibility. In addition, a comprehensive search of several databases following the recommendations proposed by the Cochrane Back Review Group, and no language limitation was set to avoid missing relevant articles. Furthermore, the risk of bias of the included studies was assessed using the validated PEDro scale [68] and the quality of evidence was assessed using the GRADE statement [27].

A potential limitation of this review is the low number, high heterogeneity and small sample sizes per comparison among the trials that were included, which prevented us to provide robust estimates of the effects of the interventions. In addition, another limitation is the potential risk of publication bias. Although it was not possible to assess publication bias using funnel plots, we did an inspection of trial registries and did not find any potential indicator of publication bias. However, the mandatory requisition for trial registry is recent which may result in publication bias from past trials.

Implications

To our knowledge, this is the most comprehensive systematic review investigating interventions for NSLBP in older adults. However, this review does not allow to formulate definitive conclusions about the effectiveness of the interventions. Even though there are studies indicating some positive results, the evidence is weak and not clinically relevant. Future research is highly likely to change any recommendation we would make. Also, efforts to design trials with low risk of bias, provide a detailed description of the interventions applied in all groups, and have an appropriate estimation of the sample size are necessary. The lack of effective evidence based interventions is a challenge for healthcare providers due to the difficulties in approaching older adults with NSLBP, affecting also patients, and policy makers that will expend financial resources with interventions that provide in the best scenario a not significant improvement of the clinical symptoms. Thus, is urgent the development of clinical trials targeting older adults with different symptoms duration and following them for long-term to allow the recommendation of evidence-based treatment to this growing population.

Key messages

- Clinical trials for older adults are usually based on passive interventions.
- Our results suggest that interventions for older adults with chronic non-specific low back pain are not clinically effective for reducing pain and disability at short or intermediate-term.
- Benefits of current treatments for low back pain in older adults are insufficient even when compared to sham or minimal interventions.

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Conflict of interest disclosures: None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.physio.2018.11.004.

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Chapter Four

Exclusion of older adults from ongoing clinical trials on low back pain: A review of the WHO trial registry database

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REVIEW ARTICLE

Exclusion of Older Adults from Ongoing Clinical Trials on Low Back Pain: A Review of the WHO Trial Registry Database

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BACKGROUND/OBJECTIVES: The burden of low back pain (LBP) is high, especially for older adults who experience a higher number of years living with a disability. However, this population is not being well represented in clinical trials (CTs). This study analyzed the International Clinical Trial Registry Platform (ICTRP) database from the World Health Organization to verify the future trend in the participation of older adults in registered CTs on LBP.

DESIGN: We performed a cross-sectional review of the ICTRP searching for prospective protocols planning interventions for LBP with registration dates from January 2015 through November 2018. From the protocols of the eligible studies, we extracted those planning to include older adults.

RESULTS: A total of 167 protocols for CTs for LBP were planning to recruit participants older than 65 years. However, only five registries (2.99%; pooled sample = 169 participants) were designed to target participants specifically older than 65 years. The exclusion of older participants was not justified and imposed through an arbitrary upper-age limit in 93.6% of the protocols. Most of the protocols are from single-center studies, and a greater number are planned to be carried out in developed regions. Higher interest was in pharmacologic interventions, devices/technology, and physical rehabilitation.

CONCLUSION: Older adults with LBP will continue to be underinvestigated in CTs for LBP in the near future. In general, ongoing trials are small, planned in developed regions, and proposing pharmacologic interventions to deal with LBP.
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Key words: ageism; low back pain; clinical trial; therapeutics; qualitative research

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The Global Burden of Disease Study showed that low back pain (LBP) is the leading cause of global disability[1] with prevalence and burden increasing with age.[2] The prevalence of complaints related to LBP in older adults is about 23%,[3] and generally the prognosis becomes worse with advancing age resulting in a high rate of nonrecovery.[4,5]

Recent research showed that the course of LBP is not as benign and favorable[6–8] as previously thought.[9,10] Older adults have a greater chance to present with a worse prognosis because LBP increases the risk of falling,[11] the main cause of fatal injuries among older adults.[12] Evidence also shows an association between LBP and increased risk of mortality in older adults per year lived, although the association does not seems to be causal.[13] Furthermore, compared with pain-free individuals, older adults with LBP have more psychosocial dysfunction, self-reported disability, and physical performance impairments,[14] that may contribute to a worse trajectory of the symptoms.[15]

As life expectancy increases,[16] the number of older adults with back complaints tends to be higher, contributing for more years living with disabilities.[1] However, despite the biopsychosocial burden of LBP in older people,[14] this population has been underinvestigated in randomized controlled trials (RCTs).[17] For instance, two systematic reviews[18,19] investigating the effectiveness of physical therapy modalities in the management of LBP in older adults were able to identify only three RCTs each. Furthermore, a review published in 2014 did not see a change in the number of CTs for older adults with LBP over the past 2 decades.[17]

A series of recently published review articles entitled "Deconstructing Chronic Low Back Pain in the Older

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Adult—Step-by-Step Evidence and Expert-Based Recommendations for Evaluation and Treatment"[20–32] offered strategies to provide rational care for older adults with chronic LBP. However, expert-based recommendations presented in this series of articles need to be evaluated through CTs. Current treatment of LBP in older adults is based mainly on results of studies involving samples of heterogeneous age groups.[33–36] Consequently, the lack of research investigating the efficacy of interventions for older adults with back complaints may contribute to unsatisfactory management in this age group.[37]

The development of CTs targeting older adults is an important step forward in LBP research because advancing age is marked by specific biopsychosocial factors characterizing older adults as a distinctive subgroup[38–40] that can require different approaches in LBP management. Interventions targeting this subgroup must be developed and tested in CTs. This study aims to record the number of ongoing prospective registered CTs on LBP planning to enroll older adults.

METHODS

We conducted a cross-sectional review of the World Health Organization (WHO) clinical trial registry.

Trial Registry Search

One investigator (P.N.) performed a search using the term "low back pain" in the International Clinical Trials Registry Platform (ICTRP) from the WHO that contains the trial registration data sets provided by several countries (eg, Australia, New Zealand, United States, European Union, Brazil, India, Netherlands, South Korea, Germany, Cuba, Ireland, Japan, Africa, Sri Lanka, Thailand, and Peru), providing one single point of access to all registered CTs globally.[41]

A CT registry database is a viable and valid source to investigate what is planned in ongoing CTs. The requirement for CT registration began in 2005 through an initiative from the International Committee of Medical Journal Editors. Based on this initiative, investigators have to provide prospective information about trial design on a free, public, and electronically searchable registry before the onset of patient enrollment.[42] The information provided varies according to each trial registry database but contains at least the 20 items of the ICTRP (Figure 1). The purpose of prospective registration is to avoid selective reporting and publication bias, to prevent unnecessary duplicates of trials, and to help people with health problems know what trials are planned or ongoing into which they might want to enroll.[42]

Eligible studies should be prospectively registered CTs and provide the age range for inclusion. One reviewer (P.N.) exported all retrieved CT protocols from the search in the ICTRP to an electronic spreadsheet. Two independent reviewers (P.N. and M.F.) screened the retrieved studies for eligibility by reading the title and full protocol. Duplicates and protocols that were not related to LBP, not CTs, or those that were not driven interventions to patients were excluded from analysis. A third reviewer was consulted in case of disagreement, providing consensus through discussion or arbitration. A standardized data extraction form was created using the software Epi Info 7 to collect the following information: sample's age range, funding, sample size, interventions, and country of recruitment. Data were double entered using the match records by fields option aiming to guarantee data quality. The search was set from January 1, 2015, to November 3, 2018, and the number of registered CTs planning to enroll older adults older than 65 years was extracted from all registered protocols investigating interventions for LBP. The starting date was established to cover the period after a previously published review[17] showed that older adults were underrepresented in CTs for LBP.

Analysis

The total number of studies registered focusing on LBP, number of studies enrolling older people, the geographic region where the study was to be conducted, the planned sample size, as well as the type of intervention investigated, was retrieved from the data set. Categorical variables are presented through descriptive statistics as numbers and frequency. Continuous data are presented using mean, median, standard deviation, and range of the data.

RESULTS

Our search resulted in 510 trial protocols, with 40 excluded as duplicates, 54 as observational research, 24 not related to LBP, and 1 for not targeting the patients. Figure 2 shows the screening process.

As of November 3, 2018, there were 391 registered trials for LBP management in the ICTRP. From the eligible registers, 4 did not state the range of age for recruitment and 64 were retrospective registers. A total of 323 trial protocols were analyzed to investigate the participation of older adults.

A total of 156 trial protocols (pooled expected sample = 16 981) were not recruiting individuals older than 65 years; 167 prospective registries (pooled expected sample = 31 199 participants) planned to include participants older than 65 years. However, among these 167 protocols, only 5 (2.99%; pooled sample = 169 participants) were

- Primary Registry and Trial Identifying Number
- Date of Registration in Primary Registry
- Secondary Identifying Numbers
- Source(s) of Monetary or Material Support
- Primary Sponsor
- Secondary Sponsor(s)
- Contact for Public Queries
- Contact for Scientific Queries
- Public Title
- Scientific Title
- Countries of Recruitment
- Health Condition(s) or Problem(s) Studied
- Intervention(s)
- Key Inclusion and Exclusion Criteria
- Study Type
- Date of First Enrolment
- Target Sample Size
- Recruitment Status
- Primary Outcome(s)
- Key Secondary Outcomes

Figure 1. List of mandatory items to be provided from the International Clinical Trial Registry Platform.

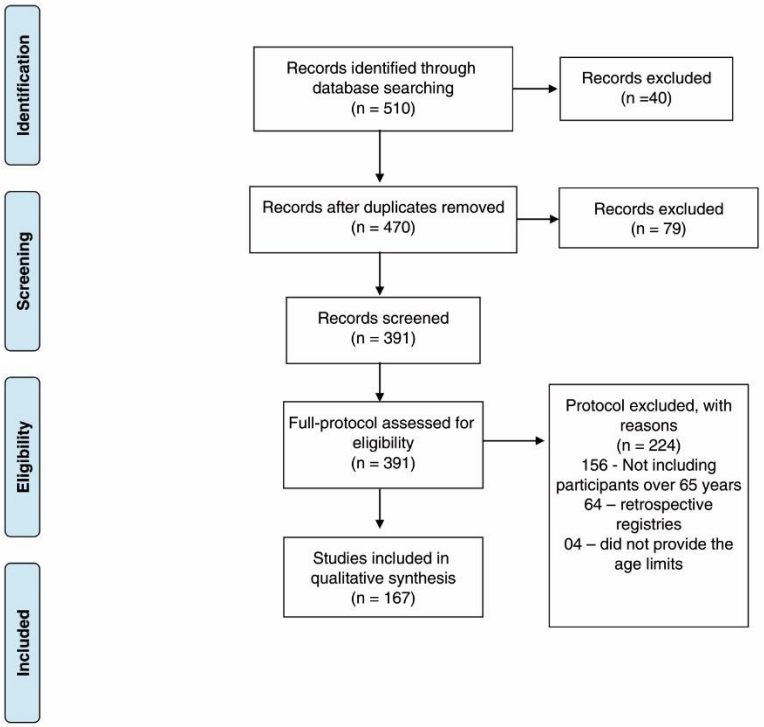

Figure 2. Flowchart for the inclusion of clinical trial protocols.

designed to include participants older than 65 years exclusively. A high number of CTs are planned or ongoing in North America (n = 58), Europe (n = 38), and Asia (n = 28); there is just one in Africa. The distribution of the 167 trials including older adults varied around the world, with a high number of registered trials from developed regions (Figure 3).

The interventions proposed in the trial registers planning to recruit older individuals covered the areas of rehabilitation (eg, physical exercise, manual therapy), behavioral therapy (eg, mindfulness meditation, cognitive therapy), education (eg, Web-driven pain education, videoconference), use of devices (eg, transcutaneous electrical stimulation, orthosis, technical equipment), complementary integrative medicine (eg, acupuncture, reflexology), prescription of drugs, and medical procedures (eg, surgery, stem cell application). There were also a few trials planning to investigate the use of combined interventions and strategies to prevent LBP (Table 1). Among the five RCT protocols focusing on older adults exclusively, two were designed to investigate

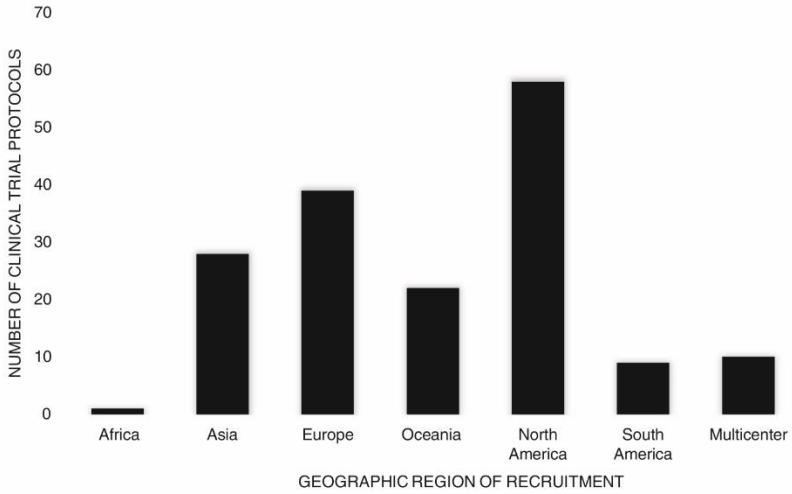

Figure 3. Number of clinical trial protocols planning to recruit older adults per geographic location.

Table 1. Characteristics of clinical trial protocols on low back pain planning to include participants older than 65 years

Characteristics	Maximum age limit > 65 y (n = 167)
Trials, n (%)	
Pharmacologic	46 (27.54)
Device and technology	40 (23.95)
Physical rehabilitation	28 (16.76)
Behavioral therapy	20 (11.97)
Invasive procedure and surgery	13 (7.78)
Education	9 (5.38)
Complementary integrative medicine	7 (4.19)
Combined	2 (1.19)
Preventive	2 (1.19)
Funding, n (%)	
Public institution/Self-funding	140 (83.83)
Industry	27 (16.17)
Sample size	
Total	31 199
Mean (SD)	186.82 (348.81)
Median (range)	68 (10-3000)
Size strata, n	
< 50	54
50-100	50
101-200	26
> 200	37
Sample size of protocols including only older adults	
Protocol 1	20
Protocol 2	10
Protocol 3	74
Protocol 4	25
Protocol 5	40
Total	169 SD
Mean	34 (11.15)

the use of physical rehabilitation strategies, one complementary integrative medicine, one behavioral treatment, and one educational techniques.

From the 156 protocols that excluded individuals older than 65 years, 10 registries (6.4%) were from studies targeting younger populations (eg, athletes, pregnant women) specifically. The remaining 93.6% of the protocols excluded individuals based on the establishment of an arbitrary upper-age limit.

DISCUSSION

The aim of this trial registry review was to document the future trend in the participation of older adults in ongoing RCTs on LBP research registered in the WHO-ICTRP. It was found that approximately 50% of the registered LBP trials in the ICTRP were planning to include participants older than 65 years, and the main exclusion criterion was the establishment of an arbitrary maximum age limit. However, only 2.99% were designed to recruit from this population specifically. Most of the identified protocols are from studies interested in investigating the administration of pharmacologic agents, the use of technological devices, and physical rehabilitation interventions. These studies are planned to occur mainly in developed countries.

Despite the importance of RCTs in providing evidence about the effectiveness of interventions, older adults are often excluded from these studies,[1,43] limiting the generalizability of results to this population. Only five protocols (2.99%) were RCTs designed to target older adults exclusively, which is in accordance with a type 2 diabetes systematic review of trials registry that found 1.4% of the eligible studies were designed for older adults.[44] Further, the five protocols planned exclusively for older adults in our review are small representing less than 1% of the sample from all eligible studies (n = 169/31 199), which generates a clinical and ethical issue.[45,46] CTs with a small sample may present insufficient statistical power and may not answer properly the tested hypothesis exposing participants to unnecessary risks and burdens in research with limited clinical value.[46,47] In addition, studies with a small sample size have a poor generalizability of their results.[48]

Our results revealed that older adults were excluded mainly by the establishment of an arbitrary upper-age limit corroborating the results from previous studies.[17,49] Evidence indicates that exclusion of participants from RCTs based on age is either unjustified or poorly justified.[49–51] According to Cherubini et al,[49] about 25% of RCTs set poorly justified upper-age limits, and 43% set exclusion criteria that exclude participation of older adults.

The establishment of an upper-age limit can be considered an easy way to reach a homogeneous sample filtering against some age-related exclusion criteria (eg, polypharmacy and comorbidities) and facilitating the screening process for eligibility, which can save money and time during RCT development.[44,51] However, when applying this strategy, researchers are decreasing the representativeness of older adults in RCTs. Barriers for inclusion of older participants need to be addressed from the perspectives of healthcare providers, participants, researchers, and funders if we are to move forward.[52–56]

The use of the cohort multiple randomized controlled trial (cmRCT) design was reported in 2015 as a strategy to improve the recruitment of older people in RCTs.[57] The cmRCT design aims to overcome problems related to recruitment, ethical dilemmas, patient preference, and challenges for treatment comparisons presented in the standard CT design.[58] In this design, a large cohort of people with the condition of interest is identified (eg, patients with acute LBP) and followed as usual.[57,58] From the cohort sample, one or more interventions can be offered to a randomly selected sample of patients eligible for that intervention who are then compared with the rest of the eligible patients who are still being followed by the original cohort.[58] The cmRCT allows the development of multiple trials and the comparison of interventions without the need to ask for further consent from the participants randomized to the control group. However, contrary to a standard RCT, in the cmRCT participants are randomized before offering the intervention that may result in post-randomization refusal contributing to selection bias.[57,59]

Most of the protocols planning to include older adults were designed to investigate pharmacologic interventions. However, these studies have a wide range of age and do not state the percentage of older adults that is planned to recruit or a subgroup analysis, which would prevent them from providing an evidence-based recommendation for older patients. The exclusion of older participants with LBP is important because in a primary care setting they are more

likely to receive a prescription for painkillers than younger adults.[37] In a systematic review, Zulman et al[60] found that pharmacologic interventions were assessed in 68.9% of the RCTs for older adults with complex health issues, whereas our results revealed that pharmacologic agents were planned for only 27.4% of the protocols. Perhaps this difference is due to the limited effectiveness of pharmacologic interventions for LBP in the literature.[61,62] More important than not showing the efficacy of pharmacologic agents, the exclusion of older adults from these CTs prevent the development of knowledge regarding adverse events.[63]

We found that most study protocols are planned for developed regions. This was an expected result considering that the prevalence of disability-adjusted life-years due to LBP is usually higher in developed countries,[2,64] where older adults are more prone to seek care.[37] In addition, there is evidence showing significant efforts in these regions to standardize and improve research on LBP.[65] However, more attention to developing countries is needed[66] because life expectancy and associated chronic diseases, including LBP, are increasing worldwide.[16]

The present study has some limitations that must be acknowledged. First, our search was restricted to the analysis of registers from the ICTRP database. Although this database contains information from several registries, it is unclear how representative our sample is of all ongoing CTs on LBP. Secondly, because we investigated future CTs, we cannot determine the actual number of older participants who will be recruited in trials planning to include older adults or without an upper-age limit. Thus, it is possible that some trials without an upper-age limit will not have recruited a representative sample of the older population.

In conclusion, despite the advancing age of the population around the world and the previous evidence about the exclusion of older adults in CTs testing interventions for LBP, we conclude that this problem will persist in the near future. Consequently, older adults will continue having limited access to evidence-based interventions. Ongoing CTs are mainly focused on investigating the effectiveness of pharmacologic agents, devices/technological equipment, and physical rehabilitation. Thus future efforts should consider developing CTs for LBP targeting older adults. At the very least, researchers need to avoid limiting the inclusion of participants based on an arbitrary upper-age limit and clearly justify the exclusion criteria, which would increase the generalizability of their results.

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Chapter Five

Perceptions and Expectation about the Participation of Older Adults in Randomized Controlled Trials: A Survey with Low Back Pain Researchers

Chapter five is submitted for publication:

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Abstract

Design: Cross-sectional survey.

Objectives: To investigate low back pain (LBP) researchers' beliefs about the exclusion of older adults from randomized controlled trials (RCTs), their previous experience with this population, and future expectations regarding the inclusion of older adults in RCTs.

Summary of Background Data: Despite the growth in life expectancy and the relationship between LBP and old age, older adults are missing from RCTs for LBP.

Methods: All attendees of the 15th International Forum on Back and Neck Pain Research in Primary Care were invited by email to answer an electronic survey with questions about their beliefs regarding the exclusion of older adults from RCTs for LBP.

Results: Most respondents believe that older adults are excluded from RCTs for LBP, which can difficult the access to evidence-based interventions for patients and providers. According to the majority of the respondents, old age itself is not a justification to prevent participants in RCTs. About half of the respondents excluded older adults from their previous RCTs and only a few respondents designed RCTs targeting older individuals. Respondents are more prone to include older adults in their current/future RCTs although, no significant change in the number of RCTs targeting older adults was observed. Respondents' years of experience influenced the beliefs about reasons to exclude older individuals from CTs.

Conclusion: LBP researchers recognize the exclusion of older adults from RCTs and its negative consequences for patients and providers. Researchers are more prone to engage and investigate older adults in their current/future RCTs. In the future, the development of educational strategies aiming to reduce the negative stereotypes from old age can improve

the participation of older adults in RCTs. Also, fund agencies and ethical borders can conditionate the access to grants and ethical clearance to the absence of unnecessary exclusion of older adults in RCTs.

Introduction

Life expectancy is growing worldwide, shifting the age pyramid towards a high number of older adults (Wang et al., 2016). As the world population grows older, the number of people living with disabilities increases due to sequelae of diseases or injuries accumulated over the years (Vos et al., 2016). According to the Global Burden of Disease Study, low back pain (LBP) was ranked in 2015 as the leading global cause of disability (Vos et al., 2016), with prevalence and burden increasing with age (Hoy et al., 2014). The impact of LBP might be higher and potentialized in low-income and middle-income countries due to an accelerated change in the age strata and the lack of resources (Buchbinder et al., 2018).

The prognosis for LBP is worse among older adults (Rundell et al., 2015) with a high risk of falls, depression, and reduction in quality of life (Rosa et al., 2016; Rudy et al., 2007; Teixeira et al., 2016). High levels of LBP disability have been associated with care-seeking increasing the societal burden due to LBP with aging (Buchbinder et al., 2018; M. L. Ferreira et al., 2010; Hoy et al., 2014). However, evidence supporting interventions for LBP in older adults is sparse and weak (Nascimento et al., 2019). In addition, recommendations from LBP guidelines are basically extracted from CTs for young and middle-aged adults (Bernstein et al., 2017; N. E. Foster et al., 2018). The lack of evidence supporting interventions for older adults with LBP results in the use of low-value care and low treatment expectations (Macfarlane et al., 2012).

Interventions targeting older adults with LBP need to be tested for safety, effectiveness, and cost-effectiveness in RCTs before the application in clinical practice (Dziechciaż & Filip, 2014). However, Paeck et al. (2014) showed that older adults are excluded from clinical trials for LBP. In addition, a prospective investigation of a clinical

trial registry database has also shown that older adults with LBP will continue being underrepresented in clinical trials for at least a few years ahead (Carvalho do Nascimento et al., 2019). In the case the exclusion of older adults from RCT for LBP remains; these patients will continue to receive low-value care with suboptimal outcomes. As a result, older adults may experience a cascade of events such as physical activity limitation and physical function decline with subsequent morbidity (Simon & Hicks, 2018a).

Regulatory authorities in many developed countries have advised researchers not to exclude older adults from RCTs solely based on age (Bernard et al., 2018; "International Conference on Harmonisation; Guidance on E7 Studies in Support of Special Populations; Geriatrics; Questions and Answers; availability. Notice," 2012). However, researchers' perceptions and biases can influence the engagement of older adults in RCTs creating barriers to their participation (Denson & Mahipal, 2014; Talarico, Chen, et al., 2004). We are unaware of any study investigating why LBP researchers usually exclude older adults from RCTs. Therefore, this study aimed to examine: (1) beliefs of LBP researchers about the exclusion of older adults from RCTs and reasons that may justify it; (2) their previous experience with this population, and (3) future expectations regarding the participation of older adults in RCTs.

Methods

Role of funding source

The funders played no role in the design, conduct, or reporting of this study.

Design

A cross-sectional survey was administered using the SurveyMonkey Platform between October 22 and November 24, 2017. All participants were contacted by e-mail and invited to complete an online version of a two-part questionnaire preceded by a consent letter. A reminder e-mail was forwarded one and two weeks after the first contact aiming to increase the response rate. We used the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) to guide reporting of results (Appendix 1) (Eysenbach, 2004). The Bruyère Research Institute and University of Ottawa Research Ethics Boards approved the study.

Participants

We surveyed a convenience sample of participants of the 15th International Forum on Back and Neck Pain Research in Primary Care. A call for the survey was presented on the event´s website and during first day of the Forum. Based on the nature of the Forum we assumed that attendees would be primarily involved in treatment and/or investigation of patients with LBP and, thus, this Forum would be an ideal place for recruitment. The study's only inclusion criterion was being registered to participate in the Forum.

Outcome measures

A two-part specific questionnaire aiming to collect demographic details of participants and information about their current research activities was developed following the best practices for survey research reports (Johnson, 2014; Kelley et al., 2003). In the first part, we invited participants to answer questions about their past and current work regarding the inclusion of older adults, subgroup analyses, thoughts about generalizability,

and barriers to include older adults in clinical trials (Denson & Mahipal, 2014; McMurdo et al., 2005; Michelet et al., 2014).

> …"Is low back pain (LBP) your primary research field?"
>
> "Have you ever been involved in conducting a randomized controlled trial (RCT) on LBP?"
>
> "Did you exclude older participants (≥ 65 years old) from your last trial?"…

The second part was intended to collect information to characterize the survey respondents (i.e., gender, occupation, expertise, and country). The survey was pilot-tested with a group of five experts in the LBP and/or Epidemiology field and revised. After modifications, the survey included 16 close-ended questions and one open-ended question (Appendix 1). The survey was presented in English because this is the official language of the Forum.

Data analysis

Data were analyzed using Stata®, statistical software release 13. Descriptive statistics were used to report frequency distributions. The relationship between perception of exclusion/reasons to exclude older adults and respondents' demographic data (years of experience and human development index (HDI) of their country of residence) was assessed with chi-square tests. For this analysis, the country of residence of the respondents were dichotomized in very high development (HDI ≥ 0.8) and high development (HDI ≥ 0.7 and <0.8) The McNemar's test was used to compare previous inclusion and targeting of older adults with current/future research.

Results

Characteristics of the participants

A total of 200 invitations were sent by email. We received 95 responses, representing a 47.5% response rate. Of responses received, 15 prospective participants refused to complete the survey, and three individuals failed to provide demographic information, resulting in a completion rate of 38.5%. The demographic and professional characteristics of respondents are presented in Table 1.

Researchers' beliefs, experience, and current/future directions

Of the respondents, 88.6% reported LBP as their primary research interest, 73.1% had been previously involved in a clinical trial for LBP, while 57.7% are currently working or planning an RCT for LBP. 50.9% of respondents included older adults in past trials, rising to 68.9% in current/future trials ($p < 0.01$). As for targeting older adults exclusively, 6.9% of respondents did so in past trials, rising to 22.6% in current/future trials, although this increase was non-significant ($p = 0.10$).

Approximately 90% of the respondents believed that older adults are underrepresented in RCTs for LBP. About 70% concurred that this underrepresentation could lead to fewer evidence-based treatments directed at this population. Furthermore, 81.2% of respondents reported this underrepresentation could create additional challenges for health providers treating older adults with LBP.

The exclusion of older adults from RCTs due to an inclusion criterion based on an arbitrary age limit is not justified for 70.1% of the respondents. Table 2 presents the possible reasons that could justify the exclusion of older adults from RCTs for LBP.
All participants were from countries with very high or high HDI. There was no difference between the beliefs about the exclusion of older adults from clinical trials or the reasons

that may justify it based on country HDI (Figure 1). Less experienced researchers (< 10 years of experience) were more prone to believe that physical inability ($p = 0.04$), cognitive inability ($p = 0.01$) or high drop-out rates ($p = 0.01$) are justifiable reasons to exclude older adults from RCTs (Figure 2).

Discussion

Statement of principal findings

To the best of our knowledge, this is the first survey investigating the exclusion of older adults from RCTs based on LBP researchers' views. The key findings of this study were that (1) most respondents believe that older adults are under-represented in CTs, which may prevent the prescription of evidence-based interventions to these individuals and creates additional challenges to healthcare providers; (2) according to the majority of the respondents, old age itself cannot justify the exclusion of older adults from RCTs; (3) comorbidities, polypharmacy, cognitive and physical disability, and higher risk of adverse events were the most cited reasons that justify excluding older individuals from RCTs; (4) about half of the respondents excluded older individuals from their previous research, and only a few designed RCTs targeting exclusively older individuals; (5) respondents showed more prone to include older adults in their current/future trials although, no significant change regarding RCTs focusing exclusively on older adults was observed; (6) Junior researchers saw cognitive inability and high drop-out rates as reasons that could justify the exclusion of older adults from RCTs.

Comparison with the current literature

The exclusion of older adults from CTs is a fact even in a sample of LBP researchers resulting in a lack of specific evidence applicable to this population. Unfortunately, the lack of participation of older adults in RCTs is present throughout the health-related field (Bourgeois et al., 2017; Cruz-Jentoft et al., 2013; Helfand et al., 2020; Hutchins et al., 1999). There is extensive literature investigating the barriers and strategies to improve recruitment and retention of older adults in RCTs (Adams et al., 2015; Clegg et al., 2015; Denson & Mahipal, 2014; Forsat et al., 2020; Kuchel, 2019; McMurdo et al., 2011). As a strategy to prevent the exclusion of older adults from RCTs, the National Institute of Health (NIH) is conditioning the applications for grant proposals to the absence of age limits (Bernard et al., 2018). According to this policy, research projects need to include participants of all ages unless a scientific or ethical reason to exclude specific age groups exists (Bernard et al., 2018). However, despite the efforts to avoid the exclusion of older adults from RCTs, the problem persists. Although subgroup-based treatment has been previously listed as a research priority for LBP (Costa Lda et al., 2013), two recent clinical practice guidelines have not mentioned specific interventions for older adults (National Guideline, 2016b; Qaseem et al., 2017).

Most respondents (70.1%) affirmed that conditioning the participation of older adults in RCTs based solely on age is not justifiable. Nevertheless, setting an arbitrary age limit as an inclusion criterion is pointed as the main barrier imposed by researchers in the recruitment of older adults (Carvalho do Nascimento et al., 2019; Cherubini et al., 2011; Zulman et al., 2011). A systematic review including 109 RCTs of different health conditions found that 20.2% of the eligible studies excluded older adults by setting an arbitrary upper-age limit inclusion criterion (Zulman et al., 2011). In addition, an analysis of data of ongoing clinical trials investigating interventions for heart failure revealed that

25.5% of the studies excluded older adults by setting an arbitrary upper age limit (Cherubini et al., 2011). Further, a similar study investigating registered protocols for LBP clinical trials showed that 93.6% of the protocols failed to present justifiable reasons to exclude older adults than setting arbitrary upper-age inclusion criteria (Carvalho do Nascimento et al., 2019).

High rate of comorbidities was the main age-related characteristic that could justify the exclusion of older people from RCTs according to 62.3% of respondents followed by polypharmacy (41.6%), cognitive disability (33.8%), physical disability (32.5%), and higher risk of adverse events (22.1%). A survey with 521 health-related professionals from different countries in the European Union reported similar results (Crome et al., 2011). Most participants described that comorbidities and polypharmacy were the main reasons that could justify using an age limit in RCTs (Crome et al., 2011). Furthermore, results from systematic reviews also showed that comorbidities (46%) and physical disability or functional limitations (18.4%) were among the most common criteria that could prevent older people from participating in RCTs (Forsat et al., 2020; Zulman et al., 2011). Although these factors have been reported as possible justifications to exclude older adults, caution is needed when setting older age as an exclusion criterion based on them. Researchers can argue that some specific comorbidities (e.g., osteoporosis), medication, physical or cognitive disability may cause harm, mask, or increase the effect, or prevent the participation in a specific intervention, respectively. However, in this case, researchers should screen the participants to rule out these characteristics instead of creating an upper-age limit as inclusion criteria to reduce the chance of having participants with them, which characterizes ageism. Moreover, over-selecting participants for an RCT will result in uncertainty about the ability of the results to be replicable to the majority of the patients

presenting with the same condition (Rothwell, 2005). In a systematic review, He et al. (2020) found that about 50% of the trials reporting exclusion or inclusion criteria that allowed to estimate exclusion rates had a median exclusion rate of 77.1% of the population with the disease of interest. Among the most frequent factors used to exclude participants, comorbidities and age ranked in second (67.2%) and third (49.4%) place, respectively (He et al., 2020). High exclusion rates among participants will consequently increase the chance of having participants in RCTs different to those seen in clinical practice (Kennedy-Martin et al., 2015). Researchers should have clear in mind that selecting participant for an RCT is an important step and will reflect the generalizability of their study, which also contributes to preventing the development of duplicate studies testing the same intervention for another population.

About 50% of the respondents excluded older adults in past trials, whereas the number fell to 30% for current/future RCTs. On the other hand, 22.6% of respondents were willing to recruit exclusively older adults in current/future RCTs. However, changes in researchers' attitudes may take some time to reflect on the results of RCTs. According to evidence from studies of ongoing RCTs, the exclusion of older people will persist at least for the next few years (Carvalho do Nascimento et al., 2019; Cherubini et al., 2011; Cruz-Jentoft et al., 2013). A systematic review of age-related inclusion criteria for LBP trials reported 41.6% of the trials excluded older adults (Paeck et al., 2014). In addition, exclusion of older adults was present in 48.3% of the ongoing RCTs for LBP in an analysis of a clinical trial registry database (Carvalho do Nascimento et al., 2019). Moreover, results from this prospective study found that studies designed exclusively for older adults accounted only for 2.9% of the total (Carvalho do Nascimento et al., 2019). Similarly, an analysis of ongoing RCTs for type 2 diabetes mellitus found that only 1.4% of the trials

targeted older adults (Cruz-Jentoft et al., 2013). The representativeness of older adults in RCTs and the development of studies investigating interventions exclusive to this population, when necessary, may optimize future clinical practice guidelines in recommending evidence-based treatments for these individuals.

We found an association between years of experience and the belief that physical inability, cognitive inability and high drop-out rates are reasons that justify the exclusion of older adults from RCTs. Researchers with less experience (< 10 years) tended to find it justifiable to exclude older adults from RCTs based on those reasons. Similar results were found in a previous investigation where young health professionals highlighted cognitive problems, the presence of comorbidities and the high number of other aging characteristics as criteria excluding older adults in rehabilitation programs (Nicholas et al., 1998). This observed belief among young researchers can be explained by the fact that usually, novice researchers are younger and young individuals tend to present stereotypes about older adults (De Biasio et al., 2016; Donizzetti, 2019). In a survey with 886 young adults (mean age = 35.8 years), Donizzetti (2019) found that anxiety about aging and knowledge are antecedents for stereotypes, which directly influence ageism. Further, a cohort investigating the attitudes of medical students during two different phases of their training found that women and older students held more positive attitudes towards old people than men and younger students (De Biasio et al., 2016). On the other hand, there is evidence that interventions focusing on education and knowledge into all aspects of ageing can change the negative attitudes towards older adults by researchers and health-care science students (Barron et al., 2015; Black et al., 2013; Jeste et al., 2018; Milutinović et al., 2015).

Strengths and limitations of the study

Despite careful considerations with the design of the questionnaire, sample selection and method to reach this sample, some potential limitations need to be acknowledged. Firstly, we could consider that the response rate of 47.5% may not reflect most LBP researchers. This response rate is, however, higher than the rate typically obtained with this type of population (< 40%) (Costa Lda et al., 2013; Cunningham et al., 2015). Secondly, we selected a convenience sample. However, participants surveyed were among the most respected researchers in the LBP field and the members from worldwide reputable research centers. Therefore, we feel the data obtained is representative of leading-edge research done in the field. The third limitation is the risk of response bias related to social desirability when using self-reported questionnaires for data collection. According to social norms, researchers cannot deny the participation of older adults in their work. Thus, the occurrence of distorted results favorable to the inclusion of older adults cannot be excluded from our results. Attempting to decrease the risk of social desirability bias, we assured anonymity and confidentiality during all data collection processes.

Conclusions

LBP researchers believe that older adults are excluded from RCTs, the exclusion based solely on age is not justifiable, and that excluding older adults from RCTs imposes difficulties to patients and health providers in having access to evidence-based interventions. Views regarding the reasons that may justify the exclusion of older adults vary according to researcher's experience. Respondents are inclined to include older adults in future RCTs with a slight improvement in research targeting this population. Respondents are prone to include older adults in future RCTs with a slight improvement in research targeting this population. These results highlight the need for strategies that act on

two fronts; educational and conditional. Educational strategies should target researchers especially during training and early-career stages, while conditional strategies could conditionate the submission of grant proposals and ethical clearance to the absence of unnecessary exclusion of older adults.

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Chapter Six

Relationship between sarcopenia and low back pain in older adults. Analysis of baseline data from the Canadian Longitudinal Study on Aging

Chapter six is submitted for publication in the *Journal of American Medical Directors Association* as:

Carvalho do Nascimento, P. R., Poitras, S., Costa, L. O. P., Ramsay, T., & Bilodeau, M.. Relationship between sarcopenia and low back pain in older adults. Analysis of baseline data from the Canadian Longitudinal Study on Aging.

Abstract

Importance: There is little understanding about the association of low back pain (LBP) with sarcopenia, comorbidities, and lifestyle factors in older adults.

Objective: To determine the association of LBP with sarcopenia in older adults according to the European Working Group on Sarcopenia in Older People updated (EWGSOP2), the International Working Group on Sarcopenia (IWGS) and the Foundation National Institute of Health (FNIH) criteria definitions for sarcopenia, and to investigate their prevalence based on these definitions. The secondary objective was to verify whether the predictive association was in the same direction independently of the definition of sarcopenia and the strength of the association

Design: Cross-sectional analysis of the baseline data from the Canadian Longitudinal Study on Aging (CLSA) collected from January 2011 to June 2015.

Setting: Population-based.

Participants: Older adults (≥65y) who completed the comprehensive part of CLSA.

Main Outcome(s) and Measure(s): Prevalence of LBP and sarcopenia based on the EWGSOP2, the IWGS and the FNIH criteria definitions. The diagnosis of sarcopenia was based on specific cut-off values applied in each definition for muscle quantity, muscle strength and muscle quality obtained from the dual x-ray absormetry (DXA), handgrip strength and time-up and go test, respectively. Analysis of the association between LBP with sarcopenia, comorbidities, and lifestyle factors.

Results: Data from 12646 older adults with a mean (SD) age of 73.1 years (5.69) were analyzed, of which 49.9% were women. One-year prevalence of LBP was 16.3% with high values in women (18.5%) than men (14%) ($x^2 = 46$, $p < 0.001$). Among participants with LBP the prevalence of pre-sarcopenia according to the IWGS criterion was higher

compared to those without LBP (67.7%, 61.7%; $x^2 = 20.25$, $p < 0.001$). Similarly, the prevalence of sarcopenia following the FNIH definition was higher when LBP was reported (6.32%, 4.45%; $x^2 = 13.83$, $p < 0.001$). The odds of having LBP were higher among those classified as sarcopenic (OR 1.28, 95%CI 1-1.64) when using the FNIH criteria, and among participants with more comorbidities and depression independently of the regression model when adjusting for sarcopenia.

Conclusions and Relevance: The prevalence of sarcopenia varies with criteria definition and among those with and without LBP. An independent positive association was found between depression and comorbidities with LBP whereas being male was associated with decreased odds of having LBP. Sarcopenia defined by FNIH criterion was associated with increased odds of having LBP suggesting that when managing LBP in older adults, sarcopenia, depression, and comorbidities should be considered as a strategy that could help to improve outcomes.

Introduction

Low back pain (LBP) complaints are present in about 23% of older adults, becoming worse with advancing age, with a prevalence peak around 80 years of age (38%), which cause high disability and economic burden to health services (Docking et al., 2011; Ferreira et al., 2019; Hoy et al., 2014). Older adults with LBP usually present a higher risk of falls, difficulty to keep a standing position for long periods, push or pull a big object and walk moderate distances (da Silva et al., 2016; Edmond & Felson, 2003; Rosa et al., 2016). Furthermore, the symptoms influence their sense of wellness, increasing the risk of depression and decreasing quality of life (Deyo et al., 2015; Teixeira et al., 2016).

Although the differential diagnosis of LBP is broad, in about 85% of all cases in the general population, a definitive diagnosis cannot be reached, which is labeled as non-specific LBP (NSLBP) (Koes et al., 2006). The lack of a clear diagnosis potentially influences negatively the results of clinical trials and practice (Delitto et al., 2012; Maher et al., 2016). Current recommendations for the management of NSLBP advocate to subgroup patients and provide targeted treatments to obtain better results (Delitto et al., 2012). Older adults could form a specific subgroup due to particular changes resulted from aging, however, they are underrepresented in clinical research for LBP (Dziechciaż & Filip, 2014; El Tumi et al., 2017; Lautenbacher et al., 2017; Paeck et al., 2014). Compared to their younger counterparts, older adults present a higher number of comorbidities and different lifestyle patterns, which has been shown as potential risk factors for LBP (Paeck et al., 2014). Some outstanding differences between older and younger adults are the loss of muscle mass, strength, and the decline in physical function observed in older people, which are associated with a high risk of mortality and cognitive deficit (Abe et al., 2011; Cooper et al., 2010; Goodpaster et al., 2006; Nilwik et al., 2013). These alterations combined

define a geriatric syndrome with multivariate etiology called sarcopenia (Cruz-Jentoft et al., 2010; Goodpaster et al., 2006).

The European Working Group on Sarcopenia in Older People (EWGSOP) (Cruz-Jentoft et al., 2010), made the first try in proposing a consensus to define sarcopenia although the consensus is not unanimous and was recently updated (EWGSOP2) (Cruz-Jentoft et al., 2019), defining sarcopenia based on grip strength decline (< 27Kg in men and < 16Kg in women), low muscle mass adjusted by height (<7.0 kg/m^2 men and <5.5 kg/m^2 women) and reduced gait speed (< 0.8m/s). In addition, other groups have proposed different definitions and cut-off points (Fielding et al., 2011; Studenski et al., 2014). However, independent of the definition used to diagnose sarcopenia, is well know that its prevalence increases with aging (Cherin et al., 2014; S. Yu et al., 2014; Zeng et al., 2015). Given the increase in life expectancy with higher prevalence of LBP in older adults, the knowledge of influence of sarcopenia markers (appendicular lean mass, strength and performance), lifestyle factors and comorbidities have on LBP is necessary to help developing better prevention and management strategies. Therefore, the main objective of this study was to evaluate the association between sarcopenia, comorbidities, lifestyle factors with LBP in community-dwelling older adults. The secondary objective was to verify whether the predictive association was in the same direction independently of the definition of sarcopenia. Lastly, we aimed to assess the prevalence of sarcopenia through the different working group definitions.

Methods

Participants

Study participants were those 65 years and older who completed the comprehensive baseline assessment of the Canadian Longitudinal Study on Aging (CLSA) (Parminder S. Raina et al., 2009). The CLSA full protocol is published elsewhere (Parminder S. Raina et al., 2009). Briefly, the CLSA is a national longitudinal study following subjects who can read and speak either French or English aged 45 to 85 years old for at least 20 years with repeated waves every three years. The CLSA recruited at the baseline a stratified random sample of over 50 000 Canadians that were assessed by phone interview (tracking assessment) or through in-home face to face interview and onsite data collection (comprehensive assessment). Participants from the Tracking cohort (n = 21241) were randomly selected from within all 10 provinces and interviewed by telephone, while the Comprehensive cohort comprised a sample of 30097 participants randomly selected from within 25–50 km of 11 data collection sites (in seven provinces) who are interviewed in person, take part in in-depth physical assessments at DCSs, and provide blood and urine samples (P. S. Raina et al., 2009). The CLSA excluded individuals living in the Canadian territories (i.e., Northwest Territories, Nunavut, and Yukon) and some remote regions, residents of Federal First Nations reserves or other provincial First Nations settlements, individuals living in long-term care facilities at the baseline, full-time members of the Canadian Armed Forces, and persons with cognitive inability to provide informed consent (Parminder S. Raina et al., 2009).

We performed a cross-sectional analysis of the baseline data of the comprehensive assessment that was collected between January 2011 and June 2015. The current study was approved by the CLSA Data Access Application, the Research Ethics Committee from the Bruyère Research Institute and the Research Ethics Board from the University of Ottawa.

Procedures

Low back pain assessment

The history and location of LBP were assessed in the CLSA using the self-developed Disease Symptoms Questionnaire (DSQ) (Raina et al., 2007). Participants were invited to answer the following questions about history of back pain ("Have you ever had pain in your back on most days for at least one month?"), presence of pain in the last 12 months ("Have you had this pain within the past 12 months?"), and location of the symptoms ("In what part of your back (is/was) the pain usually located?") pointed as lower/below the waist line.

Associated factors

Independent variables included in the analysis were considered in three groups:

a) Sarcopenia - presence of sarcopenia was based on three different sets of criteria (those of the EWGSOP2. IWGS, and FNIH) due to the lack of a consensus definition (Cruz-Jentoft et al., 2019; Fielding et al., 2011; Studenski et al., 2014). The variables used to examine the presence of sarcopenia (i.e., gait speed, muscle strength, and appendicular lean mass) were extracted respectively from the timed-up and go (TUG) test (Podsiadlo & Richardson, 1991), Handgrip Strength test (Gruther et al., 2009), and dual x-ray absormetry (DXA) exam (Blake & Fogelman, 1997). Table 1 provides the criteria for each definition to diagnosis sarcopenia.

b) Sociodemographic characteristics - age and sex.

c) Confounders – The literature presents a substantial number of factors that seem to be associated with LBP (Bento et al., 2019; Parreira et al., 2017; Saes-Silva et al., 2021; Wong et al., 2021) and sarcopenia in older adults (Li et al., 2022; Montero-

Fernandez & Serra-Rexach, 2013; Steffl et al., 2015). Attempting to obtain strict and realist models, we focused on factors commonly reported as associated with LBP and sarcopenia and present in the comprehensive CLSA data. The CLSA study uses the short form of the Center for Epidemiologic Studies – Depression (CES-D10) Scale (Irwin et al., 1999) to assess depressive symptoms. CES-D10 comprises 10 questions with an overall score ranging from 0 to 30, used to identify clinical depression with a good level of sensitivity (Irwin et al., 1999). We used the variable DEP_CESD10_COM reporting the overall score for depressive symptoms for our analysis. Physical activity and sitting time were quantified using the Physical Activity Scale for the Elderly (PASE) questionnaire (Washburn et al., 1993), a valid tool used to summarize the time spent with leisure, household and work-related activities done in the past week (Washburn et al., 1993). The time spent in each activity is summed and adjusted by activity intensity (i.e., light, moderate, strenuous, or recreational). Based on smoking status, participants were coded as smokers and non-smokers. The CLSA assesses the smoking status by questioning participants “at the present time, do you smoke cigarettes daily, occasionally, or not at all?”(P. S. Raina et al., 2009). Comorbidities were measured through the DSQ (Andresen et al., 1994; Kim et al., 2011; Linton, 2000; Montero-Fernandez & Serra-Rexach, 2013; Schneider et al., 2007; Shiri et al., 2010; Smuck et al., 2014; Steffl et al., 2015; Washburn et al., 1993; R. Yu et al., 2014). In the DSQ, the participants were asked to answer whether a physician had ever told them that they had hip osteoarthritis, knee osteoarthritis, rheumatoid arthritis, other arthritis, heart disease, heart attack, angina, asthma, chronic lungs disease, mini-stroke or transient ischemic attack, stroke, Parkinsonism, multiple sclerosis, dementia or Alzheimer,

memory problem, epilepsy, and/or migraine headaches. The CLSA presents the data for each comorbidity as indicator variables (yes/no). These variables were combined to generate a single variable, representing the total number of comorbidities for each participant (range = 0 to 17). In addition, we planned to control for body mass index (BMI).

Data analysis

Characteristics of the sample are presented by descriptive analysis reporting mean and standard deviation (SD) for continuous data, and frequency and proportion (%) for categorical data.

A series of multivariate logistic regression models were built to test the association between the independent variables and low back pain within the past 12 months. We built a general logistic model adjusting for potential associated factors (i.e., age, sex, depression, physical activity, smoking, BMI, and comorbidities) combined with the continuous variables used to diagnose sarcopenia (i.e., appendicular skeletal muscle index adjusted by the body mass index (ASMI/BMI), handgrip strength and gait speed) with the dependent variable of LBP within the past 12 months as a dichotomous variable (0 – absence, 1 – presence).

Additionally, we built individual specific multivariate logistic regression models for each definition of sarcopenia. In each model, we combined the associated factors (i.e., age, sex, depression, physical activity, smoking, BMI, and comorbidities) with the categorical variable EWGSOP2 (1 - pre-sarcopenia, 2 – sarcopenia, 3 – severe sarcopenia), or IWGS (1 – pre-sarcopenia, 2 - sarcopenia), or FNIH (1 - pre-sarcopenia, 2 – sarcopenia, 3 – severe sarcopenia) to test the independent association of each definition with LBP. The logistic

models were built using the data of women and from those with no sarcopenia as reference groups for sex and sarcopenia definition.

Results

A total of 12646 older adults participated in the comprehensive assessment of the CLSA. Mean age was 73.1 years (SD 5.69) and 49.9% of the participants were women. The characteristics of the study sample are presented in Table 2.

Presence of LBP was reported by 2056 participants (16.3%), with higher prevalence in women (18.5%), than men (14%) ($x^2 = 46$, $p < 0.001$). At least one comorbidity was reported by approximately 30% of the participants with LBP in the last 12 months.

Prevalence of sarcopenia

The general prevalence of sarcopenia varied according to the definition criteria. According to the EWGSOP2 definition, the prevalence values of pre-sarcopenia, sarcopenia and severe sarcopenia were 8.38%, 0.65%, and 0.62% in men, while in women the estimates were 8.53%, 0.71%, 0.65%. Prevalence of pre-sarcopenia and sarcopenia was 59.81% and 6.54% respectively in men, and 65.57% and 8.58% in women based on the definition of the IWGS. Based on the FNIH, the prevalence of pre-sarcopenia, sarcopenia and severe-sarcopenia were 6.03%, 4.01%, 0.99%, and 3.81%, 3.63%, 0.87% in men and women respectively.

Analysis of the prevalence of sarcopenia between participants without LBP and those with LBP revealed different values depending on the sarcopenia definition. When following the EWGSOP2, no significant difference was found on the prevalence of pre-sarcopenia between subjects with or without LBP (9.39%, 8.27%; $x^2 = 2.69$, $p = 0.1$),

similarly, prevalence of sarcopenia was not different in case of LBP or not (1.16%, 1.34%; $x^2 = 0.33$, $p = 0.56$). Based on the IWGS, the prevalence of pre-sarcopenia was higher among those with LBP compared to participants without LBP (67.7%, 61.7%; $x^2 = 20.25$, $p < 0.001$), whilst prevalence of sarcopenia was not different ($x^2 = 0.4$, $p = 0.53$). Based on the FNIH definition, the estimates for pre-sarcopenia did not differ according to the presence of LBP (5.3%, 4.8%; $x^2 = 1.4$, $p = 0.24$), however, prevalence of sarcopenia was higher when LBP was reported (6.32%, 4.45%; $x^2 = 13.83$, $p < 0.001$).

Associated factors for LBP within the past 12 months

Covariates were forced in the model however BMI was removed from the model due the high risk of multicollinearity ($r = 0.6$). The general logistic regression model (Table 3) revealed that grip strength (OR= 1.01, 95% CI 1.0-1.02, $p = 0.008$), presence of more depressive symptoms (OR= 1.07, 95% CI 1.06-1.08, $p < 0.001$) and total number of comorbidities (OR= 1.28, 95% CI 1.21-1.33, $p < 0.001$) were associated with increased odds of having LBP, whereas gait speed (OR= 0.48, 95% CI 0.35-0.67, $p < 0.001$), and the ASMI/BMI ratio (OR= 0.51, 95% CI 0.29-0.89, $p = 0.02$) were associated with decreased odds of having LBP.

EWGSOP2 logistic model (Table 4) revealed that being male was associated with decreased odds of having LBP (OR = 0.81, 95% CI 0.73-0.90, $p < 0.001$) whilst depressive symptoms (OR = 1.07, 95%CI 1.06-1.09, $p < 0.001$) and number of comorbidities (OR 1.27, 95%CI 1.22-1.32) increased the odds of having LBP.

The odds ratio of having LBP in the logistic model for the IWGS (Table 5) was higher for those with higher number of comorbidities **(**OR = 1.25, 95% CI 1.20-1.31, $p <$

0.001**),** and more depressive symptoms (OR = 1.07, 95% CI 1.06-1.08, p < 0.001), whereas being male (OR = 0.81, 95% CI 0.73-0.90, p = 0.001) was associated with decreased odds.

The FNIH logistic model (Table 6) revealed that higher depressive symptoms (OR = 1.07, 95% CI 1.06-1.08, p < 0.001), comorbidities (OR = 1.26, 95% CI 1.22-1.32, p < 0.001) and the presence of sarcopenia (OR = 1.28, 95% CI 1.0-1.64, p = 0.04) were associated with increased odds of having LBP, whilst being male (OR = 0.81, 95% CI 0.72-0.90, p < 0.001) was associated with decreased odds.

Discussion

Statement of principal findings

We found a one-year prevalence of LBP in older adults of 16.3%, with higher rates in women (18.5%) than men (14%). The general prevalence of sarcopenia varied according to the definition criteria, with higher values observed using the IWGS definition (7.5%) followed by the FNIH (3.82%), and EWGSOP2 (0.68%) while values for men and women were similar within each criterion. The prevalence of pre-sarcopenia according to the IWGS as well as the prevalence of sarcopenia using the FNIH were higher among participants with LBP compared to those without LBP. Presence of sarcopenia diagnosed using the FNIH definition was associated with increased odds of having LBP. Similarly, the odds of having LBP were associated with an increase in the number of comorbidities and depressive symptoms for all regression models, whereas being male was associated with reduced odds of having LBP.

Strengths and weaknesses in relation to other studies

To our knowledge, this is the first community-based study of a national representative sample that shows a relationship between sarcopenia markers and different sarcopenia definitions with LBP. Our findings demonstrated that sarcopenia was solely associated with LBP according to FNIH definition. This result may be related to the difference in the parameter used to adjust muscle mass across the different criteria definition. Whilst the FNIH criteria adjusts muscle mass by BMI, in the EWGSOP2, and IWGS muscle mass is adjusted by height squared (Cruz-Jentoft et al., 2019; Fielding et al., 2011; Studenski et al., 2014). This result suggests that when investigating the association of body composition and LBP, we should take in consideration the role of body composition as a ratio between muscle and fat mass instead each component isolated, since studies focusing on these components individually have shown conflicting findings (Chou et al., 2016; Hori et al., 2019a; Koyanagi et al., 2015; Y. Sakai et al., 2017; Walsh et al., 2018). Results from a systematic review showed that increased body fat was associated and LBP (Walsh et al., 2018). In addition, the findings from a sample of 2551 older Australians revealed that higher levels of obesity were associated with worse LBP symptoms and/or disability (Chou et al., 2016). Furthermore, higher odds for LBP were observed for BMI $\geq$25 kg/m^2 in a study using a nationally-representative sample in nine countries in Asia, Africa, Europe, and Latin America (Koyanagi et al., 2015). Moreover, a study investigating the association of trunk muscle mass with LBP, found a relationship between muscle mass with LBP intensity and disability when also adjusting for BMI, sex and comorbidities (Hori et al., 2019a). On the other hand, results from a study with community-dwelling older Japanese did not find a relationship between body composition and LBP (Endo et al., 2019). To date, there is only one study that investigated the relationship between a sarcopenia definition and LBP (S. Tanishima et al., 2017). In this study, the authors

investigated the association between LBP and sarcopenia in a sample of 216 older Japanese and found no difference in LBP prevalence between participants classified according to the EWGSOP as normal, pre-sarcopenic or sarcopenic (S. Tanishima et al., 2017). These results are in accordance with our findings for the EWGSOP2 analysis.

The mechanisms accounting for the association between sarcopenia and LBP are unknown. As the design of our study prevents us from determining a cause-and-effect relationship, we cannot infer whether LBP was a cause or a result of sarcopenia. Although the answer to this question must come from longitudinal data, there is evidence supporting the hypothesis of the association of sarcopenia and LBP. Because LBP is a multifactorial problem, any single factor or mechanism is not likely to play a major role in symptoms behaviour. However, sarcopenia may exert a direct and an indirect role with LBP in older adults. Directly, the occurrence of muscle atrophy/waste can interfere with the activity and function of the trunk and abdominal muscles, which is associated with LBP (Crawford et al., 2016; Crawford et al., 2019; Hofste et al., 2021; Teichtahl et al., 2015). Early research in the field showed a reduction in the CSA of the lumbar multifidus muscle (MF) in adults with acute LBP (Hides et al., 1994) and chronic LBP (Daaneels, 2000). In addition, there is evidence showing a decrease in MF CSA and fat infiltration in individuals with chronic LBP compared to controls free of back symptoms (Daaneels, 200; Parkkola, 1993). On the other hand, results from a study with 72 individuals recruited from the community (Teichtahl, 2015) revealed no association between reduction in the cross-sectional area of the MF muscle and erector spinae (ES) with LBP and related disability or bone structure. However, Teichtahl et al., 2015 found an association between high MF fat infiltration with an increased risk of high-intensity LBP and associated disability OR = 12.6 (95%CI 2.0 to 78.3). Goubert et al., 2006 demonstrated in a systematic review that lumbar muscles cross-

sectional changes vary with muscle and symptoms duration. According to this review, studies investigating patients with acute, chronic and cases with undefined LBP symptom duration reported a reduction in the cross-sectional area of the MF muscle in patients compared to control (Goubert 2006). The association between fat infiltration in MF and ES with chronic LBP had contradictory results. Results from a recent systematic review (Ranger et al., 2017) support the association between the CSA of MF muscle and LBP. This review also found conflicting evidence about the relationship between MF muscle fat infiltration and LBP. The alterations in muscle characteristics may potentialize the effects of degenerative spinal diseases related to older age (e.g., arthritis, lumbar spinal stenosis) leading to LBP indirectly (Leandro dos Santos et al., 2017; Eguchi et al., 2017b; Iwahashi et al., 2022; Park et al., 2016). Additionally, some neural changes that help justify the etiology of sarcopenia can affect motor control (Aagard, 2010; Kwan, 2013; Kwon 2017). Nevertheless, motor control alterations, especially those implicating the transversus abdominis have shown an association with LBP (Meier 2019).

Health related risk factors for LBP were investigated, including depressive symptoms, lifestyle and performance factors, ASMI/BMI ratio, and comorbidities. Our analysis observed a positive association between number of comorbidities and depressive symptoms with LBP while gait speed and the ASMI/BMI were negatively associated. These results are consistent with the results of other two population-based studies investigating LBP in Australian older men (Chou et al., 2016; Parreira et al., 2017). In their study with 1685 older men, Parreira et al. (2017) found no association of lifestyle factor with LBP, whilst the number of comorbidities was independently associated with the occurrence of LBP (OR = 1.17, 95% CI: 1.01-1.37; p = 0.05). In addition, Chou, et al. [43] analyzed the association between body composition and LBP in 820 elder men and found a

higher fat mass/fat-free mass ratio (0.74 vs 0.66, P≤0.001) in participants with LBP. Furthermore, low skeletal muscle index and high body fat ratio was found in a sample of older Japanese with chronic LBP compared to a free of back symptoms sample.[44]

Clinical implications and future directions

The relationship between sarcopenia, comorbidities, and depressive symptoms with LBP observed in this study revealed potential factors that may deserve further evaluation when treating older patients with LBP. These findings reinforce the biopsychosocial aspect of LBP, which may need a multidisciplinary approach for better results. However, this study used a cross-sectional design, which does not allow to infer causality. Moreover, further work is needed to investigate if this association is supported in other populations where prevalence of sarcopenia and low back pain are different from the estimates found in older Canadians.

Strengths and weaknesses of the study

The main strength of this study is the large sample of community-dwelling older Canadians recruited across the country. In addition, the CLSA provides a series of variables collected through objective methods allowing to test the planned associations properly. However, our study also has some limitations. First, our analysis was based on the baseline assessment, offering only a one-point measurement. Second, the results are based on a community-dwelling sample and may not be generalizable to older adults living in long-term facilities or to those who are seeking health care services. Third, there are no specific variables of LBP disability and pain intensity, which prevented more precise analyses concerning the association of sarcopenia with pain intensity and disability.

Conclusions and Implications

The prevalence of sarcopenia varied according to the criteria definition and among those with and without LBP. The general prevalence of sarcopenia was higher with IWGS definition and among participants with LBP following the FNIH criterion. Independently of the model depression and comorbidities were always associated with increased odds of having LBP and being male with decreased odds. Sarcopenia when diagnosed using the FNIH definition was associated with increased odds of having LBP. These results suggest that sarcopenia, depression, and comorbidities may influence LBP in older adults and future studies should consider to test whether the association between sarcopenia and LBP is causal.

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Chapter Seven

Analysis of sarcopenia parameters in older adults with chronic low back pain

Chapter seven was submitted for publication in *Physical Therapy* as:

Carvalho do Nascimento, P. R., Poitras, S., Pinto, R. Z. A., Pereira, L. S. M., Santos, D. A. M & Bilodeau, M.. Comparative Analysis of functional sarcopenic markers and transversus abdominis activation in older adults with chronic low back pain.

Abstract

Objective: Low back pain (LBP) is associated with muscle dysfunction; yet, the role of sarcopenia, an age-related muscle syndrome, is unknown. Therefore, we performed a cross-sectional comparison of the sarcopenia parameters for muscle function and quality between older adults with and without chronic low back pain (CLBP). In addition, we assessed the association between gait speed and the activation of the transversus abdominis muscle (TrA).

Methods: A sample of 33 community-living participants 60 years and older with CLBP (≥ 3 months) nested in a population-based cohort was recruited. We assessed grip strength, gait speed, the anticipatory activity of TrA during the rapid arm abduction test, and TrA muscle elasticity. Data from 28 older adults without CLBP recruited from a community were used for comparison. We used the Mann-Whitney U test to compare the activation of transversus abdominis and elastography behaviour between groups. The t-test was applied to test the difference between groups in grip strength and gait speed.

Results: The CLBP group presented reduction in the sarcopenic markers compared with the controls: grip strength (mean difference (MD) = 5.3, 95%CI = 1.5-9.0, p = 0.006), gait speed (MD = 0.21, 95%CI = 0.10-0.31, p<0.001), as well as a delay in activation of TrA (p = 0.002). There was a negative correlation between gait speed and TrA activation in the CLBP group (p = 0.04).

Conclusion: A delay in TrA muscle activation and reduction in muscle strength and gait speed were observed in older adults with chronic LBP compared to subjects without LBP. These findings suggest an association between sarcopenia parameters and CLBP in seniors. However, this study used a cross-sectional design and cannot be used to infer causality.

Impact statement: Preliminary data suggests that sarcopenia markers are different between older adults with and without CLBP. Thus, investigating the presence of sarcopenia in older adults with CLBP and adjusting the intervention to target sarcopenia when it is present may improve patient outcomes. Studies with longitudinal design and larger sample sizes are needed to elucidate the value of sarcopenia parameters in older adults with CLBP.

Keywords: Sarcopenia, older adults, disability, transversus abdominis, elastography.

Introduction

The prevalence of low back pain (LBP) increases with aging (Hoy et al., 2014). In older adults, LBP is associated with a high disability level and risk of depression, which can contribute to perpetuate the symptoms (Rundell et al., 2015; Teixeira et al., 2016). However, the high heterogeneity among LBP patients prevents in most cases to define an etiologic cause (Kent et al., 2009). Thus, a subgroup approach has been used as an attempt to deliver the right intervention to the right patient (Delitto et al., 1995; Delitto et al., 2012; Hill et al., 2008; National Guideline, 2016a).

Motor control dysfunction has been extensively investigated in LBP patients showing differences between people with and without LBP (Hodges, 2001) as well divergences among LBP patients (Silfies et al., 2009; Silfies et al., 2005). Although there is substantial evidence supporting the occurrence of changes in muscle activation and muscle morphology in individuals with LBP (Cholewicki & McGill, 1996; Hofste et al., 2021; Radebold et al., 2000; Sions et al., 2017), these differences vary by LBP duration, task and even within muscles (Danneels et al., 2000; P. W. Hodges & L. Danneels, 2019; Hodges & Richardson, 1999a; van Dieën et al., 2019). Differences in motor control responses combined with the fact that motor control exercises are not better than other exercise strategies to manage chronic LBP (Saragiotto Bruno et al., 2016) may suggests the existence of motor control subgroups (van Dieën et al., 2019). Age advance may lead to adverse changes in muscle quantity (muscle mass), quality (micro- and macroscopic aspects of muscle architecture and composition) and muscle function (strength, physical performance) (Goodpaster et al., 2006; Jerome et al., 2015; McGregor et al., 2014). These age-related alterations may interfere with the role that the musculoskeletal system plays in the motor control of the spine (Ainscough-Potts et al., 2006; Hebert et al., 2010; Hodges & Moseley,

2003). Moreover, loss of muscle strength, quantity and function when combined result in a muscle syndrome called sarcopenia (Cruz-Jentoft et al., 2010; Cruz-Jentoft et al., 2019). Although the criteria used to define sarcopenia are the same for different working groups (Chen et al., 2020; Cruz-Jentoft et al., 2019; Fielding et al., 2011; Studenski et al., 2014), differences exist while setting the key criterion and the cut-off values. The European Working Group on Sarcopenia in Older People (EWGSOP) (Cruz-Jentoft et al., 2010) was the first to present a consensus definition for sarcopenia based on a loss of muscle mass combined with reduced muscle quality or muscle function. The EWGSOP definition was recently revised (EWGSOP2) (Cruz-Jentoft et al., 2019) changing the focus from muscle mass to muscle strength. According to the EWGSOP2, patients with low muscle strength probably have sarcopenia. The diagnosis of sarcopenia is confirmed by combining low muscle strength with low muscle quantity or quality (Cruz-Jentoft et al., 2019). Patients presenting with low muscle strength, low muscle quantity/quality and low physical performance are diagnosed with severe sarcopenia (Cooper et al., 2010).

Many studies have investigated motor control patterns in individuals with LBP based on the onset of transverse abdominis muscle (TrA) contraction in response to rapid arm movements (Hodges, 1999; Hodges & Richardson, 1999a, 1999b). As a result, these studies found that individuals with LBP do not present a feedforward activity of TrA during rapid limb movement compared to free of LBP controls (Hodges & Richardson, 1996, 1998). Most evidence on the relationship between motor control dysfunction (i.e., recruitment, change in thickness, pre-anticipatory activation, and elasticity/stiffness) and LBP are from studies investigating young populations (Brown & McGill, 2009; L. Costa et al., 2009; P. H. Ferreira et al., 2010; Ferreira et al., 2011; Hirayama et al., 2015; Vasseljen et al., 2009; Wilson et al., 2016). However, results

from a study with subjects free of back complaints found a reduction of TrA feedforward activity in older individuals compared to young participants (Davies et al., 2016). Moreover, recent findings showed that older adults with chronic LBP (CLBP) present altered postural adjustments compared with participants in the same age strata without back problems (Garcez et al., 2021).

Based on these assumptions, we hypothesized that older adults with CLBP would present an alteration in sarcopenia parameters of muscle function (i.e., muscle strength and gait speed), and deep abdominal muscle quality (TrA recruitment and TrA elasticity) compared to a control group free of CLBP. The main objective of this study was to assess sarcopenia parameters of muscle function and deep abdominal muscle quality in a sample of older adults with CLBP compared to a control group without back complaints. Further, we investigated the association between gait speed and TrA recruitment.

Methods

Role of the Funding Source

The funders played no role in the design, conduct, or reporting of this study.

Participants

Sixty-one study participants (33 with CLBP and 28 healthy controls) aged 60 years or older, volunteered for this study. Participants from the CLBP group were recruited from participants of the Back Complaints in Elderly study, Brazil (BACE-B). The BACE study protocol has been published in detail elsewhere (Scheele et al., 2011). In summary, BACE is an observational prospective cohort following adults from the Netherlands, Brazil and Australia aged 55 years and older who were seeking care with a primary health care physician for a new

episode of LBP (Scheele et al., 2011). The BACE study defined LBP as a pain in the area between the inferior margin of the ribs and the gluteal crease (Scheele et al., 2011). We contacted participants from the BACE-B who consented to participate in future research. Participants were randomly selected and included if they had chronic non-specific LBP, defined as pain lasting for at least 3 months without a clear specific cause, with or without pain referral to the leg, but without neurological deficits. Exclusion criteria for the LBP group were: history of spinal and/or abdominal surgery, presence of glenohumeral osteoarthritis, red flags or radiculopathy signs, suspected or diagnosed serious spine pathology (inflammatory spondyloarthropathy, fracture, malignancy, cauda equina syndrome, or infection), presence of rheumatic disease of the lumbar spine, urinary incontinency, BMI $\geq 35 Kg/m^2$, and cognitive deficits assessed with the Mini Mental State Examination (MMSE) (score of MMSE < 24 points).

Participants without LBP (control group) were recruited consecutively from members of the Aging Health group, a group that offers physical activity for elders inside the University (omitted for review) campus. Participants were excluded from the control group if, in addition to the exclusion criteria listed for the LBP group, they had a history of LBP that had restricted normal daily activities or caused them to have time off work in the past six months, if they had any respiratory or neurologic disorder or pain elsewhere in the spine or lower limbs. For descriptive purposes depressive symptoms were assessed using the Geriatric Depression Scale (GDS) (Castelo et al., 2010) and the number of comorbidities documented using a standardized questionnaire in which subjects reported whether a physician had ever told them that they had diabetes, hypertension, heart or thyroid dysfunctions, osteoporosis, Paget disease, stroke, Parkinson disease, chronic obstructive lung disease, liver disease, vertebral fracture, and chronic

kidney disease or kidney stones. Ethical approval from the University (omitted for review), (omitted for review) Research Institute and University (omitted for review) research ethics boards, as well the written informed consent from all participants were obtained.

Sample size estimation

To calculate the minimum sample size needed, we used the values defined in the literature for TrA muscle activation measured using ultrasound image (USI) in young and older adults without LBP complaints (Davies et al., 2016). We used the formula for two independent means with an allocation ratio N2/N1 =1, and standard deviation of 0.02s. The effect size was calculated setting the mean value for the control group = 0.026s and between group difference = 0.015s. We found that a total sample size of 58 participants was necessary to achieve 80% power and a significance level of 0.05 using a two-sided two-sample t-test. To perform the test, we used the version 13 of the software Stata®.

Procedures

Participants were engaged in a two-stage protocol: 1) interview and 2) muscle function/quality assessment, evaluated consecutively by two independent examiners. Firstly, participants took part in a comprehensive interview performed by a research assistant. The interview was guided by a self-developed questionnaire that allowed gathering of information related to general health condition, presence of depressive symptoms, cognitive status, sex, age, LBP history, and had their anthropometrics measurements (weight and height) recorded to calculate the body mass index (BMI). Secondly, we assessed sarcopenia parameters of muscle

function (i.e., grip strength and gait speed), and deep abdominal muscle quality (i.e., activation and elasticity) measured indirectly using image ultrasound (USI).

An assessor unaware of participants' group attribution and experienced in the use of USI (PN) recorded the anticipatory activation (feedforward) of TrA associated with a rapid arm abduction movement following the protocol proposed by Davies et al. (2016). Briefly, before USI recordings, participants were positioned seated and a pair of surface electromyography (EMG) electrodes were placed over the deltoid muscle and a reference electrode over the spinous process of C7. Next, participants were invited to lay in left lateral decubitus position on a treatment table with their arms and legs relaxed and the head resting on a foam pillow. This position aimed to ensure that TrA was fully relaxed during the beginning of the task. To record the TrA activation, we placed a linear ultrasound transducer (15 MHz) transversely to the midaxillary line, about 2 cm above the superior border of the right iliac crest. After positioning the participants and the USI probe, participants were requested to execute a rapid abduction movement of the right-arm. Each participant performed the task three times. Data was recorded for each repetition and further summarized in a single value by the arithmetic mean. The task started with the verbal command (Go!) before each repetition. A resting period of at least 30s followed each trial. After the first 30s, the investigator gave the command at a random interval to prevent voluntary contraction of the TrA. Before data collection began, one investigator provided visual feedback of the task procedure performing the test for the participants once. Each participant was able to practice until he/she felt comfortable they could perform the task properly. Participants were asked to abduct their arm away from their body, starting at 0° of abduction as quickly as possible until 90° of abduction. Data were recorded for later calculation of the time difference between the onset of activity for the deltoid (EMG signal) and TrA (USI)

muscles. The onset of activity for both muscles was determined visually by one researcher (see Data acquisition section below).

The elasticity of the TrA muscle was assessed using the compression elastography mode of the USI (Figure 1).This method allows the measurement of individual muscle force throughout the assessment of muscular tissue's mechanical properties (Bouillard et al., 2011). The assessor applies a compressive force to the tissue with the USI probe leading to an axial tissue displacement (strain), which is then calculated by comparing the echo sets before and after the compression (Drakonaki et al., 2012). USI elastography is a reliable method to assess TrA elasticity for skilled and unskilled assessors (Hirayama et al., 2015). For this, participants and the ultrasound probe were kept in the same position aforementioned. An assessor (PN) blinded to group allocation asked participants to breathe naturally and then hold their breath at the end of a given expiration while a gentle pressure was applied vertically with the USI probe. The test was repeated three times and the average was used for further analysis.

Upper limb muscle strength was estimated through the assessment of handgrip strength from the dominant limb. Handgrip strength is a biomarker for aging and a risk-stratifying method for all-cause of death (Iconaru et al., 2018b; Leong et al., 2015; A. A. Sayer & T. B. L. Kirkwood, 2015). Because handgrip is a simple and low-cost method that allows predicting lower limb strength (Strandkvist et al., 2021), it is a method chosen by the EWGSOP2 to assess skeletal muscle strength when screening patients for sarcopenia in clinical and research settings (Cruz-Jentoft et al., 2019). An experienced research assistant (DS) blinded to participants' group allocation was in charge to explain the procedures to the participants and later take the handgrip measurement. Participants were seated comfortably with the shoulder in flexion and neutrally rotated, with the elbow supported on a table and flexed at 90^{o} and the forearm and wrist in a

neutral position while holding a hydraulic handheld dynamometer (JAMAR®). Participants were allowed to position the instrument in their hand for a comfortable grip and then solicited to squeeze the handle with maximum strength for 5 seconds while the assessor provided verbal encouragement by repeating the word “Go”. The test was repeated three times with one-minute of rest between each trial. The average value of the three repetitions was recorded for data analysis.

Finally, a blinded assessor (DS) evaluated gait speed to measure the overall muscle performance using the 4-m walking test (Peel et al., 2013). The 4-m usual walking speed test is a valid, quick, safe, and reliable method (Peters et al., 2013) recommended by the EWGSOP2 to assess muscle performance for diagnosing sarcopenia (Cruz-Jentoft et al., 2019). The speed test was performed in a hallway outside the test room with an 8-m course marked on the floor. We divided the course distance into acceleration zone (the first 2m), test zone (next 4m) and deceleration zone (the final 2m). Before the test, the participants observed the examiner performing and explaining how to proceed during the course. Later, the participants completed a practice trial while wearing comfortable walking shoes. After, the participants started a timed trial. The examiner instructed participants to walk the whole course (i.e., eight meters) at their usual speed. Participants started the test after the countdown “3, 2, 1, Go!”. The time it took the participants to cover the 4-m test zone at their usual pace was registered using a stopwatch for a single trial.

Ultrasonography and elastography

The recruitment and elasticity (strain ratio) of the TrA muscle were assessed using USI (ALFAMED, Magnus A7) using a L8L38C (38 mm) linear multi-frequency transducer (5-

15MHz) and compression elastography. The ultrasound probe was placed transversely to the mid axillary line, 2 cm above the superior border of the right iliac crest. During recordings, slight adjustments were made as needed to guarantee an optimal image quality of the TrA muscle (i.e., ensuring that TrA myofascial junction was positioned as horizontal as possible on the screen) due to anatomical variations. When an optimal image of the TrA was visualized on the screen, the transducer was gently pressed against the participants' abdominal wall. USI was performed by an experienced examiner with 10 years of experience with the technique.

Superficial electromyography

Activation of the deltoid muscle during arm abduction was registered using surface electromyography (sEMG). sEMG was recorded using a pair of bipolar self-adhesive electrodes (43 mm diameter, Ag/AgCl, brand, 20mm interlectrode distance; MedPex®). A reference electrode was positioned in the spinous process of C7.

Electrodes were positioned parallel to the mid deltoid muscle fibers with optimal position of electrodes confirmed by manual muscle testing. Prior to electrode placement, the skin area was shaved if necessary and cleaned using an alcohol swab to reduce skin electrical impedance. Electrode's placement and skin preparation followed the European Recommendations for Surface ElectroMyoGraphy (SENIAM) (Hermens et al., 2000).

The sEMG and USI were synchronized and displayed in real time on the same screen by adapting the system's inbuilt electrocardiogram (ECG) input channel from the US device (Figure 2). On the ultrasound screen, a split image allowed to identify the abdominal muscle layers (Figure 2, left panel) and the raw sEMG signal, which appeared as a horizontal line (Figure 2, right panel). Ultrasound images were recorded at 9 MHz during the test and saved in video

format for later analysis. The onset of deltoid's muscle activity was visually identified by an elevation in the sEMG line due to voltage variations with muscle contraction, while the beginning of TrA activity was recognized by a blur in the muscle's image because of mechanical changes. The time difference between the start of activation of both muscles was measured and the mean values from each group (CLBP x Control) compared.

Muscle function

Muscle strength and performance were evaluated using grip-strength and gait speed following the proposed cut-off points established by the European Working Group on Sarcopenia in Older People updated (EWGSOP2) recommendations (Cruz-Jentoft et al., 2019). To measure muscle strength (handgrip) and physical performance we used a hydraulic handheld dynamometer (JAMAR®), and the four-meter walking test, respectively. These tests have been shown to be valid and reliable (Mijnarends et al., 2013).

Analysis

Means, standard deviations and frequency distribution were employed to describe demographic data and muscle related variables. Data distribution was analyzed through skewness/kurtosis and the Shapiro-Wilk test. As appropriate, parametric analyses to test for the difference between the CLBP and control groups were performed using the independent t-test, while the Mann-Whitney U test was chosen as the non-parametric approach. Activation of transversus abdominis and elastography behavior between groups were analyzed with the Mann-Whitney U test, whereas grip-strength and gait speed between-groups differences were tested with independent t-test. The relationship between sarcopenia parameters and LBP was investigated with

pairwise correlation. A significance level of 5% was chosen a priori. Statistical analysis was performed using Stata® version 13.0 (StataCorp LP, College Station, TX, USA).

Results

Sixty-one participants with a mean age of 71.47 years (range 60 to 86). Most participants were female (78.69%), no-smokers (91.8%) and did not have the habit of drinking alcohol. Table 1 shows baseline demographic data, sarcopenia parameters of deep abdominal muscle quality and muscle function from participants of LBP and control groups. There were no significant between-group differences in demographic characteristics (age, BMI, and sex).

No significant difference was found for the value of TrA's strain ratio ($p = 0.6$) between the two groups, whereas TrA activation was significantly delayed in the LBP group ($p=0.002$). Two independent t-test were run to determine if there were differences in grip strength and gait speed based on the presence or absence of CLBP. The results showed that participants presenting CLBP had statistically significantly lower grip strength compared to participants without CLBP (Mean Difference (MD) = 5.3 Kg, 95%CI = 1.5-9.0, $t(59) = 2.808$, $p = 0.006$). Participants with CLBP were also slower that participants without CLBP (MD = 0.21 m/s, 95%CI = 0.10-0.31, $t(58) = 4.020$, $p < 0.001$).

Analysis of correlation found a negative association between gait speed and TrA activation ($r = -0.36$, $p = 0.04$) among participants of the LBP group.

Discussion

This study compared sarcopenia parameters of deep abdominal muscle quality and function (muscle strength and gait speed) of older adults with and without CLBP. Our main findings were

that older adults with CLBP have delayed activation of TrA in response to upper limb displacement, lower grip strength and are slower than older adults free of back complaints.

Concerning the effects of CLBP on TrA activation, our results agree with those of previous studies that evaluated younger adults with CLBP. Ferreira et al. (2004) found changes in the automatic control of TrA in a group of subjects with LBP compared to a control group free of back symptoms. Although they investigated a sample of younger adults assessing TrA function through changes in muscle thickness from resting to an active test, their result combined with our findings suggest that alterations in TrA function is associated with LBP in both young and older adults. In addition, TrA function is impaired in older compared with young adults free of back pain (Davies et al., 2016). Furthermore, there is evidence showing that individuals with CLBP and poor ability of recruiting TrA tend to show a reduction in disability when engaged in a program of motor control exercise targeting lumbopelvic movements and stability (P. H. Ferreira et al., 2010). To our knowledge, our study is the first to show a delay in the activation of TrA in older adults with CLBP compared to controls in the same age strata. The alterations in muscle structure and function with aging that result in sarcopenia may contribute to an impairment in the activation of the TrA, possibly predisposing older adults to LBP.

We found that grip strength was reduced in the LBP group. Similar findings were observed in a survey with a matched sample of Korean adults with CLBP and others free of back symptoms (Park et al., 2018). The authors observed that low handgrip strength was associated with LBP, especially in women aged 50 years or older compared with men within the same age group (Park et al., 2018). In addition, a study with 95 older Malaysians (Ishak et al., 2016) found a relationship between back and abdominal muscle strength with grip strength in women presenting LBP. These

results suggest that grip strength could be used in clinical settings to estimate back and abdominal muscle strength, which is difficult to measure and require expensive tools (Cho et al., 2014).

We also found that older adults with CLPB are slower than their counterparts free of back symptoms. Decline in gait speed is observed in older adults (Jerome et al., 2015), and is associated with morbidity (Middleton et al., 2015) and mortality (Studenski et al., 2011). Several studies (Hicks et al., 2017; Kim et al., 2017; Reid et al., 2005) have investigated the association between LBP and gait speed showing results similar to ours. A prospective study with 659 older adults from the USA observed that participants who presented with restricting LBP at baseline became slower after a follow-up period of 18 months (Reid et al., 2005). Hicks et al. (2017) investigated a group of 54 older Americans with CLBP matched to a control group of 54 pain-free seniors and found that the CLBP group walked slower than their pain-free peers during self-selected pace and fast walking, as well as during stair ascent and stair descent. The authors also found that the CLBP group tended to walk with a wider base of support (Hicks et al., 2017). However, despite the existence of evidence showing an association between LBP and gait speed, all studies cited previously (Hicks et al., 2017; Reid et al., 2005) and including ours, followed an observational design preventing the establishment of a cause-effect relationship.

Grip strength and gait speed combined with muscle mass are markers used to diagnose sarcopenia, providing parameters for muscle strength, performance, and muscle quantity (Cruz-Jentoft et al., 2019).To our knowledge, there is only a single study that investigated the association between a sarcopenic marker and LBP (Hori et al., 2019a). Following a cross-sectional design, Hori et al. (2019a) conducted a multicenter study with older Japanese adults who were seen at one of 10 different spinal outpatient clinics. Data regarding pain intensity, disability, and quality of life

related to LBP were measured as well muscle mass revealing a relationship between reduction in muscle mass and LBP.

We did not find a significant difference between the CLBP and control groups for the elastography measurements of TrA. Since we used an ultrasound system that evaluates elastography by compression, it is possible that this may have led to a less sensitive measure, because the type of equipment can influence the results (Drakonaki et al., 2012). Considering that the TrA muscle is in the deep abdominal layer, a considerable force of compression would be necessary to assess TrA elasticity, causing discomfort to the participants. This is likely the main limitation of our study. We were not able to find any other study investigating TrA function through elastography, although passive and active stiffness of superficial and deep MF were assessed by Murillo et al. (2019) in a group with LBP and an asymptomatic control group. The findings of this study showed that LBP participants had higher passive muscular stiffness of the superficial MF and a lower strain ratio compared to the asymptomatic group.

Limitations

There are limitations to our study that need to be considered. The cross-sectional design does not establish a temporal relation between sarcopenic markers, TrA function and CLBP that prevents the assumption of causality. Additionally, we cannot guarantee whether the assessors responsible for evaluating sarcopenia parameters were unaware about the presence of back complaints among the participants despite the attempt of blinding.

Conclusion

This study provides novel information related to sarcopenia parameters and low back pain in older adults. A reduction in handgrip strength, gait speed, and a delay in the activation of

the TrA muscle were observed in the CLBP group. These alterations in muscle function may increase the risk of LBP chronicity in older adults. However, this study used a cross-sectional design, which does not allow to infer causality.

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Chapter Eight

How do we define and measure sarcopenia? Protocol for a systematic review

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Systematic Reviews

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How do we define and measure sarcopenia? Protocol for a systematic review

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Abstract

Background: The loss of muscle mass is a natural aging consequence. A reduction of muscle mass that surpasses the physiological rate is considered the key factor responsible for the development of a geriatric syndrome called sarcopenia. However, a new understanding of the importance of muscle quality over quantity is rising; as a result, different definitions for sarcopenia has been used. Due to the negative impact on elder's health and quality of life, the number of research investigating the causes, prevalence, and management of sarcopenia is increasing, although a consensus on sarcopenia definition is still missing. This systematic review will assess observational studies reporting the presence of sarcopenia aiming to verify how sarcopenia is defined, the diagnosis criteria, and the tools used for assessment. In addition, we will investigate the influence of the definition and diagnostic tools on the prevalence rate.

Methods: Keywords related to the condition, population, and type of study will be combined to build a search strategy for each of the following databases MEDLINE, EMBASE, CINAHL (*Cumulative Index to Nursing and Allied Health Literature*), Web of Science, and Google Scholar. Two independent reviewers will analyze the retrieved papers for eligibility and the methodological quality of eligible studies. The definition of sarcopenia and diagnostic tools used in each study and the prevalence estimates will be extracted. Descriptive statistics will be used to report the definitions of sarcopenia, diagnostic tools, and whether these influence or not, the prevalence rates.

Discussion: Sarcopenia is receiving greater attention in geriatrics research in recent years. Therefore, it is important to investigate how this condition is defined in the literature and whether these definitions can interfere with the reported estimates devoting more efforts on the topic. The results of this study can help to determine the most used definitions of sarcopenia reported in the literature, its strengths and limitations, and open a discussion about a need for a more valid, easy, and suitable one.

Systematic review registration: PROSPERO CRD42015020832

Keywords: Sarcopenia, Aging, Aged, Bias, Epidemiology

Background

Sarcopenia is a geriatric syndrome affecting older adults, which was firstly described by Rosenberg [1] as the loss of muscle mass in seniors. In addition to the loss of muscle mass [2, 3], aging is also accompanied by a reduction in muscle strength [4, 5] and decline in physical function [6, 7], which are combined to define sarcopenia according to a contemporary definition [8]. These alterations may be associated with changes in muscular quality [3, 9] due to the reduction in the size [10–12], number [10, 12], and contractility of the muscle fiber [13, 14], as well as fat tissue infiltration in the muscle [15, 16].

Prevalence of sarcopenia increases with age advance [17, 18]. However, it is not possible to rely on this estimates due to the lack of a universal definition of sarcopenia. Despite the effort from the European Working Group on Sarcopenia in Older People (EWGSOP) [8] to diagnose sarcopenia, results from two recent systematic

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reviews [19, 20] pooling the prevalence estimates for sarcopenia presented discrepant values of 10 and 29%, respectively. The difference in the results of these reviews seems to be due to the lack of similarity in defining sarcopenia.

A clear definition of sarcopenia is important since the number of publications on this syndrome is increasing [19, 21–24], and especially due to the fact that sarcopenia is associated with an increased risk for all-cause of mortality (OR = 3.64, 95% CI = 2.94 to 4.51) and functional decline (OR = 2.58, 95% CI = 1.33 to 4.99) [24], summed to a high economic cost [25]. Considering that older adults are a growing population group around the world [26], the burden due sarcopenia tends to be higher. The negative consequences resulted from sarcopenia have stimulated the development of studies about its prevalence [19, 20] and management [20]. However, to date, no study has comprehensively evaluated the definitions and tools used in the literature to define and determine the presence of sarcopenia.

The lack of a consensus on defining sarcopenia prevents estimating the prevalence and prognosis and comparing the effectiveness of interventions between clinical trials. The EWGSOP [8] was the first group attempting to provide a consensus definition for sarcopenia followed by the International Working Group on Sarcopenia (IWGS) [27], and by the Asian Working Group for Sarcopenia (AWGS) [28], respectively. These groups defined sarcopenia based on the appendicular muscle mass adjusted by the height squared, the handgrip strength, and/or gait speed presenting a certain variation from each other. Further, an initiative from the Foundation for the National Institutes of Health (FNIH) proposed that sarcopenia should be defined based on muscle mass adjusted by the body mass index (BMI) with cutoff values of (< 0.789 kg/m^2 men and < 0.512 kg/m^2 women) and grip strength (< 26 kg men and < 16 kg women) [29].

Although the definitions provided by the EWGSOP, IWGS, AWGS, and FNIH use different strategies and cutoff points to normalize and define loss of muscle mass, reduction in muscle strength, and low gait speed, the loss of muscle mass is considered the starting point for the development of sarcopenia. However, recent studies provided information that reduction in muscle quality surpass the loss of muscle mass and that the aging decline is respectively greater in muscle power, strength, and mass [30–32]. Furthermore, in a recent study, dos Santos et al. [33] observed that in a population of older adults (+ 90 years old), participants with low muscle mass had 1.65 (95% CI 1.27–2.31) increased odds for being at risk for losing physical independence and participants with low muscle force had 6.19 (95% CI 5.08–7.53) increased odds for being at risk of losing physical independence. As a result, new views on the criterion to define sarcopenia are emerging, not limiting sarcopenia to loss of muscle mass but, instead, as a loss of muscle strength due to alterations in the muscle quality related to the age advance [34]. Nevertheless, it is unclear whether these definitions are used in research reporting sarcopenia estimates and how they influence the results. Thus, the primary aim of this systematic review will be to identify how sarcopenia is defined and measured in the literature reporting its prevalence. Secondly, we will evaluate how different definitions can affect prevalence estimates.

Methods

Protocol and registration

This protocol is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P checklist) [35] according to the elaboration and explanation guideline [36]. The PRISMA-P checklist is included as an additional file [see Additional file 1]. This protocol is registered with PROSPERO no. CRD42015020832.

Selection criteria

All indexed observational population-based studies published, in which the prevalence of sarcopenia in community-dwelling older adults was reported, will be considered for review independent of the language of publication and publication date.

Exclusion criteria

We will exclude articles reporting on the prevalence of sarcopenia in participants with specific health issues (e.g., diabetes, cancer, and organ transplantation). Furthermore, we will not include articles written in languages other than English, French, or Portuguese, which could not be translated by the authors.

Search strategy

An electronic search will be conducted using the databases MEDLINE, EMBASE, CINAHL (*Cumulative Index to Nursing and Allied Health Literature*), Web of Science (Core Collection), and Google Scholar. A search strategy was built for each database (Appendix 1) using a combination of specific terms for (a) target population—"elderly," "older adults," "older people," "older person," and "community-dwelling;" (b) condition—"sarcopenia," "aging," and "muscular atrophy;" and (c) type of study—"prevalence," "incidence," "epidemiology," "cross-sectional," and "cohort studies." We will include studies that analyzed prevalence of sarcopenia published in peer-reviewed journals through February 2018.

Additionally, we will perform a comprehensive examination of reference lists from eligible studies. Data pertaining to individuals under 60 years old will not be considered.

BP, but a longer timeframe would be needed to examine its association with heart attacks.

The issue of timeframe is important to enable meaningful analysis of the relationships between exposures and outcomes to be conducted. This often requires at least several years, especially when looking at health outcomes, but it depends on the research question and outcomes being examined.

Cross-sectional analyses allow no time to see an effect, since the exposures and outcomes are assessed at the same time, so those would get a "no" response.

Question 8. Different levels of the exposure of interest

If the exposure can be defined as a range (examples: drug dosage, amount of physical activity, amount of sodium consumed), were multiple categories of that exposure assessed? (for example, for drugs: not on the medication, on a low dose, medium dose, high dose; for dietary sodium, higher than average US consumption, lower than recommended consumption, between the two). Sometimes discrete categories of exposure are not used, but instead exposures are measured as continuous variables (for example, mg/day of dietary sodium or BP values).

In any case, studying different levels of exposure (where possible) enables investigators to assess trends or dose-response relationships between exposures and outcomes—e.g., the higher the exposure, the greater the rate of the health outcome. The presence of trends or dose-response relationships lends credibility to the hypothesis of causality between exposure and outcome.

For some exposures, however, this question may not be applicable (e.g., the exposure may be a dichotomous variable like living in a rural setting versus an urban setting, or vaccinated/not vaccinated with a one-time vaccine). If there are only two possible exposures (yes/no), then this question should be given an "NA," and it should not count negatively towards the quality rating.

Question 9. Exposure measures and assessment

Were the exposure measures defined in detail? Were the tools or methods used to measure exposure accurate and reliable—for example, have they been validated or are they objective? This issue is important as it influences confidence in the reported exposures. When exposures are measured with less accuracy or validity, it is harder to see an association between exposure and outcome even if one exists. Also as important is whether the exposures were assessed in the same manner within groups and between groups; if not, bias may result.

For example, retrospective self-report of dietary salt intake is not as valid and reliable as prospectively using a standardized dietary log plus testing participants' urine for sodium content. Another example is measurement of BP, where there may be quite a difference between usual care, where clinicians measure BP however it is done in their practice setting (which can vary considerably), and use of trained BP assessors using standardized equipment (e.g., the same BP device which has been tested and calibrated) and a standardized protocol (e.g., patient is seated for 5 min with feet flat on the floor, BP is taken twice in each arm, and all four measurements are averaged). In each of these cases, the former would get a "no" and the latter a "yes."

Here is a final example that illustrates the point about why it is important to assess exposures consistently across all groups: If people with higher BP (exposed cohort) are seen by their providers more frequently than those without elevated BP (non-exposed group), it also increases the chances of detecting and documenting changes in health outcomes, including CVD-related events. Therefore, it may lead to the conclusion that higher BP leads to more CVD events. This may be true, but it could also be due to the fact that the subjects with higher BP were seen more often; thus, more CVD-related events were detected and documented simply because they had more encounters with the health care system. Thus, it could bias the results and lead to an erroneous conclusion.

Question 10. Repeated exposure assessment

Was the exposure for each person measured more than once during the course of the study period? Multiple measurements with the same result increase our confidence that the exposure status was correctly classified. Also, multiple measurements enable investigators to look at changes in exposure over time, for example, people who ate high dietary sodium throughout the follow-up period, compared to those who started out high then reduced their intake, compared to those who ate low sodium throughout. Once again, this may not be applicable in all cases. In many older studies, exposure was measured only at baseline. However, multiple exposure measurements do result in a stronger study design.

Question 11. Outcome measures

Were the outcomes defined in detail? Were the tools or methods for measuring outcomes accurate and reliable—for example, have they been validated or are they objective? This issue is important because it influences confidence in the validity of study results. Also important is whether the outcomes were assessed in the same manner within groups and between groups.

An example of an outcome measure that is objective, accurate, and reliable is death—the outcome measured with more accuracy than any other. But even with a measure as objective as death, there can be differences in the accuracy and reliability of how death was assessed by the investigators. Did they base it on an autopsy report, death certificate, death registry, or report from a

family member? Another example is a study of whether dietary fat intake is related to blood cholesterol level (cholesterol level being the outcome), and the cholesterol level is measured from fasting blood samples that are all sent to the same laboratory. These examples would get a "yes." An example of a "no" would be self-report by subjects that they had a heart attack, or self-report of how much they weigh (if body weight is the outcome of interest).

Similar to the example in Question 9, results may be biased if one group (e.g., people with high BP) is seen more frequently than another group (people with normal BP) because more frequent encounters with the health care system increase the chances of outcomes being detected and documented.

Question 12. Blinding of outcome assessors

Blinding means that outcome assessors did not know whether the participant was exposed or unexposed. It is also sometimes called "masking." The objective is to look for evidence in the article that the person(s) assessing the outcome(s) for the study (for example, examining medical records to determine the outcomes that occurred in the exposed and comparison groups) is masked to the exposure status of the participant. Sometimes the person measuring the exposure is the same person conducting the outcome assessment. In this case, the outcome assessor would most likely not be blinded to exposure status because they also took measurements of exposures. If so, make a note of that in the comments section.

As you assess this criterion, think about whether it is likely that the person(s) doing the outcome assessment would know (or be able to figure out) the exposure status of the study participants. If the answer is no, then blinding is adequate. An example of adequate blinding of the outcome assessors is to create a separate committee, whose members were not involved in the care of the patient and had no information about the study participants' exposure status. The committee would then be provided with copies of participants' medical records, which had been stripped of any potential exposure information or personally identifiable information. The committee would then review the records for prespecified outcomes according to the study protocol. If blinding was not possible, which is sometimes the case, mark "NA" and explain the potential for bias.

Question 13. Follow-up rate

Higher overall follow-up rates are always better than lower follow-up rates, even though higher rates are expected in shorter studies, whereas lower overall follow-up rates are often seen in studies of longer duration. Usually, an acceptable overall follow-up rate is considered 80% or more of participants whose exposures were measured at baseline. However, this is just a general guideline. For example, a 6-month cohort study examining the relationship between dietary sodium intake and BP level may have over 90% follow-up, but a 20-year cohort study examining effects of sodium intake on stroke may have only a 65% follow-up rate.

Question 14. Statistical analyses

Were key potential confounding variables measured and adjusted for, such as by statistical adjustment for baseline differences? Logistic regression or other regression methods are often used to account for the influence of variables not of interest.

This is a key issue in cohort studies, because statistical analyses need to control for potential confounders, in contrast to an RCT, where the randomization process controls for potential confounders. All key factors that may be associated both with the exposure of interest and the outcome—that are not of interest to the research question—should be controlled for in the analyses.

For example, in a study of the relationship between cardiorespiratory fitness and CVD events (heart attacks and strokes), the study should control for age, BP, blood cholesterol, and body weight, because all of these factors are associated both with low fitness and with CVD events. Well-done cohort studies control for multiple potential confounders.

Some general guidance for determining the overall quality rating of observational cohort and cross-sectional studies

The questions on the form are designed to help you focus on the key concepts for evaluating the internal validity of a study. They are not intended to create a list that you simply tally up to arrive at a summary judgment of quality.

Internal validity for cohort studies is the extent to which the results reported in the study can truly be attributed to the exposure being evaluated and not to flaws in the design or conduct of the study—in other words, the ability of the study to draw associative conclusions about the effects of the exposures being studied on outcomes. Any such flaws can increase the risk of bias.

Critical appraisal involves considering the risk of potential for selection bias, information bias, measurement bias, or confounding (the mixture of exposures that one cannot tease out from each other). Examples of confounding include co-interventions, differences at baseline in patient characteristics, and other issues throughout the questions above. High risk of bias translates to a rating of poor quality. Low risk of bias translates to a rating of good quality. (Thus, the greater the risk of bias, the lower the quality rating of the study).

In addition, the more attention in the study design to issues that can help determine whether there is a causal relationship between the exposure and outcome, the higher quality the study. These include exposures occurring prior to outcomes, evaluation of a dose-response gradient, accuracy of measurement of both exposure and outcome, sufficient timeframe to see an effect, and appropriate control for confounding—all concepts reflected in the tool.

Generally, when you evaluate a study, you will not see a "fatal flaw," but you will find some risk of bias. By focusing on the concepts underlying the questions in the quality assessment tool, you should ask yourself about the potential for bias in the study you are critically appraising. For any box where you check "no" you should ask, "What is the potential risk of bias resulting from this flaw in study design or execution?" That is, does this factor cause you to doubt the results that are reported in the study or doubt the ability of the study to accurately assess an association between exposure and outcome?

The best approach is to think about the questions in the tool and how each one tells you something about the potential for bias in a study. The more you familiarize yourself with the key concepts, the more comfortable you will be with critical appraisal. Examples of studies rated good, fair, and poor are useful, but each study must be assessed on its own based on the details that are reported and consideration of the concepts for minimizing bias.

Additional file

Additional file 1: PRISMA-P checklist. (DOCX 30 kb)

Abbreviations

AWGS: Asian Working Group for Sarcopenia; BMI: Body mass index; CINAHL: *Cumulative Index to Nursing and Allied Health Literature*; EWGSOP: European Working Group on Sarcopenia in Older People; FNIH: Foundation for the National Institutes of Health; IWGS: International Working Group on Sarcopenia; PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols

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Availability of data and materials

We will include all data generated or analyzed during the systematic review in the published article [and its supplementary information files]. In case the journal does not provide support to publish the supplementary files online, the datasets generated and/or analyzed during the systematic review will be available from the corresponding author on reasonable request.

Authors' contributions

PN is the guarantor of this review. All authors drafted the study protocol and contributed to the development of the selection criteria, the risk of bias assessment strategy, and data extraction criteria. PN developed the search strategy. SP provided epidemiology expertise, and MB provided expertise on aging. All authors read, provided feedback, and approved the final protocol.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Chapter Nine

How do we define and measure sarcopenia? A meta-analysis of observational studies

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SYSTEMATIC REVIEW

How do we define and measure sarcopenia? A meta-analysis of observational studies

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Abstract

Objective: this study aimed to investigate how sarcopenia has been defined and measured in the literature reporting its prevalence, and how different definitions and measurement tools can affect prevalence estimates.
Design: systematic review and meta-analysis.
Setting and participants: community-dwelling older people.
Methods: meta-analysis of data collected from observational studies. We performed an electronic search in five databases to identify studies reporting the prevalence of sarcopenia. We used descriptive statistics to present data pertaining sarcopenia definition and measurement tools, and the quality-effects model for meta-analysis of pooled prevalence.
Results: we found seven different operational definitions for sarcopenia and a variety of tools applied to assess the sarcopenic markers; muscle mass, muscle strength and physical performance. The prevalence of sarcopenia varied between the definitions with general estimates ranging from 5% based on the European Working Group on Sarcopenia in Older People (EWGSOP1) criterion to 17% with the International Working Group on Sarcopenia. According to the tool used to assess muscle mass, strength and physical performance, prevalence values also varied within definitions extending from 1 to 7%, 1 to 12% and 0 to 22%, respectively.
Conclusion and implications: the criteria used to define sarcopenia, as well as the measurement tools applied to assess sarcopenic markers have influence in the prevalence of sarcopenia. The establishment of a unique definition for sarcopenia, the use of methods that guarantee an accurate evaluation of muscle mass and the standardisation of measurement tools are necessary to allow a proper diagnosis and comparison of sarcopenia prevalence among populations.

Keywords: sarcopenia, older people, muscle atrophy, systematic review, meta-analysis, DXA scan

Key points

- The prevalence of sarcopenia varies with the criteria used to define it and the tools used to assess each sarcopenic marker.
- Standard methods to define and measure sarcopenia are necessary to obtain the real picture regarding the prevalence of sarcopenia.
- The tool used to assess muscle mass plays an important role in the prevalence value.
- Prevalence of sarcopenia in men and women depends on the sarcopenia definition.

Background

The definition of sarcopenia is evolving since Rosenberg [1] defined it as the loss of muscle mass from advancing age. The European Working Group on Sarcopenia in Older People (EWGSOP1) proposed a definition criterion that added to the loss of the of muscle strength combined with or without a decrease in muscle function [2]. On its update, the EWGSOP1 changed the key role from muscle mass towards muscle strength and proposed new cut-off points (EWGSOP2; [3]). Other groups, such as the International Working Group on Sarcopenia (IWGS; [4]), the Asian Working Group for Sarcopenia (AWGS1; [5]) and its update in 2019, the AWGS2 [6], have also established specific sarcopenia parameters for different populations. Although most study groups adjust muscle mass by height to diagnose sarcopenia, the Foundation for the National Institutes of Health (FNIH) adjusts muscle mass adjusted by the body mass index (BMI) [7]. Lately, in contrary to the previous definitions of sarcopenia that are based on experts opinion, an evidence based on Sarcopenia Definition and Outcomes Consortium (SDOC; [8]) emerged presenting cut-points for lean mass and muscle strength to define sarcopenia that vary with age, race/ethnicity, comorbid conditions and population.

The prevalence of sarcopenia in the general population is unclear and the results of systematic reviews present discrepant values ranging from 9.9 to 40.4% [9–11]. Even though all sarcopenia working groups base the determination of the presence of sarcopenia on appendicular muscle mass adjusted by height squared or BMI, handgrip strength and/or gait speed, there are differences between them. Until recently, all working groups on sarcopenia considered loss of muscle mass as the starting point for the development of sarcopenia, but this changed with the EWGSOP02, which proposes that reduced muscle strength is the key characteristic of sarcopenia, whereas muscle quantity and quality are used to confirm the diagnosis and severity [3]. The revised consensus is in line with the results of recent studies that have demonstrated a pronounced reduction in muscle quality compared with muscle mass [12–14]. Furthermore, recent evidence showed that the very old population (+90 years old) presenting low muscle force had 6.19 (95% CI 5.08–7.53) increased odds for being at risk of losing physical independence [15.]

As the number of older adults is growing worldwide [16], the prevalence of sarcopenia should follow this trend leading to an increase in mortality and morbidity [17,] and health related economic burden [18]. As a result, there is a recent concern to investigate the prevalence and management of sarcopenia [9–11]. However, the definition used in research reporting sarcopenia estimates varies across studies, and whether or how this influences prevalence results is unclear. To our knowledge, there is only one study that evaluated the prevalence of sarcopenia across different definitions and the impact of sex, age and measurement tools in the estimates as well [11]. No study has comprehensively evaluated the definitions and tools used in the literature to define sarcopenia and measure sarcopenic markers. We hypothesise that these variables are able to influence prevalence estimates as they change. The lack of a consensus on defining sarcopenia prevents estimating the prevalence, prognosis and assessing intervention effectiveness in trials. Thus, the primary aim of this systematic review is to identify the definitions and measurement tools/tests used to diagnose sarcopenia in observational studies reporting its prevalence in community-dwelling older adults. Second, we evaluated how different definitions can affect prevalence estimates.

Methods

Protocol and registration

This systematic review is reported following the tool for reporting meta-analysis of observational studies in epidemiology [19]. The protocol for the study was registered with PROSPERO no. CRD42015020832 and published elsewhere [20].

Search strategy and selection criteria

An electronic search was conducted using the databases Medline, EMBASE, CINAHL, Web of Science (Core Collection) and Google Scholar. A search strategy was built for each database (Appendix 1, supplementary data are available in *Age and Ageing* online) using a combination of specific terms for: (i) target population: 'elderly', 'elderly adults', 'elderly people', 'elderly person' and 'community-dwelling'; (ii) condition: 'sarcopenia', 'ageing' and 'muscular atrophy' and (iii) type of study: 'prevalence', 'incidence', 'epidemiology', 'cross-sectional' and 'cohort studies'. All indexed observational population-based studies published in peer-reviewed journals throughout December 2020 reporting prevalence of sarcopenia in community-dwelling older adults were considered for review independent of the publication date. Additionally, we performed a comprehensive examination of reference lists from eligible studies. Data pertaining to individuals under 60 years were not considered.

All retrieved papers were exported to a reference manager software (Endnote®), then independently examined by two researchers (PN and MB), through the readings of the title, abstract and full-text. In each stage, studies that did not fulfil eligibility criteria were excluded. Cases of disagreement between the two researchers were resolved by consensus.

Exclusion criteria

We excluded articles reporting on the prevalence of sarcopenia in participants with specific health issues (e.g. diabetes, cancer, organ transplantation, HIV, etc.). Furthermore, we did not include articles written in languages other than English, French or Portuguese, which could not be translated by the authors.

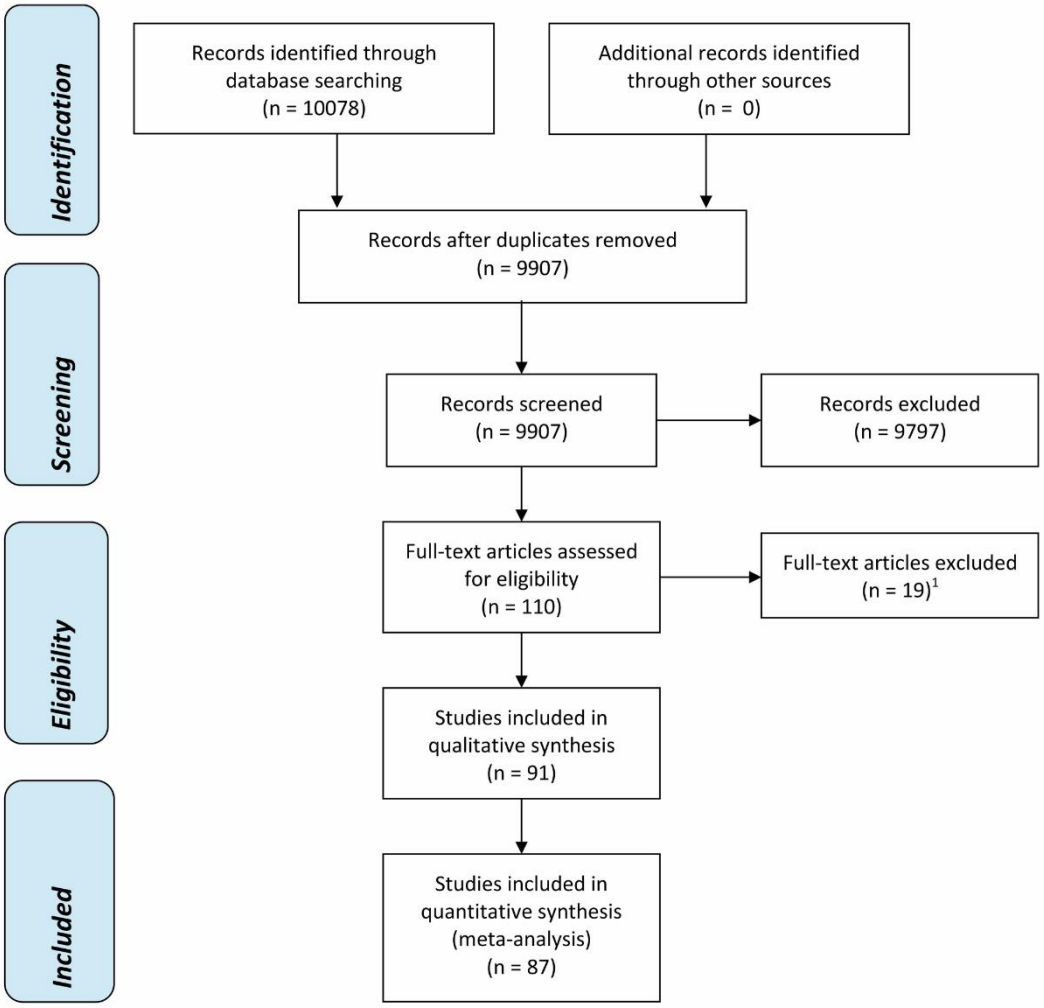

Figure 1. Flow diagram for study selection. Reasons for exclusion: $n = 7$ (no community based sample), $n = 3$ (duplicate dataset analysis), $n = 7$ (sample < 60 years old), $n = 1$ (specific site sarcopenia) and $n = 1$ (language other than English, French or Portuguese).

Quality appraisal

Two independent researchers (PN and MB) assessed the risk of bias of each eligible study, whereas one author (PN) was responsible to extract the information from the articles (Appendix 2, supplementary data are available in *Age and Ageing* online).

Results

The search strategy retrieved 10,078 articles, 171 of which were duplicates. After the screening process (titles, abstracts and full text reading), 91 studies (with a population of 116,848 individuals and samples varying from 70 to 12,592 participants) met the inclusion criteria, whereas 87 were included in the meta-analysis. Figure 1 shows the flow diagram of this review.

The definition of sarcopenia varied across seven different operational criteria, namely the EWGSOP1, EWGSOP2, AWGS1, AWGS2, IWGS, FNIH and a criterion based on muscle mass alone (MM). Excepting eight studies [23–30] that defined sarcopenia using the EWGSOP2, all eligible studies described loss of muscle mass as the key point to diagnose sarcopenia. Twelve studies [23, 26, 29–38] reported

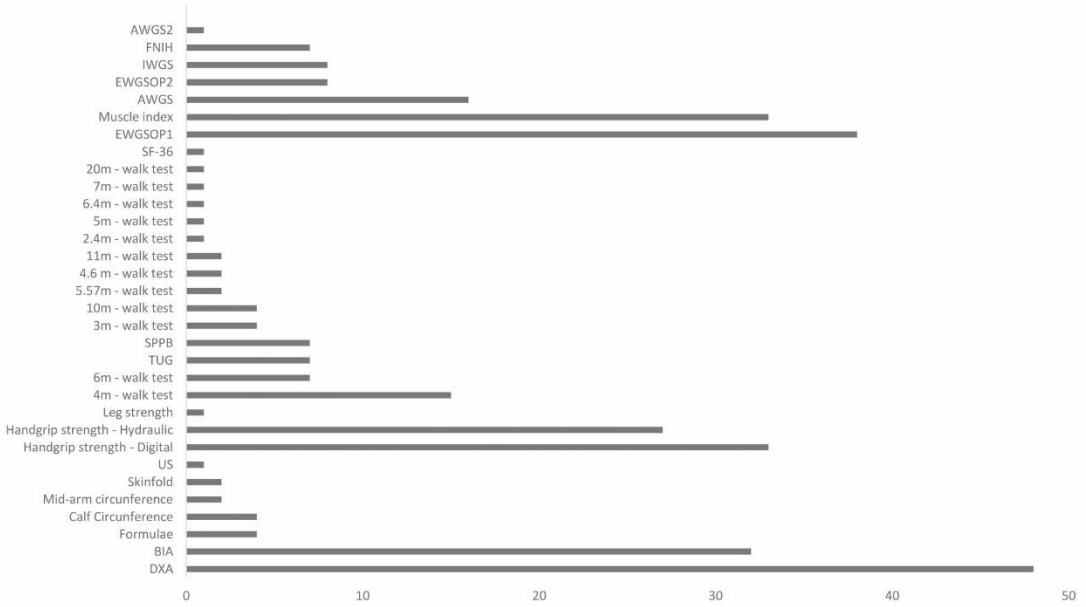

Figure 2. Number of studies per sarcopenia definition and measurement tool.

Table 2. General Sarcopenia Prevalence Stratified by definition

Definition Criteria	Number of Studies*	Participants	Prevalence (%)	95% CI	Heterogeneity	Forest Plot (%)
Muscle Mass	24	25,305	12	7.0–17.0	98% ($p < 0.001$)	
EWGSOP1	31	36,811	11	7.0–14.0	98% ($p < 0.001$)	
EWGSOP2	4	6,624	5	1.0–10	98% ($p < 0.001$)	
AWGS	13	17,070	8	3.0–15.0	99% ($p < 0.001$)	
IWGS	5	6,993	17	11.0–23.0	95% ($p < 0.001$)	
FNIH	5	13,338	15	5.0–28.0	100% ($p < 0.001$)	

*Some studies used more than one definition criteria; due to this reason, the number of studies in the table exceeds the total number of studies in the text.

the prevalence through more than one definition. Prevalence of sarcopenia was mainly investigated using the EWGSOP1 definition (38 studies; [23, 26, 30–36, 39–67]), followed by the MM (34 studies; [68–101]), AWGS (16 studies; [26, 31, 34, 37, 38, 63, 102–111]), IWGS (8 studies; [26, 29, 33–37, 112]), FNHI (7 studies; [26, 29, 31–33, 37, 97]), AWGS2 (1 study; [38]; Figure 2.)

Seventy one studies [24, 26, 29–32, 34–40, 42, 43, 45–55, 57–59, 61–67, 69, 72–77, 79–85, 87, 89, 91–95, 97, 99, 101–104, 106, 108, 110–114] reported the prevalence of sarcopenia for men and women separately. Twelve studies only reported grouped values for men and women [27, 28, 36, 45, 62, 64, 74, 102, 107, 109, 112, 114], 7 studies were exclusively focused in the prevalence in women [41, 44, 71, 78, 86, 88, 90] and 6 targeted only men [23, 25, 33, 56, 68, 98]. Table 1 (Appendix 3—supplementary data are available in *Age and Ageing* online—presents a summary description of all eligible studies).

The type of the screening tools used to assess sarcopenic markers varied across the studies (Figure 2). Among the seven different measurement tools used to quantify muscle mass, the preference was for DXA (48 studies) and BIA (33 studies). Grip strength was the main test applied to investigate muscle strength using either a digital (33 studies) or hydraulic (27 studies) handheld dynamometer. Although gait speed was the main test applied to assess physical performance, the course length was heterogeneous, with 12 different distances varying from 2 to 20 m.

Summary of prevalence estimates

General prevalence

The general prevalence of sarcopenia was assessed in 68 studies [24, 26–28, 31, 32, 34–37, 39, 40, 42, 43, 45–55, 57–59, 61–64, 67, 69, 72–77, 79–85, 87, 91–95, 97, 99, 101–104, 106, 107, 109–115] generating 82 estimates that varied from 0% [69, 72] to 32.1% [31]. Data extracted from these studies were pooled in a meta-analysis revealing a general pooled prevalence of 11%. However, we cannot rely on this estimate, due to its high heterogeneity. A subgroup analysis by criteria used to define sarcopenia showed the highest prevalence value when using the IWGS and FNHI criteria

(17 and 15%, respectively), followed by the definition based on muscle mass alone (12%), EWGSOP1 (11%), AWGS (8%) and the EWGSOP2 (5%; Table 2). Nevertheless, the subgroup analysis was not able to explain such heterogeneity.

Impact of measurement tools on sarcopenia prevalence

The high heterogeneity observed in the studies that fulfilled eligibility criteria prevented a pooled analysis based on the same definition and measurement tools to assess all sarcopenic markers (muscle mass, muscle strength and physical performance) at once. Thus, we evaluated the impact of the measurement tools used to assess each sarcopenic marker separately in each definition of sarcopenia, generating a high number of estimates. To present the prevalence variability because of measurement tools we calculated the difference between the minimum and maximum estimates Table 3 (Appendix 4, supplementary data are available in *Age and Ageing* online).

Muscle mass measurement tool

General prevalence of sarcopenia varied differently according to the tool used to measure muscle mass among its operational definitions. When comparing the estimates between DXA, BIA and other tools, the difference ranged from 1 (EWGSOP2, IWGS and FNIH) to 7% (AWGS and MM). In general, estimates derived from studies that used BIA equipment found higher values regardless the sarcopenia definition.

We found a variability among measurement tools for sex-specific prevalence with estimates ranging from 0 (FNIH) to 19% (EWGSOP2) in men, and 2 (FNIH) to 23% (IWGS) in women.

Muscle strength measurement tool

General prevalence of sarcopenia varied from 1 (EWGSOP1) to 12% (IWGS), based on the type of handheld dynamometer used to assess muscle strength. Measurements taken with the HHHD resulted in high prevalence in the EWGSOP2, IWGS and FNIH definitions, whereas estimates derived from DHHD were higher, when the EWGSOP1 and AWGS definitions were applied.

A prevalence variability of 1% between the types of handheld dynamometer was found when men were compared with women, independently of the sarcopenia definition.

Physical performance measurement tool

The different set of tools used to assess physical performance generated heterogeneous prevalence values from 0 to 22% based on the results of SF-36 questionnaire and 10-m walking test, respectively. The 4 and 6-m walking tests were the most frequent strategies used to assess physical performance. Sarcopenia prevalence reported by studies that used the 4-m walking test ranged from 5 (EWGSOP2) to 17% (AWGS), whereas estimates generated based on the 6-m walking test varied from 4 (EWGSOP2) to 14% (EWGSOP1). On the other hand, when the prevalence between men and women was compared, the difference of the results taken from 4 or 6-m walking tests were similar for all definitions of sarcopenia.

Risk of bias

The number of unmet criteria in the eligible studies ranged from 0 to 5 out of a possible 10, whereas the average of met criteria was 7.6. The number of studies presenting low or moderate risk of bias were similar ($n = 44$ studies) and ($n = 46$ studies), respectively, whereas only 1 (one) study [81] presented a high risk of bias. A greater risk of bias was found in criteria related to external validity. Nine studies investigated a sample that was representative of the national population [24, 26, 28–30, 38, 107, 109, 110], whereas a close or true representation of the target population was assessed in 35 studies [23, 24, 26, 28–30, 33, 38, 41, 46, 59, 61, 64–66, 68, 71–74, 79, 80, 87–90, 94, 97, 99, 102, 107, 109, 110, 112, 114]. Furthermore, 28 studies [24, 31, 33–36, 39, 41, 47, 49, 50, 55, 58, 59, 64, 71–74, 79, 80, 85, 89, 94, 97, 99, 104, 114] used some form of random system to select the sample. The items referring to internal validity, specifically of sarcopenia definition, and reliability and validity of assessment tools were not completed in 8 [54, 69, 81, 84, 85, 87, 90, 97] and 2 studies [81, 107], respectively. Table 4 (Appendix 5, supplementary data are available in *Age and Ageing* online) shows the criteria for evaluating risk of bias in each study.

Discussion

Seven different definitions for sarcopenia were found and the choice was in general based on the targeted population. Most studies were from countries in Asia, Europe and America, whilst the EWGSOP1, MM and AWGS were the most frequent definitions.

We found a general pooled prevalence of sarcopenia of 11%, which, when stratified by criteria definition, presented higher estimates with the IWGS (17%) followed by the FNHI (15%), reduction of muscle mass alone (12%), EWGSOP1 (11%), AWGS (9%) and EWGSOP2 (5%). These results were expected due to different criteria and cut-off points employed in each definition and that was also observed in a recent systematic review [11]. In this review, estimates from the definition based only on muscle mass retrieved the highest prevalence of sarcopenia (40.4%) and the IWGS criterion brought the lowest prevalence (9.9%) whilst values from FNIH (18,6%), EWGSOP/AWGS (12.9%) were similar to our results. In addition, when comparing FNIH, EWGSOP1 and IWGS definitions, Dam and Peters [116] observed a low agreement among these criteria in identifying sarcopenia. Moreover, in a study investigating the prevalence of sarcopenia based on different criteria definition, Bijlsma and Meskers [76] found divergent estimates of prevalence, where only one out 654 participants was identified as having sarcopenia through the seven criteria used to diagnose sarcopenia.

The type of tool used to measure muscle mass contributed for different prevalence of sarcopenia. Independently of the criteria definition used for sarcopenia, the prevalence was higher when using BIA to measure muscle mass. In a recent systematic review, Mayhew and Amog [11] also observed high prevalence for BIA derived estimates although independent values were not reported. On the other hand, Beaudart and Reginster [62] found high values of prevalence with estimates derived from DXA compared with BIA in a study measuring sarcopenia using different tools for assessing muscle mass and muscle strength. The existence of previous work with low rates of sarcopenia when using BIA is not a surprise due to the fact that BIA is known to overestimate muscle mass compared with DXA [117, 118], consequently, estimates of sarcopenia using BIA to assess muscle quantity should be analysed with caution once is expected the occurrence of more false negative results. The variability of prevalence with muscle mass measurement tool was not unexpected because the tools used in the eligible studies allowed to measure approximations of muscle mass as the lean body mass or fat free mass [119]. Thus, it is necessary to overcome barriers and stimulate the application of methods with adequate sensibility to quantify muscle mass, as the 3-D creatine dilution, generating reliable results and comparison [120.]

We found that the pooled sex-specific prevalence of sarcopenia also varied through the different criteria definition. Its prevalence in men varied from 3 (EWGSOP2) to 15% (MM), whereas estimates from women ranged from 2 (EWGSOP2) to 10% (EWGSOP1). Excepting the prevalence estimates based on the MM criteria that presented a higher difference in prevalence in men (15%) compared with women (9%), sarcopenia prevalence between both genders was similar. The current literature has shown that sex-specific prevalence of sarcopenia varied across studies [9, 76, 122, 123]. Results from a systematic review on the prevalence of sarcopenia showed similar prevalence (13%) for men and women [9], whereas there are reports showing prevalence variations between sexes based on sample ethnicities and criteria for diagnosis [11, 122, 124].

The subgroup analyses of the sex-specific prevalence based on the tool used to assess muscle mass showed a higher variability between estimates derived from DXA, BIA or other simplest methods. The highest differences were observed in the EWGSOP2 (19%) and MM (12%) definitions in men and the IWGS (23%) in women. The fact that the difference in prevalence of sarcopenia based on sex can vary according to the measurement tool used to estimate muscle mass is a novel finding. We hypothesise that this sex by measurement tool interaction perhaps occurs due to a combination of different factors as the large number of elements that can affect the reliability of each measurement tool, the sex-specific changes with ageing and the methods that applied in the studies included in our review. For example, estimates of muscle mass differ according to the characteristics of the BIA device, assessor ability, subject related factors and environmental conditions [125.]

When studies based on the tool used to assess muscle strength were grouped, we found that prevalence values varied in each sarcopenia definition, based on the type of dynamometer (i.e. hydraulic or digital) used to measure muscle strength. Despite the high heterogeneity observed in prevalence values for the general population, the variability between men and women was low.

The difference in the prevalence values, when pooling studies by muscle strength, can be explained by a series of factors other than the equipment [126, 127], as the hand used to test [128], posture [129] and joint position [129, 130]. There are standardised protocols that provide recommendations for the posture of the participant during the handgrip strength test, upper limb joints position, type of device and even the position for lower limbs [131], as those from the American Society of Hand Therapy (ASHT; [132]) and the Southampton protocol [131]. However, we observed that most studies neither mentioned the protocol used in the measurement of HGS, nor included a full description of it. Consequently, the high heterogeneity between the protocols prevented a proper comparison among the studies.

A broad diversity of strategies were used to assess physical performance generating a wide variety of prevalence estimates. We found that the 4 and 6-m walking tests were the most constant, with a variability of up to 9% between them for a same definition of sarcopenia.

The lack of uniformity among the measurement tests of gait speed is not an exceptional finding from our study. Results from a systematic review about this criterion [133] also found that summed with the 10-m course, walking 6 and 4 m was the most common used distances. Graham and Ostir [133] reported that common methodological factors might influence the clinical interpretation of gait performances and that there is no consensus regarding the optimal measurement protocol including walking distance, instructed pace and start mode. Although the walking distance is slightly related to the mean velocity in older adults, the choice of different lengths provides some confusion about the optimal method to assess gait speed. On the other hand, pace velocity and whether the test begins from a static position or in a dynamic way seem to be relevant for achieved results [134]. Furthermore, the act of providing verbal encouragement during the walking test may influence the results [135]. Additional investigations are needed to determine the influence of walk testing methods in performance results.

In our protocol published elsewhere [20], we call attention to the existence of new views concerning criteria used to define sarcopenia based on loss of muscle strength due to alterations in muscle quality instead of focusing on loss of muscle mass. The EWGSOP2 [3] changed the main marker to diagnose sarcopenia from low muscle mass to reduction in muscle strength. This criterion also became more restrictive, decreasing the cut-off for grip strength from 30 to 27 Kg in men and 20 to 16 Kg in women although the recommendation for BMI adjusted values was removed. In the update, the authors also decreased the cut-off for muscle

quantity in men when using the appendicular skeletal muscle mass (ASM) adjusted by squared height (ASM/h^2) to <7.0 Kg/m^2 and included a cut-off for crude ASM of <20 Kg for men and <16 Kg for women. In addition, another option to assess muscle strength inserted in the recommendation was the chair stand test, with a cut-off >15 s for five rises [3.]

Despite recent efforts, such as the update to the EGWSOP02 [136] and the development of the SDOC [8], we believe that the problem will be only partially solved. As we stated before [20] the movement towards changing the focus from muscle mass to muscle strength is significant and primordial for the diagnosis of sarcopenia. Beyond that, in our view, the problem that remains rest specifically in the definition of what is a reduction in muscle strength, loss of muscle mass and performance. We believe that cut-off points for muscle strength and quality should be adjusted for BMI considering the weight and height of the participants, which can influence muscle power and performance, especially in women [137, 138]. In addition, we believe that setting a unique cut-off for performance tests could underestimate low performance among women since they tend to be slower than men at every age with marked differences after the age of 55 [139]. Moreover, studies aiming to set cut-off values for muscle mass in a sample at least representative of the target population and using young subjects to provide reference values are in need. Such studies need to be developed where the methods applied will provide not only internal validity, but also guarantee external validity for generalizability [140] and the use of measurement tools to prevent measurement errors that can distort the results and decrease reproducibility [141.]

As most studies, this study is subject to limitations. In our opinion, the main flaw of this study was the restriction to studies written in English, French or Portuguese, which could prevent the inclusion of some studies. However, currently, indexed papers have the abstract published in English, allowing us to perform the eligibility screening based at least on title and abstract. As a result, a single study with 229 participants was excluded due to the language of the publication.

Conclusion and recommendations

The criteria used to define sarcopenia varied, usually according to the targeted population. Sarcopenia definition, as well the tools used to estimate each sarcopenic marker have an effect on prevalence. The measurement of muscle mass and performance provided the highest discrepancy on prevalence estimates.

Future efforts must focus on finding a single definition of sarcopenia. In addition, its urge the need to standardise the measurement tools used to assess sarcopenic markers. Furthermore, it is necessary guarantee that muscle mass is in fact assessed, as well as to establish a clear strategy to normalise its data. Only after solving these issues, we can estimate the prevalence of sarcopenia properly, allowing the comparison among different populations and the recognition of its burden in older people.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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Part III

Chapter Ten

Discussion

10.1 Participation of older adults in clinical trials

Chapter four of this thesis showed that approximatelly 50% of all clinical trials for LBP registered in the WHO clinical trial registry database from 2015 to 2018 were allowing the participation of older adults, whereas older adults were the targeted population only in about 3% of those. The restriction in the participation of older adults in clinical trials seems to be a frequent flaw among diverse disciplines in the health related field (Cherubini et al., 2011; Cruz-Jentoft et al., 2013; Zulman et al., 2011). Exclusion of older adults as clinical trial participants is higly problematic, because age-related diseases account for approximatelly 51.3% of all global burden (A. Y. Chang et al., 2019), while symptoms such as LBP ranks at the top of the disability burden (Hoy et al., 2014).

As observed in the survey presented in chapter four, researchers recognise that older adults are under-represented and age-based exclusion is not justified. As a consequence, older adults are probably receiving less evidence-based treatments than their younger counterparts. There is evidence that older adults are more prone to receive pharmacological treatments for LBP (Macfarlane et al., 2012). However, the effectiveness of these interventions is not supported by current evidence and their harm may surpass their benefits (Maher et al., 2016). In addition, despite the statement from the FDA that patients included in clinical studies should reflect the population that will receive the drug when it is marketed, older adults have been excluded from studies investigating the effectiveness of pharmacological drugs that are frequently prescribed for them (Konrat et al., 2012).

Chapter five also revealed that, at the present time, researchers seem to be more prone to include older adults in their investigations, as well as in developing studies specifically for

this population. According to the results of chapter five, the high number of comorbidities, high medication intake, a reduced level of physical and cognitive abilities usually observed in older adults may justify their exclusion from RCTs. In addition, the survey respondents pointed out that studies targeting specific populations (e.g., athletes, members of the military forces, working populations, and so on) have clear reasons to exclude older participants. As life expectancy is getting higher, leading to an associated economic and health burden due to the aging population, the engagement of older adults in RCTs becomes a matter of urgent necessity. Herrera et al. (2010) provided some recommendations for inclusion of older adults based on the process of proper recruitment ensuring equal enrollment, retention by minimizing drop-out rates, and return including a posttrial environment where those involved in the trial (i.e., researchers, sponsors, and pharmaceutical companies) interact with the community to provide accountability and tangible benefits. Furthermore, there is a claim that ethical committees have the power to reduce the ageist behavior in research by requesting a reasonable justification whenever protocols impose an arbitrary upper-age limit for recruitment (Bayer & Tadd, 2000). Also, the existence of targeted federal funding encouraging clinical trials specific to older individuals (Denson & Mahipal, 2014) is another strategy to consider. Thus, the inclusion of a representative number of subjects in clinical trials on the basis of age is vital to provide trustfull knowledge in the safety and efficacy of treatments that are generalizable to seniors.

10.2 Definition and measurement of sarcopenia

Chapter nine showed that the general prevalence of sarcopenia is about 11%, although estimates vary with the different definitions. Results from previous systematic reviews showed prevalence values can be as low as 1%, but reaching a value of 40.4% in community

dwelling older adults (Cruz-Jentoft et al., 2014; Mayhew et al., 2019). The difference across the different definitions is a matter of concern as estimates of sarcopenia are different even whithin a same sample when examined with more than one definition for sarcopenia. Cruz-Jentoft et al. (2014) performed the first systematic review on the subject of sarcopenia following the EWGSOP definition and found a great variation in the reported estimates across the studies, thus preventing the pooling of these estimates into a single value. Even before the publication of the systematic review by Cruz-Jentoft et al. (2014), the concordance between the definition criteria for sarcopenia was a subject of interest and revealed that the agreement between the FNIH, IWGS and EWGSOP was low for men (7% to 32%) and women (5% to 19%), although the percentage of agreement between them to rule out sarcopenia was very high (95%) (Dam et al., 2014).

Different prevalence values of sarcopenia were also observed in chapter nine when using different measurement tools to assess muscle mass in the same population with the same definition and even within the same sex. The influence of the tool(s) used to assess muscle mass in the prevalence was previously reported by Shafiee et al. (2017) who found higher estimates of sarcopenia prevalence when using BIA (13%) to measure muscle mass compared to DXA (8%). These discrepancies are not unexpected due to the lack of a gold standard tool for measuring muscle mass, compounded by the fact that each technique has limitations and a shortage of information regarding accuracy. However, DXA has recently been recommended as a reference standard in the measurement of muscle mass (Buckinx et al., 2018). Because of the shift in the diagnosis of sarcopenia towards muscle strength (versus muscle mass alone) proposed with the EWGSOP2 (Cruz-Jentoft et al., 2019), the impact of the tools used to quantify muscle mass in estimating the prevalence of sarcopenia may be

reduced because with this definition, muscle mass plays a lesser role. However, new concerns may arise with regards to the occurrence of the same problem with measurements of muscle strength, since there is evidence showing that different equipments, positions, and handle interfaces introduce variability in the assessment of grip strength (Beaudart et al., 2015; Lucado et al., 2019).

Chapter nine also revealed high variability in the prevalence of sarcopenia when stratifying by the muscle performance measurement tool. Although most studies used gait speed to assess muscle performance, the distance used for the test varied significantly, ranging from 2.4 to 20 m. This finding reflects the results of a systematic review aiming to describe the assessment of gait speed in clinical research (Graham, Ostir, Fisher, et al., 2008). Graham, Ostir, Fisher, et al. (2008) found that instructed pace (i.e., usual, fast or not reported), start protocol (i.e., static, static (turn), dynamic, not reported), and distance (i.e., 2-400 m) for walking tests vary widely between studies, which creates a barrier for comparison. Although the same research group found that only intended pace significantly impacted the mean gait speed in older adults, the authors recognized that walking test procedures (i.e., pace, start and distance) may influence the interpretation of physical performance (Graham, Ostir, Kuo, et al., 2008).

Another finding of chapter nine was that the sex-specific prevalence of sarcopenia varied according to the definition used. The study of the influence of sex on sarcopenia prevalence has shown contraditory results, with reports of no difference between men and women (Shafiee et al., 2017), a higher prevalence in women than men (Cruz-Jentoft et al., 2014; Volpato et al., 2014), greater values in men than women (Du et al., 2019; Kim et al., 2016),

as well as a shift in the higher value between men and women with different ages (Kirchengast & Huber, 2009). There is evidence showing that physical activity can provide a protective effect against sarcopenia (Buckinx et al., 2018; Marzetti et al., 2017; Yoshimura et al., 2017), and previous research has shown that men are more physically active than women (Bennett et al., 2017; Guthold et al., 2018; Sun et al., 2013), which could lead to lower prevalence of sarcopenia in men. However, the results of the chapter nine do not allow to differentiate the prevalence estimates between men and women because the lack of agreement among the different definition criterion for sarcopenia,. Thereby, the indentification of sex-specific risk factors for sarcopenia is dificult because the variability of the estimates seems to rely mainly in the definition of sarcopenia.

10.3 Association between sarcopenia and low back pain

Chapter six showed that low muscle mass (i.e., pre-sarcopenia) as defined by the IWGS as well as the combination of low muscle mass plus a reduction in grip strength (i.e., sarcopenia) as defined by the FNIH criterion were more prevalent in subjects with LBP. Results from a recent systematic review showed that reduction in the cross-sectional area of deep paraspinal muscle (i.e., multifidus) is a recurrent finding in people with LBP (Ranger et al., 2017). The same research group followed 588 subjects with LBP for one-year and found that muscle CSA was negatively associated with LBP disability but not pain intensity (Ranger et al., 2019). However, these findings typically represent observations from middle-aged adults. In a previous review assessing the role of abdominal and paraspinal muscles on physical function in older adults, Cuellar et al. (2017) found that rectus abdominus (RA), internal oblique (OI) and external oblique (OE) muscle CSA was decreased by 36% to 48% in older compared to young adults. This review also found that older adults with low muscle quality

determined by the accumulation of intramuscular fat had worse LBP symptoms as well as decreased physical function assessed by a lower extremity performance battery, including time to complete five chair stands, timed standing balance (semi-tandem, full-tandem, and single-leg stands), timed usual pace 6-m and narrow 6-m walking test. These results are similar to those found by Shahtahmassebi et al. (2017), who investigated the associations between functional ability (i.e., 6-minute walk test, 30-second chair stand test, sitting and rising test, balance and TUG) and trunk muscle strength (isokinetic) and morphology of RA, OI and OE assessed with USI. When performing a multivariate analysis controlling for age and BMI, Shahtahmassebi et al. (2017) found an association between trunk strength and rectus abdominis morphology with better performance in the sitting and rising test. Moreover, when examining older adults with and without CLBP, Sions et al. (2017) found that older adults with CLBP have more MF intramuscular fat infiltration and small CSA of the ES. However, the existing evidence is from cross-sectional or case-control studies preventing the establishment of a firm conclusion on causality. Our results are comparable with the previous evidence presented above. Although we used grip strength to register muscle strength and the ratio of appendicular muscle mass/height or appendicular muscle mass/BMI to evaluate muscle quantity, we found an association between LBP with muscle strength and quantity, whether isolated or combined.

To date, the evidence about the relationship between sarcopenia and LBP comes from cross-sectional studies that classify the participants as having sarcopenia or LBP and further investigate their concomitant (Iwahashi et al., 2022; Yoshihito Sakai et al., 2017; Seo & Kim, 2019; Shahtahmassebi et al., 2017; Sions et al., 2017). Independently, of whether sarcopenia leads to LBP or vice-versa, health professionals dealing with these participants

must intervene to prevent or treat sarcopenia because it is a major risk factor for loss of independence (L. Dos Santos et al., 2017) and a predictor of mortality among older adults (Kim et al., 2014; Yang et al., 2017).

Another finding from chapter six was that the odds of having LBP was higher in subjects with sarcopenia according to the FNIH and amongst those with more comorbidities and depressive symptoms. As life expectancy is growing, accompanied by an increase in the prevalence and burden of sarcopenia and LBP in older adults, the association between sarcopenia and LBP is starting to receive some attention among researchers (Chen et al., 2020; Skorupska, 2018). S. A.-O. Tanishima et al. (2017) assessed a sample of 216 Japanese men and women aged 40 years and older for the presence of LBP, disability related to LBP and sarcopenia following the AWGS definition and found that LBP disability was higher in the group classified as sarcopenic compared to the pre-sarcopenia and healthy groups. In another study with a sample from Japan, (Y. Sakai et al., 2017) compared the cross-sectional area of the lumbar MF and the ES muscles, and sarcopenic status based on a reduction in skeletal muscle mass index (i.e., appendicular lean mass divided by height squared) in subjects with and without CLBP. The authors found that the squeletal muscle index, and cross-sectional area of the MF and of the ES muscles were reduced in the CLBP group compared with the group without CLBP. Furthermore, sarcopenia has been shown to be associated with other spine problems, such as degenerative lumbar scoliosis (Eguchi et al., 2017a). However, these investigations used cross-sectional design, preventing the assupntion of a causal association.

The influence of comorbidities and depressive symptoms on the odds of having LBP as shown in chapter six reinforces the fact that LBP is a multifactorial symptom that can be associated with different diseases (Maher et al., 2016). This result is supported by data from a prospective cohort study with 7523 Norwegian adults presenting with CLBP wich revealed that during a folow-up period of eleven months the probability of recovering from LBP symptoms was lower as the number of pain sites increased and depressive symptoms were present (Nordstoga et al., 2017). In addition, results from a case-control study showed that participants who presented with LBP had a high number of comorbidities in the year before the onset of LBP (OR 1.39, 95% CI 1.20-1.61; $p < 0.001$) compared to the control group without LBP (Ramond-Roquin et al., 2015). Similarly, a cohort study with older men from Australia demonstrated that each additional commordidity was able to increase the odds of developing LBP (OR = 1.17, 95% CI 1.01-1.37; $p = 0.05$) (Parreira et al., 2017). Furthermore, there is evidence that middle-aged adults with LBP are more likely to become long-term users of care for LBP as the number of comorbidities increases (OR: 1.53, 95% CI 1.50-1.57) (Rundell et al., 2017). Likewise, the presence of comorbidities was shown to be associated with patients receiving a poor care for LBP (Ramanathan et al., 2018).

The association between depression and depressive symptoms with LBP is a usual finding (Pinheiro et al., 2016; Pinheiro et al., 2015). Results from a systematic review investigating longitudinal studies that evaluated adults presenting LBP for less than 12 weeks showed that participants that had depression at baseline experienced worse LBP intensity, disability, quality of life, patient satisfaction, return to work and developed chronic LBP (Pinheiro et al., 2016). In addition, when summarizing the results of cohort studies with populations free of LBP, the same research group found that symptoms of depression increased the risk of

developing new or recurrent episodes of LBP (OR = 1.59, 95%CI 1.26 to 2.01), with a higher risk among participants presenting severe depressive symptom (OR = 2.51, 95%CI 1.58 to 3.99). In another systematic review, Wong et al. (2021) found that not only depression but also the presence of comorbidities and weak abdominal muscles, among other factors, are associated with an increased prevalence of CLBP in older adults. When investigating a sample of 164 older Australians with LBP, Ramanathan et al. (2018) found that about 62% of the individuals had at least one other comorbidity from a list of 17 comorbidities documented. Furthermore, a longitudinal study investigating the influence of comorbidities on the course and prevalence of LBP found that every additional comorbitdity increased the risk of developing LBP in older men from Australia free of LBP at baseline (Parreira et al., 2017). Older adults with more comorbidities have a greater risk of being physically disabled (Quiñones et al., 2016; Sharma et al., 2021) establishing a vicious circle between comorbidities, physical disability and sedentary behaviour (Calderón-Larrañaga et al., 2019; Dunlop et al., 2015), which may contribute to the occurrence of muscle dysfunction (i.e., sarcopenia) (Therakomen et al., 2020). Although our results revealed an association between sarcopenia and LBP even when controlling for the number of comorbidities, our study's design does not allow to show a causal link. However, based on the studies mentioned above, adding sarcopenia to this scenario will further increase the total number of comorbidities, which also can increase the prevalence of LBP. According to these findings, older adults who usually present more comorbidities may represent a subgroup for LBP.

An important implication of our research is that LBP should not be treated in isolation. The presence of depressive symptoms, comorbidities and sarcopenia should be evaluated routinely in older adults with LBP to determine appropriate treatments that can results in maximal effects when these conditions are targeted simultaneously.

According to our results presented in chapter seven, older adults with chronic LBP show a delay in the activation of TrA, reduced grip strength and gait speed compared to a control group without LBP. The association between TrA activation and LBP was extensively investigated in past studies with younger participants (Hides et al., 2009; Hodges & Richardson, 1996, 1998, 1999a) showing an alteration in the automatic recruitment of the TrA muscle in subjects with LBP. Moreover, there is evidence that improvements in the recruitment of the TrA after intervention are associated with an important reduction in pain (Unsgaard-Tøndel et al., 2012) and disability (P. H. Ferreira et al., 2010). However, whether these results are similar in older adults is not known, and to our knowledge the study presented in chapter seven was the first to show a reduction of TrA pre-activation in older individuals with CLBP compared to controls without LBP. Moreover, this study was the first to investigate and reveal the absence of difference in TrA elasticity (strain ratio) when comparing older adults with and without CLBP. The occurrence of alterations in TrA pre-activation but not in TrA elasticity in older adults with CLBP suggests that muscle dysfunction in these individuals is related to alterations in the CNS (feedforward) rather than a mechanical problem (elasticity). Future research should investigate if TrA pre-activation and elasticity are different in older adults with acute symptoms of LBP because, in these patients, the central and mechanical adaptations are not established yet.

Chapter seven showed that older adults with CLBP were 0.21m/s slower than controls without CLBP. Our finding is supported by the results of a secondary cross-sectional analysis of 108 older adults (age range 60 to 85 years, matched by age ± 2 years, 54 with CLBP), participants in a clinical trial for CLBP (Hicks 2017). In their study, Hick et al., 2017 found

that older adults with CLBP are slower than their peers without CLBP at both self-selected (MD = -.158 m/s, 95%CI −.272 to −.014, $p < 0.001$) or fast (MD = −.143 m/s, 95%CI −.244 to −.073, $p = 0.030$) gait speeds. These results are similar to those found in a prospective study that followed 659 community-dwelling older adults (≥ 70 years) for an 18-months follow-up to investigate the association between restricting LBP and low extremity physical function (Reid 2005). As a result, Reid et al., 2005 observed that the number of months with restricting back pain was independently associated with being slower ($p < 0.001$) with a decline in rapid gait speed of 11.3% in participants with no months of restricting LBP and 33.2% for those who experienced four or more months with restricting LBP. Cury et al., 2021 presented in a recent systematic review that older adults have reduced pelvic rotation ROM at a comfortable speed (SMD = − 0.90, 95%CI −1.35 to −0.45) and fast walking speed (SMD = −1.55, 95%CI −3.43 to −0.33) when compared with younger adults. Because of our study's design, we cannot infer the existence of a causal relationship between CLBP and gait speed. However, when coupling our results with the previously mentioned studies, we suggest that longer and disabling LBP symptoms lead to reduced gait speed, reinforcing disability and perpetuating the problem. In addition, the alterations in the pelvic and trunk pattern during gait among older adults may be a predisposing factor to back pain leading to localized mechanical stress with subsequent spinal degeneration and/or muscle dysfunction (i.e., shortening and/or fatigue) in the lumbar area. Future research should focus on testing the effectiveness of an intervention program based on the pelvic and trunk muscles pattern during the gait to prevent LBP among older adults and treat those experiencing LBP.

Chapter seven also showed lower values of grip strength in older adults with CLBP compared to their peers free of LBP. Although grip strength has been used as a biomarker for ageing,

disability and mortality (Iconaru et al., 2018a; A. A. Sayer & T. B. Kirkwood, 2015) the literature investigating its association with LBP is sparse. A sample of older Korean adults was investigated by Park et al. (2018) who found an association between reduced grip strength and LBP among older women. Furthermore, a prospective study with 12 months follow-up investigating older women with new episode of LBP found that handgrip strength at baseline was associated with physical disability (gait speed) but not with LBP related disability (Rolland Morris questionnaire) in the follow-up assessment (Felício et al., 2017).

Results from chapters 6 and 7 combined with previous literature investigating the relationship of sarcopenia markers and LBP (Crawford et al., 2016; Crawford et al., 2019; Hicks et al., 2017) provide some information that allows us to hypothesize the existence of a relationship between sarcopenia and LBP. However, current evidence about the association of sarcopenia and LBP comes from observational studies (Iwahashi et al., 2022; Y. Sakai et al., 2017; Sakai et al., 2022; S. Tanishima et al., 2017); thus, we can not point to a causal direction of the association. Table 2 from chapter 6 showed that decreased grip strength has a positive association with LBP while a fast gait speed provides a protective effect against LBP. In addition, older adults with CLBP who participated in the study described in chapter 7 presented greater reduction in grip strength and gait speed than participants from the control group without CLBP. Similar results were reported by Hicks et al. (2017) when comparing gait speed between older adults (age range 60 to 85 years) with and without CLBP. Furthermore, Park et al. (2018) found the presence of an association between low handgrip strength and low back pain in a sample of community-dwelling older persons with (n=429) and without (n = 429) LBP. Besides being markers for sarcopenia, handgrip strength and gait speed are also biomarkers for morbidity and mortality in older adults (Cooper et al., 2010).

Thus, based on the patient-centred care approach (Hutting et al., 2022; Wijma et al., 2017), patients with LBP presenting with reduced grip strength and gait speed should receive interventions aiming to restore grip strength and gait speed independently if they are or not the cause of LBP symptoms. Thus, additional efforts should be taken to assess the existence of a sarcopenic subgroup among older adults with LBP.

The world population is aging because of increments in life expectancy (Angela Y. Chang et al., 2019; Wang et al., 2016). As people are living longer, the next step is to improve healthy life expectancy (i.e., a long and healthy life) (Vos et al., 2017). LBP remains the leading global cause of disability across all age groups, accounting for 52.7% or 64.9 million years lived with disability in 2017 (Wu et al., 2020). Recently, The Lancet Series launched a call to action to reduce low-value care for LBP reinforcing that any treatment should be available only in trials until adequately tested (Buchbinder et al., 2018). In this context, the authors also mention that social changes such as populational ageing will exacerbate the burden of LBP (Buchbinder et al., 2018), which is already high (James et al., 2018). To provide valuable care for older adults with LBP, clinical trials including these individuals are in need. The identification of a specific cause for LBP is rare (Maher et al., 2016). However, age-related biopsychosocial characteristics may be associated with LBP, which can help to identify possible subgroups. Thus, research regarding LBP subgroups for older adults based on their biopsychosocial components such as sarcopenia (i.e., a biological component) should be investigated and tested in clinical trials. Once interventions are sufficiently tested, the results tend to be grouped and analyzed with meta-analysis establishing robust evidence to guide treatment of specific subgroups.

10.4 Strengths and limitations

This thesis is composed of seven research papers published or submitted to high-impact journals designed to contribute to the field of physiotherapy/epidemiology. The main strength of this thesis lies in the development of studies that demonstrated the underrepresentation of older individuals (≥ 60 y) in clinical trials for managing LBP and the problems regarding sarcopenia definition and diagnosis. The findings may lead to the re-evaluation of the current impact of healthcare providers with older individuals with LBP due to the limited effective evidence-based interventions for this population, as well as promote the interest in the establishment of a solid definition and proper tools to diagnose sarcopenia. In addition, this thesis showed an association between sarcopenia and LBP, using a population-based sample of 12464 community-dwelling older adults with adequate control for comorbidities.

Although each study inserted in this thesis was carefully designed, the thesis is not free of shortcomings. The main limitation of this thesis is the lack of a design that allows inferring causality in the experimental studies. Two studies presented in the thesis found an association between sarcopenia parameters and LBP in older adults, but because of their cross-sectional design, we cannot infer whether the association is causal. Another limitation of the thesis comes from the survey presented in chapter five. Although the respondents were participants from a main LBP research event, we cannot assume that their thoughts represent those of most LBP researchers, nor whether their intention to include more older adults in clinical trials will lead to concrete actions.

Chapter Eleven

Conclusions

11.1 Principal findings

The broad aim of this thesis was to develop a series of high-quality studies contributing to a better understanding about low back pain, sarcopenia, and their association in older adults. Our work provides new findings regarding the association of sarcopenia and LBP in older adults that establishes a starting point for studies on causality (Chapters 6 and 7). A cross-sectional analysis of data from a cohort study with 12646 Canadians 65 years of age and older revealed that the prevalence of sarcopenia among participants with LBP varied depending on the sarcopenia definition and stage. Sarcopenia, comorbidities, and depressive symptoms showed being associated with an increase in the odds of having LBP. The cross-sectional study (Chapter 7) comparing participants with CLBP with a group without CLBP found that participants with CLBP presented with a delay in the activation of TrA, and an impairment in both functional markers for sarcopenia, grip strength and gait speed. However, we did not find between-group differences regarding TrA elasticity assessed by USI compression elastography.

The systematic review about how sarcopenia has been defined and measured (Chapter 9) identified that the definition criterion used to diagnose sarcopenia as well the measurement tool can influence the reported prevalence. According to studies with low risk of bias there is an urgent need to find a consensus definition for sarcopenia and define standard measurement tools. Depending on the criterion used to define sarcopenia, the variation in the estimates can show up to three-fold differences. Pooled prevalence values were found to be as low as 5% when sarcopenia was based on the AWGS definition, 10% for the EWGSOP, 12% for estimates based on low muscle mass alone, and as high as 16% and 17% when using the FNIH and IWGS criteria to define sarcopenia, respectively. Similarly,

measurements taken from the same samples resulted in disparate prevalence values when muscle mass was measured with DXA = 15%, BIA = 11% or derived from prediction equation = 23%, even with all using a definition for sarcopenia based solely on muscle mass. Also, the pooled prevalence of sarcopenia was 11%, with estimates in men and women varying with the diagnosis criteria used for sarcopenia.

This thesis also provides important information with regards to the participation of older adults in RCTs for LBP (Chapters 4 and 5). Data collected using an electronic survey with participants of the 15th International Forum on Back and Neck Pain Research in Primary Care presented in Chapter 5 found that there is an agreement among LBP researchers that older adults are underrepresented in clinical trials for LBP and that exclusion based solely on age is not justified. As a result of the lack of representativeness, researchers believe that older adults with LBP are not receiving the most appropriate care. Consequently, researchers showed to be more prone to include older adults into their current/future clinical trials for LBP, as well as being more interested in developing clinical trials targeting older adults exclusively. However, as shown in Chapter 4, about half of the clinical trials registered for LBP in the WHO clinical trial registry database from January 2015 to November 2018 were allowing the recruitment of older adults, whereas only about 3% of those were designed specifically to investigate the aged population. Ideally, to guarantee the generalizability of the results of clinical trials to patients in the real world, researchers should not establish an upper age limit when their study aims to test an intervention intended for the general population. A well-trained research assistant with sufficient time for screening patients for eligibility can investigate whether selected older

adults can be enrolled or not in the study. In addition, using stratified randomization helps to have a sample representative of different age strata. In contrast, the development of clinical trials excluding or targeting older adults should be acceptable only when the research question covers a specific characteristic or outcome of the targeted population. For example, in clinical trials aiming to assess the return to work of members of the armed forces or an intervention targeting participants with back complaints due to bone or joint degeneration conditions, it would be acceptable to exclude and target older adults, respectively.

11.2 Implications and suggestions for future research

11.2.1 Clinical trials for older adults with back complaints

The findings of Chapter 5 from a survey with LBP researchers showed that they recognize that older adults have been neglected in clinical trials for LBP and the negative impact that this creates with regards to the care for this population. According to the survey, researchers are showing a change in their behavior towards the inclusion of older adults as well as a higher interest in targeting older adults exclusively in their current/future clinical trials. This changing behavior may be due to the fact that life expectancy is growing (Wang et al., 2016) and interventions to deal with LBP in older adults are not covered by current clinical practice guidelines (Delitto et al., 2012; National Guideline, 2016a). However, the WHO trial register database review presented in Chapter 4 demonstrated that older adults will continue being underrepresented in clinical trials for LBP at least until the next few years. Because the number of older adults presenting with LBP will increase with the

growth of the older population, the development of high-quality clinical trials investigating treatment strategies to manage back symptoms and the associated disability in older adults is urgently needed. Furthermore, research ethics boards and funding agencies should make clear in their statements and regulations that clinical trials that do not present a reasonable justification to exclude or limit the participation of older adults will not be granted. This document should detail the accepted justifications for setting an upper age limit such as a high number of comorbidities, polypharmacy, physical inability, cognitive inability, and so on. It is also necessary to clarify the cases allowing the exclusion of older adults, for example, clinical questions targeting athletes, military or working populations.

11.2.2 Sarcopenia diagnosis

The criteria used to diagnose sarcopenia have been changing since the first time the term was used by Rosenberg (1989) to describe the enhanced loss of muscle mass due to aging as a health problem. Following the recognition of the condition, a criterion to define sarcopenia was established based on the reduction of muscle mass alone through assessment of the skeletal muscle index, which is a ratio of appendicular lean mass over height squared (ALM/h^2) (Baumgartner et al., 1998). According to this criterion, subjects with a reduction in the skeletal muscle index of 2 SD or more compared to a reference group of young adults from the same population were diagnosed with sarcopenia (Baumgartner et al., 1998). Following the definition of threshold values to diagnose sarcopenia, a diverse number of approaches also based on reduction of muscle mass alone emerged (Janssen, 2011).

With the evolution of the concept a series of working groups on sarcopenia started to define sarcopenia as the combination of the loss of muscle mass plus a reduction in muscle strength and/or gait speed (Chen et al., 2014; Chumlea et al., 2011; Cruz-Jentoft et al., 2010; Studenski et al., 2014). Although these working groups used the same criteria to define sarcopenia, they differed in terms of cut-off values for muscle mass, grip strength and gait speed, with some also using different methods to normalize muscle mass (Dam et al., 2014). In addition to this, different tools or even different tests can be used to measure each parameter included in the definition of sarcopenia, especially muscle mass, which is frequently assessed with DXA or BIA (Dam et al., 2014). Consequently, Chapter 9 shows the lack of agreement in prevalence estimates of sarcopenia with the different operational definitions and measurement tools. A step forward was taken recently with an update in the EWGSOP definition, setting the reduction of muscle strength which is more closely related with functional limitations, as the key element in the diagnosis of sarcopenia, surpassing the role of muscle mass (Cruz-Jentoft et al., 2019). In summary, the lack of a clear consensus for the definition of sarcopenia as well as the use of unstandardized measurement tools can prevent the recognition of the real burden of sarcopenia as a health problem, the exchange of knowledge obtained with different populations, and where to apply the efforts to prevent and treat it. To our understanding, the establishment of muscle strength as the main criteria for the diagnosis of sarcopenia as proposed by the EWGSOP2 should be promoted across the different definitions. The handheld dynamometer is an optimal tool to assess muscle strength due to its validity, reliability, accessibility, and ability to predict total body strength. However, future efforts should focus to standardize the type of equipment (i.e., digital vs analogic, hydraulic vs pneumatic), and procedures (i.e., body and hand position, side tested, number of trials, reporting the average or

maximum value, time of contraction/squeezing, use of visual feedback and verbal stimulus). When assessing muscle quantity, we recommend that muscle lean mass should be adjusted for BMI as recommended by FNIH instead of considering only height as proposed by other definition criteria. The use of BMI to normalize lean mass allows one to account for muscle fat infiltration, which seems to have a major role in muscle health. In addition, methods that allow to visualize and measure lean mass and fat infiltration directly should be preferable over the use of algebraic formulas and other indirect methods. Further, additional efforts are necessary to assess physical performance throughout walking tests due to the high variability of strategies providing results that are not interchangeable. Research attempting to standardize walking tests should consider the practicality of the distance, the pace during the test (i.e., usual, or maximum speed) and the starting mode (i.e., static, or dynamic), and the use of a stopwatch to register the walking speed.

11.2.3 Association of sarcopenia with low back pain

Chapters 6 and 7 present important findings about the association between LBP and sarcopenia or sarcopenia parameters in older adults. Despite the substantial number of studies investigating the association of LBP with muscle impairments, such as reduction in cross-sectional area (Hides et al., 1996; Paul W. Hodges & Lieven Danneels, 2019; Ranger et al., 2019; Ranger et al., 2017) and activation (Critchley & Coutts, 2002; Hides et al., 2009; Paul W. Hodges & Lieven Danneels, 2019; Kiesel et al., 2008; Kiesel et al., 2007) in young adults, the results remain inconclusive (Wong et al., 2014) and information on older adults is lacking. Results from a systematic review that grouped the studies measuring abdominal and MF muscles quality (accumulation of intramuscular fat) and function in

older adults showed that this group presented a reduction of 36% to 48% in muscle thickness of rectus abdominis, internal oblique and external oblique compared with younger adults (Cuellar et al., 2017). In addition, results extracted from studies with LBP patients showed that muscle quality is poor in cases of moderate to extreme symptoms and could predict physical function outcomes although, the evidence has significant limitations (Cuellar et al., 2017). Based on our findings, we suspect that alterations in muscle health among older adults with CLBP are related to changes in the CNS as observed by the delay in TrA pre-activation, reduced grip strength and slow gait speed, which have a central component. The lack of difference in TrA elasticity between older adults with CLBP and controls without back pain reinforces our CNS suspicions as muscle elasticity represents mechanical characteristics.

We found a link between LBP and sarcopenia, but the association depends on how sarcopenia was defined. An increased number of comorbidities and depressive symptoms were also related to LBP. Currently, evidence on the association between sarcopenia and LBP come from two small cross-sectional studies with significant methodological issues (Y. Sakai et al., 2017; S. A.-O. Tanishima et al., 2017). S. A.-O. Tanishima et al. (2017) investigated the presence of sarcopenia, LBP, and LBP disability in a sample of 216 older Japanese adults. However, due to the flawed recruitment strategy, the number of participants with LBP was more than 60% in all groups which could contaminate the results, and the analysis was restricted only to correlations. Another study with older Japanese adults (Y. Sakai et al., 2017) compared subjects with and without CLBP with regards to the presence of sarcopenia finding more cases of sarcopenia in the CLBP group. Unfortunately, in this study, the presence of sarcopenia was based only on a reduction of muscle mass and the reference

values used were derived from a different sample. In summary, the available studies on the association between sarcopenia and LBP have limitations, such as improper recruitment strategy and case definition, which can make the validity of the results questionable. In addition, considering that depression and sarcopenia are also concurrent diseases, this would increase the total number of comorbidities by two, which may suggest that the elevated number of comorbidities is the most important factor in older adults with LBP. The clarification of the association between sarcopenia and LBP in older adults is necessary as it could help to identify modifiable factors that could improve the quality of life of older adults. Therefore, high quality studies in this area are urgently needed.

Part IV

Statement of contribution

Statement of authorship contribution in the paper "Effectiveness of interventions for non-specific low back pain in older adults. A systematic review and meta-analysis".

Paulo Nascimento has made the following contributions: Conception and design of the research, Database search, Data analysis Drafting the manuscript. Amanda Araújo contributed with Database search, Data analysis, Revision of the manuscript. Leonardo Costa, Stéphane Poitras and Martin Bilodeau contributed with the definition of the search strategy, data analysis and interpretation, edition, revision and commented on the writing of the article.

Statement of authorship contribution in the paper "Exclusion of Older Adults from Ongoing Clinical Trials on Low Back Pain: A Review of the WHO Trial Registry Database".

Paulo Nascimento has made the following contributions: Conception and design of the research, Data extraction and analysis, Data interpretation, and Drafting of the manuscript. Manuela Ferreira, Stéphane Poitras and Martin Bilodeau contributed with data analysis and interpretation, commented, edited, and revised the writing of the article.

Statement of authorship contribution in the paper "Perceptions and Expectations about the Participation of Older Adults in Randomized Controlled Trials: A Survey with Low Back Pain Researchers".

Paulo Nascimento has made the following contributions: Conception and design of the research, Development of the questionnaire, Data analysis and interpretation, and drafting the manuscript. Manuela Ferreira, Stéphane Poitras and Martin Bilodeau contributed with development of the survey questionnaire and have reviewed, commented, and edited the writing of the article.

Statement of authorship contribution in the paper "Relationship between sarcopenia and low back pain in older adults. Analysis of baseline data from the Canadian Longitudinal Study on Aging"

Paulo Nascimento has made the following contributions: Conception and design of the research, Data analysis and interpretation, and drafting the manuscript. Stéphane Poitras and Martin Bilodeau contributed with the development of the protocol for data requisition. Tim Ramsay provided suggestions regarding the data analysis strategies, and Leonardo Costa, Tim Ramsay, Stéphane Poitras and Martin Bilodeau edited, revised, and commented on the writing of the article.

Statement of authorship contribution in the paper **"Comparative Analysis of functional sarcopenic markers and transversus abdominis activation in older adults with chronic low back pain".**

Paulo Nascimento has made the following contributions: Conception and design of the research, Data collection, analysis, and interpretation, and drafting the manuscript. Daysiane Santos contributed with Data collection. Rafael Zambelli, Stéphane Poitras, Leani Maximo, Daysiane Malta and Martin Bilodeau contributed with data interpretation, revised, and commented on the writing of the article.

Statement of authorship contribution of paper "How do we define and measure sarcopenia? Protocol for a systematic review"

Paulo Nascimento has made the following contributions: Conception and design of the protocol, Writing of the manuscript and critical appraisal of the content. Stéphane Poitras and Martin Bilodeau provided collaboration with the development of the search strategy, edited, revised, and commented on the writing of the research protocol and the final article.

Statement of authorship contribution of the paper "How do we define and measure sarcopenia? A systematic review and metanalysis"

Paulo Nascimento has made the following contributions: Conception and design of the research, database search, data extraction, analysis, and interpretation. Martin Bilodeau had the role of being the second reviewer in charge of judging for study eligibility and risk of bias assessment. Stéphane Poitras and Martin Bilodeau edited, revised, and commented on the writing of the article.

Part V

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Supplementary files

Supplement Chapter 3

Embase search strategy

1. Clinical Article/
2. exp Clinical Study/
3. Clinical Trial/
4. Controlled Study/
5. Randomized Controlled Trial/
6. Major Clinical Study/
7. Double Blind Procedure/
8. Multicenter Study/
9. Single Blind Procedure/
10. Phase 3 Clinical Trial/
11. Phase 4 Clinical Trial/
12. crossover procedure/
13. placebo/
14. or/1-13
15. allocat$.mp.
16. assign$.mp.
17. blind$.mp.
18. (clinic$ adj25 (study or trial)).mp.
19. compar$.mp.
20. control$.mp.
21. cross?over.mp.
22. factorial$.mp.
23. follow?up.mp.
24. placebo$.mp.
25. prospectiv$.mp.
26. random$.mp.
27. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).mp.
28. trial.mp.
29. (versus or vs).mp.
30. or/15-29
31. 14 or 30
32. exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
33. human/ or normal human/ or human cell/
34. 32 and 33
35. 32 not 34
36. 31 not 35
37. dorsalgia.mp.
38. back pain.mp.
39. exp LOW BACK PAIN/
40. exp BACKACHE/
41. (lumbar adj pain).mp.
42. lumbago.mp.
43. back disorder$.ti,ab.
44. or/37-43
45. aged/
46. frail elderly/

47. (Aged, 80 and over).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]
48. or/45-47
49. 31 and 36 and 44 and 47

Medline search strategy

1. Randomized controlled trial.pt.
2. randomized controlled trial.pt.
3. comparative study.pt.
4. clinical trial.pt.
5. randomized.ab.
6. placebo.ab,ti.
7. drug therapy.fs.
8. randomly.ab,ti.
9. trial.ab,ti.
10. groups.ab,ti.
11. or/1-10
12. (animals not (humans and animals)).sh.
13. 11 not 12
14. dorsalgia.ti,ab.
15. exp Back Pain/
16. backache.ti,ab.
17. exp Low Back Pain/
18. (lumbar adj pain).ti,ab.
19 lumbago.ti,ab.
20 back disorder$.ti,ab.
21 or/14-20
22 Aged/
23 "Aged, 80 and over"/
24 Frail Elderly/
25 or/22-24
26 13 and 21 and 25

PEDro

Older$
Aged
Seniors
Elderly

Central

1. MeSH descriptor Back Pain explode all trees.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]
2. dorsalgia.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]
3. backache.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]
4. MeSH descriptor Low Back Pain explode all trees.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]
5. lumbar next pain.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]
6. MeSH descriptor Spine explode all trees.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]
7. MeSH descriptor Spinal Diseases explode all trees.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]
8. lumbago.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]
9. back disorder*.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. older adults.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]
12. elderly.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]
13. older people.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]
14. senior.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]
15. veterans.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]
16. frail elderly.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]
17. 11 or 12 or 13 or 14 or 15 or 16
18. 10 and 17

Search strategy for CINAHL (EBSCO)
Part A: Generic search for randomized controlled trials and controlled clinical trials

S1 (MH "Clinical Trials+")
S2 "randomi?ed controlled trial*"
S3 clinical W3 trial
S4 double-blind
S5 single-blind
S6 triple-blind
S7 S1 or S2 or S3 or S4 or S5 or S6
S8 (MH "Placebo Effect")
S9 (MH "Placebos")
S10 placebo*
S11 random*
S12 S8 or S9 or S10 or S11
S13 (MH "Random Sample")
S14 (MH "Study Design+")
S15 latin square
S16 (MH "Comparative Studies")
S17 (MH "Evaluation Research+")
S18 (MH "Prospective Studies+")
S19 S13 or S14 or S15 or S16 or S17 or S18
S20 follow-up stud*
S21 followup stud*
S22 control*

S23 prospectiv*
S24 volunteer*
S25 S20 or S21 or S22 or S23 or S24
S26 S7 or S12 or S19 or S25
S27 (MH "Animals")
S28 S26 NOT S27
S29 "dorsalgia"
S30 (MH "Back Pain+")
S31 (MH "Low Back Pain")
S32 "backache"
S33 lumbar W1 pain
S34 lumbar N5 pain
S35 S29 or S30 or S31 or S32 or S33 or S34
S36 (MH "Coccyx")
S37 (MH "Sciatica")
S38 "sciatica"
S39 "coccyx"
S40 "coccydynia" OR "back disorder*"
S41 (MH "Lumbar Vertebrae")
S42 lumbar N2 vertebra
S43 S36 or S37 or S38 or S39 or S40 or S41 or S42
S44 (MH "Thoracic Vertebrae")
S45 (MH "Spondylolisthesis") OR (MH "Spondylolysis")
S46 "lumbago"
S47 S44 or S45 or S46
S48 S35 or S43 or S47

Supplement Chapter 5

Appendix 1: Preliminary Questionnaire

(1) Do you accept to participate in this research conducted by the research team headed by Dr. Martin Bilodeau from the Bruyére Research Institute and the Faculty of Health Science of the University of Ottawa?

☐Yes ☐No

(2) Is low back pain (LBP) your primary research field?

☐Yes ☐No

(3) Have you ever been involved in conducting a randomized controlled trial (RCT) on LBP?

☐Yes ☐No

(4) Did you exclude older participants (≥ 65 years old) from your last trial?

☐Yes ☐No ☐Not Applicable

(5) Was this trial recruiting exclusively older adults (≥ 65 years old)?

☐Yes ☐No ☐Not Applicable

(6) Are you running or planning a RCT on LBP?

☐Yes ☐No

(7) Are including older adults (≥ 65 years old) in your RCT?

☐Yes ☐ No ☐Not Applicable

(8) Are older adults (≥ 65 years old) the population of interest in this RCT?

☐Yes ☐No ☐Not Applicable

(9) Do you believe that older people (≥ 65 years old) are under-represented in clinical trials about LBP?

☐Yes ☐No

(10) Do you believe that older adults (≥ 65 years old) receive less evidence-based treatment for LBP because of under-representation in clinical trials?

☐Yes ☐ No

(11) Do you believe that under-representation of older adults in clinical trials creates additional challenges for health providers when treating this population?

☐Yes ☐No

(12) Do you believe that it is justified to have an upper age limit (≥ 65 years old) in a clinical trial based on age alone?

☐Yes ☐No

(13) According to you, which of the following factor could justify the exclusion of older adults in clinical trials? (Check all that apply)

☐ differing rates of comorbidity

☐ differing rates of polypharmacy?

☐ differing life expectancy

☐ differing levels of physical ability

☐ differing levels of cognitive ability

☐ differing levels of adverse events

☐ differing drop-out rates

☐ differing time and resource requirements for recruitment

☐ differing consent rates

☐ differing family involvement for recruitment and consent

☐ differing levels of interest

☐ differing levels of compliance

☐ similar results applicability from young participants

☐ Other: (Please, specify)

(14)What is your occupation? Please, fill all that apply.

☐ Scientist

☐ Graduate student

☐ Clinician

☐ Other: (Please, specify)

(15) How long have you been involved in LBP research?

☐ Less than 5 years ☐ 5-10 years ☐ > 10 years

(16)What is your gender?

☐ Male ☐ Female

(17) Please state your country of residence_____

Supplements Chapter 9

Appendix 1: Search strategy

Web of Science	Google Scholar	Medline	EMBASE	CINAHL
# 1 TS= (sarcopen* OR aging OR muscle atrophy) # 2 TI= (prevalence OR incidence OR cross-sectional OR cohort) # 3 TI=(older adults OR elder* OR seniors OR community-dwelling) (#3 AND #2 AND #1)	Sarcopenia prevalence Prevalence of sarcopenia	1. Sarcopenia/ 2. sarcopenia.ti,ab. 3. 1 or 2 4. Muscular Atrophy/ 5. (musc* adj1 atrophy).ti,ab. 6. 4 or 5 7. aging.ti,ab. 8. Aging/ 9. 7 or 8 10. 6 and 9 11. "Aged, 80 and over"/ or Aged/ 12. Prevalence/ 13. Cross-Sectional Studies/ 14. 12 or 13 15. 3 or 10 16. 11 and 14 and 15	1. Sarcopenia/ 2. sarcopenia.ti,ab. 3. 1 or 2 4. Muscular Atrophy/ 5. (musc* adj1 atrophy).ti,ab. 6. 4 or 5 7. Aging/ 8. aged.ti,ab. 9. 7 or 8 10. 6 and 9 11. Aged/ 12. "Aged, 80 and over"/ 13. 11 or 12 14. Prevalence/ 15. Incidence/ 16. Cohort Studies/ 17. Cross-Sectional Studies/ 18. 3 or 10 19. 14 or 15 or 16 or 17 20. 13 and 18 and 19	S1. TI Sarcopenia OR AB Sarcopenia S2. TI (MH "Muscular Atrophy") S3. S1 OR S2 S4. TI Aged OR AB Aged S5. (MH "Aged, 80 and Over") S6. S4 OR S5 S7. (MH "Prevalence") OR (MH "Cross Sectional Studies") OR (MH "Surveys") OR (MH "Epidemiological Research") S8. S3 AND S6 AND S7

Appendix 2: Methods

Quality appraisal

Two independent researchers (PN and MB) assessed the risk of bias of each eligible study using the Risk of Bias Tool for Prevalence Studies adapted from Hoy, Brooks [21]. This instrument allows verifying the risk of bias for factors related to external and internal validity, allowing classification of the risk of bias as low, moderate, or high. This instrument was chosen mainly because it is easy to use, shows high inter-examiner agreement, and it was developed specifically to measure the risk of bias in prevalence studies [21].

The quality analysis was based on the following items: (1) representativeness of the study sample in relation to the national population, allowing generalization of the results; (2) sampling system that represents the target population; (3) sample selection method; (4) probability of non-response bias; (5) how the target response was obtained; (6) definition of sarcopenia used for the sample selection; (7) reliability and validity of the study tools; (8) standardization of data collection; (9) appropriate target prevalence period; and (10) presence of error in calculating and/or reporting the numerator and denominator of the target parameter. The first four criteria relate to the study's external validity, and the other items report the risk of bias for internal validity. At the end, the studies were classified as presenting low risk of bias when at least eight criteria were met, moderate risk of bias for studies where 6 to 7 criteria were met, and high risk of bias when the studies showed five or less met criteria [21]. The reviewers discussed the cases in which there was no agreement and classification was determined by consensus.

Data extraction and analysis

The information about the articles (author, type of study, data collection strategy, sample size, mean age, gender, definition of sarcopenia, measurement tools, and prevalence rate) was extracted independently by one researcher (PN) using an electronic sheet. Frequency distribution was used to present the prevalence of sarcopenia, definitions and tools used to diagnose sarcopenia through the studies. Heterogeneity between estimates was assessed using the I^2 statistic, which describes the percentage of variation not due to sampling error across studies. An I^2 value above 75% indicates high heterogeneity [22]. A meta-analysis of prevalence was undertaken for definition criteria and sex-specific prevalence rates of sarcopenia for cases allowing pooling three or more studies. Overall estimates were calculated using the quality effects model, which allows explicit accounting for study quality in the meta-analysis. Subgroup analyses were performed in the general model according to the different definition criteria for sarcopenia while in the specific models' subgroups were based on the tool used to quantify muscle mass. For the analysis of publication bias, we used the funnel plot. All analyses were carried out using METAXL (version 5.3), a freely available (http://www.epigear.com) add-on for Microsoft Excel®.

19. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA : the journal of the American Medical Association. 2000 Apr 19;283(15):2008-12.

20. Carvalho do Nascimento PR, Poitras S, Bilodeau M. How do we define and measure sarcopenia? Protocol for a systematic review. Systematic reviews. 2018;7(1).

21. Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol. 2012;65(9):934-9.

22. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Bmj. 2003 Sep 6;327(7414):557-60.

Appendix 3: Summary of the studies that fulfilled the eligibility criteria

Author/year	Study design	Sarcopenic marker - Tool	Sample Size (N)	Participants	Mean Age (Years)	Gender	Sarcopenia Definition	Prevalence (%)				
Baumgartner et al., 1998	Cross-sectional	Muscle mass – Predictive equation	808	Older adults from USA	M= 73.6 W= 73.7	M= 426 (52.7%) W= 382 (47.3%)	ASMI – more than 2 *SD* below the gender specific young adults. Based on values of previous study.	**Age (y)**			**M**	**W**
								<70			15.2	23.6
								70-74			19	34.2
								75-80			31.5	35.6
								>80			55.1	51.6
Kyle et al., 2001	Cross-sectional	Muscle mass - DXA	191	Older adults 64-94y from Switzerland	Not informed	M= 91 (48%) W= 100 (52%)	RSMI BCM index More than 2SD below the sex specific mean in health young adults. Based on values of previous study.				**M**	**W**
								RSMI			11	11
								BCM			45.1	30
Iannuzzi et al., 2002	Cross-sectional	Muscle mass - DXA	337	Older adults 64-93y from USA	M= 73.8y W= 75y	M= 142 (42.1%) W= 195 (57.9%)	A- ASMI B- TSMI More than 2 SD below the gender specific young-normal mean. Based on values from previous studies. Based on values from previous studies				**M**	**W**
								A			26.8	22.6
								B			1.5	13
Janssen et al., 2002	Cross-sectional	Muscle mass - BIA	4502	Older adults ≥ 60y from USA	M= 70y W= 71.3y Based on mean for each group	M= 2224 (49.4%) W= 2278 (50.6%)	SMI - between 1 and 2 SD of young adults' values = Sarcopenia class I. Based on a		**M**		**W**	
								Age	Class 1	Class II	Class I	Class II
								60-69	47	6	59	9

							young adults' reference group SMI – more than 2SD below of young adults' values = Sarcopenia class II. Based on a young adults reference group	70-79	42	7	57	11
								80+	43	7	61	11
Tanko et al., 2002	Cross-sectional	Muscle mass - DXA	162	Older women ≥ 60y from Denmark	W = 48.2	W= 100%	A - LTM_A Index and B - LTM_A - below 2SD of young women. C - LTM_A Index and D- LTM_A between 1 and 2 SD below of young women. Reference values based on a sample of young women.	Age (y)	A	B	C	D
								60-69	43.5	24	20	9.4
								>70	40.3	32.9	40.2	12.3
Castillo et al., 2003	Cross-sectional	Muscle mass - BIA	1700	Adults 55-98y from USA	M= 73y W= 73.4y	M= 694 (41%) W= 1006 (59%)	FFM - 2SD or more below of the gender specific mean of a young adult. Based on previous study	Age (y)	**M**	**W**		
								60-69	1.9	2.5		
								85+	16	13		
								Overall	6.2	5.9		
Gillette et al., 2003	Cross-sectional	Muscle mass - DXA	1321	Older women > 75y from France	NA	W = 100%	ASMI - 2SD below of the mean for young women. Based on previous study	Age (y)	W			
								76-85	8.9			
								86+	10.9			
Newman et al., 2003	Cross-sectional	Muscle mass - DXA	2984	Older adults 70-79y from USA	Overall= 73.6	M= 1435 (48%) W= 1549 (52%)	A - aLMI – below sex-specific lowest 20% of the distribution of the index B - aLM% - below 20th percentile of the distribution of residuals.		**M**	**W**		
								A	8.9	7.1		

								B	15.4	21.7	
Rolland et al., 2003	Cross-sectional	Muscle mass – DXA	1311	Older women ≥ 70y from France	W= 80.3y	W= 100%	SMI – more than 2SD below of the mean for young women. Based on previous study	9.5%			
Lau et al., 2005	Cross-sectional	Muscle mass - DXA	527	Older adults ≥ 70y from Hong Kong	M= 73.8 W= 76.9	M= 262 (49.7%) W= 265 (50.3%)	A – Lean body mass B – Appendicular skeletal muscle mass C – Appendicular muscle skeletal index. D – Total skeletal muscle mass More than 2SD below of the mean for young sample of Chinese men and women	**M**	A	B	C	D
								Age (y)				
								70-74	15.9	19.1	10.2	19.2
								75-79	27.9	29.8	15.4	29.8
								Overall	20.7	23.4	12.3	23.4
								W				
								70-74	59.4	34.8	10.1	34.8
								75-79	62.3	34.6	6.2	34.6
								≥ 80	58.5	43.1	6.2	43.1
								Overall	61	36.7	7.2	36.7
Chien et al., 2008	Cross-sectional	Muscle mass - BIA	302	Older adults ≥ 65y from Taiwan	M=76.6 W= 74.4	M= 157 (52%) W= 145 (48%)	A – FFM B – FFMI C – SM D – SMI 2SD or more below the normal sex specific mean in a young sample for four measures	**M**	A	B	C	D
								Age (y)				
								65-69	23	17	33	20
								70-79	25	13	43	24
								≥ 80	26	11	43	26
								Overall	24	13	42	24
								W				
								65-69	20	14	37	17

								70-79	27	13	37	18
								≥ 80	39	16	39	19
								Overall	28	14	37	19
Tichet et al., 2008	Cross-sectional	Muscle mass - BIA	218	Older adults 60-78y from France	M= 64.2 W= 64.7	M= 112 (51.4%) W= 106 (48.6%)	A - MMI or B – SMI% 2SD below the mean of the distributions for a sample of healthy adults <40y	Index		**M**		**W**
								A		3.6		2.8
								B		12.5		23.6
Bouchard et al., 2009	Cross-sectional	Muscle mass - DXA	894	Older adults 68-82y from Canada	NA	M= 432 (48.3%) W= 462 (51.7)	ASMI - 2SD below of the mean of a young reference group.	**M**				**W**
								20.1				6.9
Kim et al., 2009	Cross-sectional	Muscle mass - DXA	200	Older adults ≥60y from South Korea	NA	M= 79 (39.5%) W= 121 (60.5%)	A- ASM - 2SD below of the mean of a young reference group B- ASM - two lower quintiles in the study population C - SMI - 2SD below of the mean of a young reference group D - Residual method - sex specific values < 20% of the distribution based on ASM predicted by regression analysis			**M**		**W**
								A		6.3		4.1
								B		54.4		40.5
								C		15.4		22.3

								D	5.1	14.2
Kirchengast and Huber. 2009	Cross-sectional	Muscle mass - DXA	139	Older adults 59-92y. from Austria	M= 71.5 W= 71.8	M= 63 W= 76	ASM – more than 2SD below of the mean for young women. Based on previous study	Age (y)	**M**	**W**
								<70	18.2	31
								70-80	28.6	30
								>80	50	43.8

Hairi et al., 2010	Cross-sectional	Muscle mass - DXA	1612	Older men ≥70y. from. Australia	NA	M= 100%	A - aLM relative to height squared. B - aLM relative to fat mass. C - the residual method based on regression analysis Values< 20% of the distribution for three measures. Based on sample values.	Age (y)	A	B	C
								70-74	14.4	19.3	15
								75-79	18	20.3	17.8
								80-84	25.3	21	27.2
								85-89	44.6	31.3	44.6
								≥90	58.3	16.2	54.3

Hedayati and Dittmar. 2010	Cross-sectional	Muscle mass - BIA	110	Older adults ≥60y from Germany	M= 68.4 W= 67.8	M= 55 (50%) W= 55 (50%)	A – BCM % B = LBM% C = BCMI D= LBMI Values between 1 and 2 SD of young adults = Sarcopenia class I.	Index	**M**		**W**	
									Class I	Class II	Class I	Class II
								A	40	22	29	20

							Values more than 2SD below of young adults = Sarcopenia class II. Based on a reference sample of young men and women.	B	22	4	18	11
								C	18	2	16	0
								D	4	0	2	0
Sanada et al., 2010	Cross-sectional	Muscle mass - DXA	1488	Adults 18-85y from Japan	NA	M= 434 (29.2%) W= 1054 (70.8%)	Sarcopenia class I - SMI less than 1SD below the sex specific means of the study reference data Sarcopenia Class II - SMI more than 2SD below the sex specific mean		**M**		**W**	
								Age (y)	Class I	Class II	Class I	Class II
								70-85	6.7	56.7	6.3	33.6
Frisoli et al., 2011	Cross-sectional	Muscle mass - DXA	250	Older women ≥75y from USA	W= 79.6	W= 100%	aLM/h^2 more than 2SD below of young women. Based on previous study.	42.4%				
Wen et al., 2011	Cross-sectional	Muscle mass – DXA Muscle strength – DHD	72	Older adults ≥60y from China	M= 64.8 W= 64.1	M= 33 (46%) W= 39 (54%)	A- SMI - more than 2SD below of sex specific mean of young adults B- SMI% - Sarcopenia class I – value within 1 or 2SD below the sex specific mean of young adults	Criteria	**M**		**W**	
								A	0		0	

							C- SMI% - Sarcopenia class II – 2SD below the sex specific mean of young adults D – Residual method – based on regression analysis Reference values based on a young reference group	B	39.4	25.6
								C	0	17.9
								D	33.3	25.6
Arango et al., 2012	Cross-sectional	Muscle mass – calf circumference Muscle Function – DHD Physical performance – gait speed SPPB	345	Older adults ≥70y from. Mexico	M= 78.5 W= 78.6	M= 161 (46.7%) W= 184 (53.3%)	EWGSOP. Reference values based on previous studies. A - Moderate sarcopenia B - Severe sarcopenia	**M**	Overall	A	B
								Age (y)			
								<80	8.5		
								>80	18.9		
								Overall		6.2	18.6
								W			
								<80	17		
								>80	31.5		
								Overall		5.9	34.7
Kim et al., 2012	Cross-sectional	Muscle mass - DXA	3179	Older adults ≥ 65y from South Korea	NA	M= 1341 (42.2%) W= 1838 (57.8)	A - ASM adjusted by height or B - ASM adjusted by weight between 1 and 2 SD of young adults= class I sarcopenia Class II sarcopenia= height or weight adjusted ASM below 2SD Based on a young reference group.	**M**	A		B	
								Age (y)	Class I	Class II	Class I	Class II
								60-69	26.5	6.1	29.4	5.5
								70-79	29.6	18.2	30.4	10.3
								≥ 80	41	18	30.5	25.6
								W				
								60-69	4.1	0	32.4	7.7

								70-79	14	0	35.6	12.4
								≥ 80	12	0.7	15.4	9.4
Landi et al., 2012	Cross-sectional	Muscle mass – MAMC Muscle strength - HDH Physical performance - 4m test.	260	Older adults ≥ 80y from Italy.	86.7	M= 83 (31.9%) W= 177 (68.1)	EWGSOP Cut-offs based on previous study	Total			25.4	
								M			**W**	
								25.3			25.4	
Lee et al., 2012	Cross-sectional	Muscle mass - DXA	1260	Adults ≥ 65y from South Korea	NA	M= 1249 (43.2%) W= 1644 (56.8%)	SMI – more than 2SD below of the mean in sex-matched young reference group. Based on a sample of young men and women.	9.2				
Masanes et al., 2012	Cross-sectional	Muscle mass - BIA	200	Older adults ≥ 70y from Spain	M= 73.9 W= 74.7	M= 90 (45%) W= 110 (55%)	MMI – more than 2SD of the mean of a reference healthy young adult group	**M**			**W**	
								10			33	
Bijlsma et al, 2013	Cross-sectional analysis	Muscle mass – BIA Muscle strength - HHD	449	Older adults ≥ 65y	M= 64.5 W= 61.8	M= 325 (49.7%) W= 329 (50.3%)	A – ALMI – more than 2 SD below a reference population from Baumgartner et al, 1998 B - ALMI under 20th percentile C - ALMI > 2 SD below a reference population Kelly et al, 2009 D – Residual method under 20th percentile		**M**		**W**	
									60-69y	≥ 70y	60-69y	≥ 70
								A	4.3	6.5	2.9	0
								B	4.3	6.5	3.5	0
								C	0	0	0	0
								D	18.8	29	21.8	25.8
								E1	9.1	25.8	4.7	12.9
								E2	0	1.6	0	3.2
								F1	31.2	45.2	0	3.2
								F2	0	1.6	0	0
								G	0.1	8.1	3.5	0

							E (1) (2) – SMI% - 1–2 SD below reference population is class I sarcopenia >2 SD below reference population is class II sarcopenia F (1) (2)– SLMI - ROC analysis was used to develop cut points associated with moderate (1) and high (2) physical disability G – HS and GS – below optimal cut point.					
Coin et al., 2013	Cross-sectional analysis	Muscle mass - DXA	670	Older adults ≥ 65y from Italy	NA	M= 545 (81.3%) W= 125 (18.7%)	A - ASMI- more than 2SD below the mean of a young reference group. B - ASMI- 1SD below the mean for the 15th percentile of the distribution of the young population. C - ASMI- below the 20th percentile of the distribution for an elderly population	Criteria	**M**	**W**		
								A	0	0.3		
								B	19.2	12.6		
								C	20	20		
Domiciano et al., 2013	Cross-sectional	Muscle mass - DXA	611	Older women ≥ 65y. from Brazil.	W= 73.3	W= 100%	A – ASM adjusted for height below the 20th percentile of the study population B – ASM adjusted for fat below the 20th percentile of the study population	Criteria				
								A		3.7		
								B		19.9		

<table>
<tr><td>Lee et al., 2013</td><td>Cross-sectional analysis</td><td>Muscle mass – DXA
Muscle strength – HHD
Muscle performance – gait speed – 6m walking test</td><td>386</td><td>Older adults ≥ 65y from Taiwan</td><td>M= 74.4
W= 72.8</td><td>M= 223 (57.8%)
W= 163 (42.2%)</td><td>A – IWGS
And
B - EWGSOP
RASM or SMI – lower 20th percentile from the mean of the young reference group.</td><td></td><td colspan="2">RASM</td><td colspan="2">SMI</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>M</td><td>A</td><td>B</td><td>A</td><td>B</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>65-74y</td><td>2.3</td><td>3.9</td><td>4.7</td><td>6.3</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>75-84y</td><td>11.9</td><td>20.2</td><td>17.9</td><td>27.7</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>≥ 85y</td><td>0</td><td>18.2</td><td>27.3</td><td>18.2</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>Subtotal</td><td>5.8</td><td>10.8</td><td>10.8</td><td>14.9</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>W</td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>65-74y</td><td>0.9</td><td>1.8</td><td>8</td><td>11.6</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>75-84y</td><td>4.1</td><td>8.2</td><td>18.4</td><td>34.7</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>≥ 85y</td><td>0</td><td>0</td><td>50</td><td>50</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>Subtotal</td><td>1.8</td><td>3.7</td><td>11.7</td><td>19</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>Total</td><td>4.1</td><td>7.8</td><td>11.1</td><td>16.6</td></tr>
<tr><td>Legrand et al., 2013</td><td>Cross-sectional</td><td>Muscle mass – BIA
Muscle strength – DHD
Muscle performance – SPPB modified</td><td>288</td><td>Older adults ≥ 80y from Belgium</td><td>M= 84.6
W= 85</td><td>M= 103 (35.8)
W= 185 (64.2)</td><td>EWGSOP
Low muscle mass + low muscle strength + low physical performance.
Reference values based on previous studies.</td><td colspan="3">M</td><td colspan="2">W</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td colspan="3">12.6</td><td colspan="2">12.4</td></tr>
<tr><td>Lin et al., 2013</td><td>Cross-sectional</td><td>Muscle mass - DXA
Grip strength - DHD</td><td>761</td><td>Older adults ≥ 65y from Taiwan</td><td>NS</td><td>M= 354
W= 407</td><td>EWGSOP</td><td colspan="3">M</td><td colspan="2">W</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td colspan="3">12.8</td><td colspan="2">13.3</td></tr>
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<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td colspan="3">Age (y)</td><td colspan="2"></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td colspan="3">65-74</td><td colspan="2">7.4</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td colspan="3">75-84</td><td colspan="2">17.5</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td colspan="3">≥85</td><td colspan="2">38.5</td></tr>
<tr><td>Patel et al., 2013</td><td>Cross-sectional</td><td>(Sample 1) Muscle mass – DXA and SFT
(Sample 2)</td><td>Sample 1 – 103</td><td>Older adults from UK</td><td>Sample 1
M= 72.5</td><td>Sample 1
M= 103 (100%)</td><td>EWGSOP algorithm</td><td>Criteria</td><td colspan="3">M</td><td>W</td></tr>
</table>

		Muscle mass - SFT Muscle strength – HHD Physical performance – TUG and 3m test	Sample 2 1787		Sample 2 Overall = 67	Sample 2 M= 765 (42.8%) W= 1022 (57.2)	A – Lowest third of DXA based on sex specific distribution B- Lowest third of skin fold based on sex specific distribution.	Sample 1	A	6.8		
									B	7.8		
								Sample 2	B	4.6	7.9	
Patil et al., 2013	Cross-sectional	Muscle mass - DXA Muscle strength – HDH Physical performance – SPPB and TUG	409	Older women ≥ 70y from Finland	W= 74.2	W= 100%	A - EWGSOP and B - IWGS. Reference Values based on a sample of young health women.	A		B		
								0.9		2.7		
Pongchaiyakul et al., 2013	Cross-sectional	Muscle mass - DXA	238	Older adults ≥ 60y from Thailand	NS	M = 334 (40.1%) W= 498 (59.9%)	SMI between 1 and 2 SD of young adults' values = Sarcopenia class I SMI – more than 2SD below of young adults' values = Sarcopenia class II. Based on previous study	Age	**M**		**W**	
									Class 1	Class I	Class 1	Class II
								60-69	32.7	18.2	35.6	9.9
								70+	32.1	12.5	25.42	10.2
								Overall	35.3		34.7	
Ryu et al., 2013	Cross-sectional	Muscle mass - DXA	2264	Older adults ≥ 65y from South Korea	NA	M= 940 (41.5%) W= 1324 (58.5%)	SMI% – more than 2 SD below the mean of healthy young adults reference group	**M**		**W**		
								10.9		12		
Volpato et al., 2013	Cross-sectional analysis	Muscle mass – BIA	730		Overall= 77.1	M= 339 (46.5%) W= 391 (53.5%)	EWGSOP	Age (y)	**M**		**W**	

		Muscle strength – HHD Physical performance – 4m test		Older Italian ≥ 65y from Chianti			low muscle mass + (low muscle strength or low physical performance). Reference values based in previous studies.	70-74	1.2	2.6
								≥ 80	17.4	31.6
								Overall	7.5	
Yamada et al., 2013	Cross-sectional	Muscle mass – BIA Muscle strength – HHD Physical performance – 10m test	1882	Older adults ≥ 65y from Japan	Overall = 74.9	M= 568 (30.2%) W= 1314 (69.8%)	EWGSOP Low muscle mass + low muscle strength + low physical performance	Total	22	
								Age (y)	**M**	**W**
								65-69	2.6	11.5
								70-74	5.3	11.8
								75-79	23.3	27.1
								80-84	43.9	35.6
								85-89	75	54.3
								Overall	21.8	22.1
Abe et al., 2014	Cross-sectional	Muscle mass - ultrasound	760	Older adults ≥ 60y from Japan	NS	M= 331 (43.5%) W= 429 (56.5%)	SMI – more than 2 SD below the mean for young adults. Based on previous study Site specific - thigh muscle thickness ratio (A50/P50MTH) value of 2 SD below the mean for young adults. Based on a subsample of young adults in the current study		SMI		Thigh MTH	
								Age (y)	**M**	**W**	**M**	**W**
								60-69	33	7	40	67
								70-85	47	24	58	58
Akune et al., 2014	Cross-sectional	Muscle mass - BIA Grip strength - DHD	1000		M= 75.7 W= 74.4	M= 349 (34.9%) W= 651 (65.1%)	EWGSOP	Age (y)	**M**		**W**	
								65-69	1.6		0.6	

		Functional performance – 6m walking test		Older adults ≥60y from Japan				70-74	5.7	5.5
								75-79	17.8	13.8
								80-84	23.2	22.9
								≥85	31.8	62.2
Alexandre et al., 2014	Cross-sectional	Muscle mass – Equation Muscle strength – DHD Physical performance – walking part of SPPB	1149	Older Brazilian >60y from São Paulo	Overall = 69.6	M= 437 (38%) W= 712 (62%)	EWGSOP Low muscle mass + low muscle strength + low physical performance. Reference value for muscle mass based on 20% percentile of the population distribution.	Total	23.1	
								Age (y)	**M**	**W**
								60-69	7.6	7.7
								70-79	19.5	19.4
								≥ 80	44.7	46.6
								Overall	14.4	16.1
Batsis et al., 2014	Cross-sectional	Muscle mass - prediction equation	4652	Older American ≥ 60y	M= 70 W= 71.1	M= 2283 (49.1%) W= 2369 (50.9%)	SMI between 1 and 2 SD of young adults' values = Sarcopenia class I SMI – more than 2SD below of young adults' values = Sarcopenia class II. Reference values based on previous study		**M**		**W**	
								Age (y)	Class I	Class II	Class I	Class II
								60-70	54.9	3.2	15.4	2.1
								70-80	68.0	10.8	31.0	8.4
								80+	66.3	21.9	38.1	14.3
								Overall	75.5		35.4	
Beaudart et al., 2014	Cross-sectional	Muscle mass – DXA Muscle strength – HHD Muscle performance – 4m test	400	Older adults ≥ 65y from Belgium	M=74 W= 73.8	M= 157 (39.25%) W= 243 (60.75%)	EWGSOP using two cut-offs for each domain assessed A – Cut-off 1+ Cut-off1+ Cut-off1	**M**	65-69y	70-74y	75-79y	≥80y
								A	7.41	16.7	13.2	27.6
								B	3.7	16.7	13.2	27.6
								C	7.41	16.7	13.2	27.6

							B - Cut-off 1+ Cut-off1+ Cut-off2 C - Cut-off 1+ Cut-off2+ Cut-off1 D – Cut-off 1+ Cut-off2+ Cut-off2 F – Cut-off 2+ Cut-off1+ Cut-off2 G – Cut-off 2+ Cut-off2+ Cut-off1 H - Cut-off 2+ Cut-off2+ Cut-off2	D	3.7	16.7	13.2	27.6
								E	7.41	16.7	13.2	27.6
								F	3.7	16.7	13.2	27.6
								G	7.41	16.7	13.2	27.6
								H	3.7	16.7	13.2	27.6
								W	65-69y	70-74y	75-79y	≥80y
								A	4.71	15	25	28.6
								B	3.53	15	21.4	26.2
								C	2.35	5	19.6	19
								D	1.18	3.33	10.7	16.7
								E	7.06	16.7	30.4	38.1
								F	5.88	16.7	28.6	35.7
								G	4.71	5	25	28.6
								H	3.53	3.33	16.1	26.2
Cherin et al., 2014	Cross-sectional	Muscle mass – DXA Muscle strength - HHD	575	Older adults ≥ 65years from France	M= 63.6 W= 62.7	M= 139 (29.3%) W= 436 (70.7%)	EWGSOP (muscle mass + strength)			**M**		**W**
								64-74y		13.5		14.5
								75-84		63.8		19.4
								≥85y		45.4		33.3
Figueiredo et al., 2014	Cross-sectional analysis from a survey	Muscle mass - DXA	399	Older men ≥ 65y. from São Paulo, Brazil.	M= 72.7	M= 100%	A – ASMI – more than 2SD below the mean of a sex specific group. according previous study. B – ASM below the 20th percentile of the study population	Criteria				
								A			13.5	
								B			19.8	
Ishii et al, 2014	Cross-sectional analysis	Muscle mass– BIA Muscle strength – DHD Physical performance 11m test	1971	Older Japanese ≥ 65y from Kashiwa.	M= 73.1 W= 72.8	M= 977 (49.6) W= 994 (50.4%)	EWGSOP Low muscle mass + (low muscle strength or low physical performance). Muscle mass reference values was based on values of a young men and	**M**			14.2	
								W			22.1	
								T			18.2	

							women from previous study. Other variables were based on the lowest quintile of the study population.							
Meng et al, 2014	Cross-sectional	Muscle mass – DXA Muscle strength – DHD Physical performance 6m test	101	Older men ≥ 80y from China	M= 88.8	M=100%	EWGSOP Low muscle mass A – RASM or B – SMI% + (low muscle strength or low physical performance) or the presence of the three. Muscle mass reference value was based in a young men group.	A				B		
								45.7				53.2		
Tanimoto et al., 2014	Cross-sectional	Muscle mass – BIA Muscle strength – HDH Physical performance 11m test	1110	Older adults ≥ 65y from Japan	M= 73.7 W= 73.3	M= 372 (33.5%) W= 738 (66.5%)	EWGSOP low muscle mass + (low muscle strength or low physical performance)	**M**				**W**		
								13.4				14.9		
Yoshida et al, 2014	Cross-sectional	Muscle mass – BIA Muscle strength – DHD Physical performance – 6.4m	4811	Older Japanese ≥ 65y. from Aichi	M= 72.2 W= 72.1	M= 2343 (48.7%) W= 2468 (51.3%)	A- EWGSOP B- Muscle mass and strength algorithm - using sex-specific quintile points (lowest 20%) as cut-off values from a subsample of health members from the study sample.	Age (y)	**M**	**W**	Overall			
									A	A	A	B		
								60-69	5	4	7.5	7.3		
								70-74	5	5				
								75-79	8.5	10				
								≥ 80	25	12.2				
								Total	8.2	6.8				

<table>
<tr><td>Wu et al, 2014</td><td>Cross-sectional</td><td>Muscle mass – BIA
Muscle strength – DHD
Physical performance – SPPB</td><td>549</td><td>Older adults ≥ 65y living in a rural community- from Taiwan</td><td>Overall= 76</td><td>M= 285 (52%)
W= 264 (48%)</td><td>EWGSOP

A- Pre-sarcopenia - low muscle mass
B- Sarcopenia - low muscle mass + (low muscle strength or low physical performance).
C- Severe sarcopenia - low muscle mass + low muscle strength + low physical performance.
Reference value based on previous studies.</td><td></td><td colspan="2">M</td><td>W</td></tr>
<tr><td colspan="2">A</td><td colspan="2">4.2</td><td>7.2</td></tr>
<tr><td colspan="2">B</td><td colspan="2">3.9</td><td>10.6</td></tr>
<tr><td colspan="2">B
Overall</td><td colspan="2">7.1</td><td></td></tr>
<tr><td colspan="2">C</td><td colspan="2">4.2</td><td>7.2</td></tr>
<tr><td colspan="2">C
Overall</td><td colspan="3">5.6</td></tr>
<tr><td>Yu et al., 2014</td><td>Cross-sectional analysis from cohort studies</td><td>Muscle mass – DXA
Muscle strength - HHD</td><td>986</td><td>Older adults ≥ 65y from Australia</td><td>M= 72.7
W= 73.2</td><td>M= 611 (62%)
W= 375 (38%)</td><td>A- SMI – more than 2SD below of the mean for young health adults. Based on a young reference sample.
B- SMI below the lowest 20th percentile of the study population
C- sex specific values below the 20% of the distribution based on ASM predicted by regression analysis</td><td></td><td>60-79y</td><td>≥ 80y</td><td colspan="2">Overall</td></tr>
<tr><td rowspan="3">M</td><td>A</td><td>1.9</td><td>7</td><td>2.5</td></tr>
<tr><td>B</td><td>4.4</td><td>19.7</td><td>6.2</td></tr>
<tr><td>C</td><td>5</td><td>16.9</td><td>6.4</td></tr>
<tr><td rowspan="2">W</td><td>A</td><td>0</td><td>1.6</td><td>0.3</td></tr>
<tr><td>B</td><td>6.7</td><td>22.6</td><td>9.3</td></tr>
</table>

									C	7	16.1	8.5
Beaudart et al., 2015	Cross-sectional	Muscle Mass – DXA and BIA HHD and DHD Physical performance – SPPB and 4m test.	400	Older adults > 65y from Belgium	74.1	M= 157 39.3(%) W= 243 (60.7%)	EWGSOP A – DXA+HD+UGS B – DXA+HD+SPPB C - DXA+PD+UGS D - DXA+PD+SPPB E - BIA+HD+UGS F - BIA+HD+SPPB G - BIA+PD+UGS H - BIA+PD+SPPB	A			14	
								B			14.8	
								C			27.6	
								D			27.6	
								E			8.4	
								F			8.4	
								G			17.2	
								H			17.2	
Gao et al., 2015	Cross-sectional	Muscle mass - Calf-circumference Grip strength - DHD Functional performance – 20m walking test	329	Older adults ≥60y from China	70.4	M= 137 (41.6%) W= 192 (58.4%)	AWGS	Age (y)		**M**		**W**
								60-69		0		3.9
								70-79		6.5		9.3
								≥80		11.8		40
Han Peipei et al., 2015	Cross-sectional	Muscle mass - BIA Grip strength - DHD Functional performance – 4m walking test	1069	Older adults ≥60y from China	M= 70.54 W= 69.25	M= 467 (43.69%) W= 602 (56.31%)	AWGS	**M**				**W**
								6.4				11.5
Kemmler et al., 2015	Cross-sectional	Muscle mass - BIA Grip strength - HHD Functional performance – 10m walking test	1325	Old women ≥70y from Germany	76.4	W= 1325 (100%)	EWGSOP	4.5				
Wen et al., 2015	Cross-sectional	Muscle mass - DXA Grip Strength - DHD Functional performance – SF36	286	Older adults ≥ 65y from China	M= 66.5 W= 65.4	M= 136 (47.5%) W= 150 (52.5%)	EWGSOP AWGS IWGS			**M**		**W**
								EWGSOP		0.8		0
								AWGS		7.4		4.7
								IWGS		5.9		0.7
Woo et al., 2015	Cross-sectional	Muscle mass – DXA Muscle strength – HHD Muscle performance – 5m test	4000	Older Chinese ≥ 65y	M= 72.2 W= 79.1	M= 2000 (50%) W= 2000 (50%)	A – AWGS B – FNIH C – FNIH (slowness) D – EWGSOP E – IWGS			**M**		**W**
								A		9.35		5.3
								B		7.7		3.4
								C		2.6		1.3

							F – SARC-F	D	9.5		8.55	
								E	22.1		18.25	
								F	1.55		5.95	
Zeng et al., 2015	Cross-sectional	Muscle mass – BIA Muscle strength – DHD Muscle performance 6m test	395	Older Chinese ≥ 65y	M= 72.4 W= 72.4	M= 199 (50.4%) W= 196 (49.6%)	A- AWGS B- Proposed Chinese criteria – SMI- 2SD below of the mean for young health adults. Based on a young sample Handgrip or speed - lowest than 20th percentile value measured in the elderly. Values presented for more than one criteria fulfilled.	Age (y)	**M**		**W**	
									A	B	A	B
								65-74	16.1`	29.2	24.6	26.1
								≥ 75	21.7	46.4	41.8	46.3
Barbosa-Silva et al., 2016	Cross-sectional	Muscle mass - CC Grip strength - DHD Functional performance – 4m walking test	1291	Older adults ≥ 60y from Brazil	NS	M= 537 (37%) W= 914 (63%)	EWGSOP	Age (y)	Pre-sarcopenia		Class I	Class II
								60-69	11.7		6.7	1.8
								70-79	8.4		9.6	5.1
								≥ 80	7.4		16.2	19.3
								M	9.5			
								W	8.4			
								T	8.8			
Batsis et al., 2016	Cross-sectional	Muscle mass - DXA	4984	Older adults ≥ 65y from USA	71.1	M= 2453 (49.2%) W= 2531 (50.8%)	FNIH	ALM			29.9	
								ALM:BMI			23	
Bianchi et al., 2016	Cross-sectional analysis	Muscle mass – BIA Muscle strength – HHD Musclel performance – 4m test	538	Older adults ≥ 65y from Italy	Overall= 77.1	M= 250 (46.5%) W= 288 (53.5%)	EWGSOP low muscle mass + (low muscle strength or low physical performance). Reference values	10.2				

							based in previous studies.				
Dorosty et al., 2016	Cross-sectional	Muscle mass - BIA Grip strength - HHD Functional performance – 6m walking test	644	Older adults ≥ 60y from Iran	70.8	M= 310 (41.1%) W= 334 (51.9%)	EWGSOP		**M**	**W**	**T**
								EWGSOP	27.1	6.6	32.5
								AWGS			16.5
								FNH			16.1
Jung et al., 2016	Cross-sectional analysis	Muscle mass - BIA Grip strength - DHD Muscle performance – 4m test	382	Older adults ≥ 65y from Korean	M= 74.9 W= 73.7	M= 167 (43.7%) W= 215 (56.3)	AWGS	**M**		28.1	
								W		27.7	
								Overall		27.8	
Han et al., 2016	Cross-sectional analysis	Muscle mass – BIA Muscle strength – HHD Muscle performance – 7m test	878	Older Taiwanese > 65y from Taiwan	M= 73.7 W= 71.9	M= 402 (45.8%) W= 476 (54.2%)	EWGSOP A – SMI based on height - less than two SDs below the gender-specific young adult reference value B – SMI based on weight - less than two SDs below the gender-specific mean value of the young reference group	(EWGSOP)	3.3		
									M	**W**	
								A	6.7	0.4	
								B	4	10.7	
Spira et al., 2016	Cross-sectional	Muscle mass - DXA Grip strength - DHD Functional performance -TUG	1405	Older adults ≥ 60y from Germany	M= 68.4 W= 67.9	M= 622 (44.3%) W= 783 (55.7%)	SMI SMI+TUG SMI+GS		**M**	**W**	
								Total	4.4		
								SMI	25.7	23.1	
								SMI+TUG	3	2.4	
								SMI+GS	6.4	2.3	
Wang et al., 2016	Cross-sectional	Muscle mass - DXA Grip strength - HHD Functional performance – 6m walking test	944	Older adults ≥ 60y from China	68.7	M= 462 (49%) W= 482 (51%)	AWGS	Age (y)	**M**	**W**	
								60-64	2.7	1.9	
								65-74	4.0	7.1	
								≥ 75	15.4	25.5	
								Overall ≥ 65y	8.2	12.5	
Dodds et al., 2017	Cross-sectional	Muscle mass - BIA Grip strength - DHD Gait speed - TUG	719	Older adults ≥ 85y from UK	85.5	M= 282 (39.2%) W= 437 (60.8%)	EWGSOP	21.0			
Lera et al., 2017	Cross-sectional	Muscle mass - DXA Grip Strength - DHD	1006	Older adults ≥ 60 years from Chile	M= 67.7 W= 67.6	M= 319 (31.7%) W= 687 (68.3%)	EWGSOP	Age (y)	**M**	**W**	
								60-64	8.1	14.3	
								65-69	13.5	13.2	

		Functional performance – 3m walking test						70-74	20.3		17.2
								75-79	29.7		25.2
								≥80	39.3		38.2
Kemmler et al., 2017	Cross-sectional	Muscle mass - BIA Grip strength - HHD Functional performance – 10m walking test	965	Old men ≥70y from Germany	77.3	M= 965 (100%)	EWGSOP IWGS FINH	Age (y)	EWGSOP	IWGS	FINH
								70-79	2.5	2.0	1.0
								80-95	10.9	8.0	10.2
Santos et al., 2017	Cross-sectional	Muscle mass - DXA Functional performance – 3m walking test	116	Older adults ≥ 85y from Brazil	M= 83.3 W= 83.8	M= 47 (40%) W= 69 (60%)	SMI+GS	**Total**		18.1	
								M		**W**	
								25.5		11.3	
Tramontano et al., 2017	Cross-sectional	Muscle mass - BIA Functional performance – 4m walking test	222	Older adults ≥ 65y from Peru	75	M= 102 (45.9%) W= 120 (54.1%)	IWGS	17.6			
Velazquez et al., 2017	Cross-sectional	Muscle mass – DXA and CC Grip strength - HHD Functional performance – SPPB and TUG	137	Older women ≥ 65y from Mexico	73.8	100% W	EWGSOP a) SMI b) CC	a		14.6	
								b		11.0	
Davies et al., 2018	Cross-sectional	Muscle mass - DXA Grip Strength - HHD Functional performance – 3m walking test	1611	Older adults ≥ 65y from Spain	75.42	M= 711 (44.1%) W= 900 (55.9%)	EWGSOP FNIHs FNIH		**M**		**W**
								EWGSOP	31.08		14.5
								FNIH	21.4		20
								FNIHs	10.3		42.2
Sousa-Santos et al., 2018	Cross-sectional	Muscle mass - Skinfold (mid-arm) Grip strength - DHD Functional performance – 4.6m walking test	1493	Older adults ≥ 65y from Portugal	74 (median)	M= 625 (41.9%) W= 868 (58.1%)	EWGSOP		**M**		**W**
								Sarcopenia (Class I)	8.3		6.5
								Severe Sarcopenia (Class II)	5.3		3.8
Uemura et al., 2018	Cross-sectional	Muscle mass - BIA Grip strength - HHD	3958	Older adults ≥ 65y from Japan	71.8	M= 1970 (49.8) W= 1988 (50.2%)	AWGS	5.6			

		Functional performance – 2.4m walking test										
Alexandre et al., 2019	Cross-sectional	Muscle mass - DXA Grip strength - DHD Muscle performance - 4m test	2123	Older adults from Korea	M= 76.4 F= 75.5	M= 1070 (50.5%) F= 1053 (49.5%)	AWGS1 AWGS2	AWGS1		AWGS2		
								M	W	M	W	
								10.3	8.1	21.3	13.8	
Aryana, 2019	Cross-sectional	Muscle mass - BIA Handgrip strength - DHD Muscle performance - 4.57m	70	Older adults ≥60y from Indonesia	69.4	M= 35 F= 35	AWGS1	12.9%				
Du, 2019	Cross-sectional	Muscle mass - BIA Handgrip strength - HHD Muscle performance - 6m	631	Older Chinese >65y from Shanghai	NS	M= 213 (33.7%) F= 418 (66.3%)	AWGS1	M		W		
								19.2%		8.6%		
Frazon, 2019	Cross-sectional	Muscle mass - BIA Handgrip strength - HHD Muscle performance - 10m	287	Old men from Sweden	87	M = 100%	EWGSOPO1 EWGSOP2	EWGSOP1		EWGSOP2		
								21		20		
Marques, 2019	Cross-sectional	Muscle mass - DXA Handgrip strength - DHD	596	Older adults from Brazil	NS	M= 207 F = 389	EWGSOP1	M		W		
								9.8		5.1		
Mori, 2019	Cross-sectional	Muscle mass – BIA Handgrip strength - HHD Muscle performance - HHD	331	Older adults from Japan	71.5	M= 93 F= 239	AWGS1	5.7				
Kim, 2019	Cross-sectional	Muscle mass - DXA Grip strength - DHD Muscle performance - 4m	2099	Older adults from Korea	M= 76.4 F= 75.4	M= 1053 (50.2%) F= 1046 (49.8%)	EWGSOP1 EWGSOP2 IWGS AWGS FNIH		General	M	W	
								EWGSOP1	20.80	25.5	16.2	
								EWGSOP2	9.30	11.9	6.7	
								IWGS	15.50	15.3	15.7	
								AWGS	9.10	10.2	8	
								FNIH	6.50	8.4	4.7	
Sousa-Santos, 2019	Cross-sectional	Muscle mass - tape	1500		NS	M= 628	EWGSOP02	EWGSOP02		MAMC		

		Grip strength - HHD Muscle performance - 4.6m		Older adults from Portugal		F = 872 (58.1%)	MAMC	4.4						6.2				
Badrasawi, 2020	Cross-sectional	Muscle mass - BIA Grip strength - HHD	145	Older adults >60y from Palestin	69.5	M= 70 F= 75	EWGSOP1	General			M			W				
								26.9			35.7			18.7				
Chew, 2020	Cross-sectional	Muscle mass - DXA Muscle Strength - HHD Repeated chair stand (RCS)	20	Older adults >60y from Singapore	67.9	M= 63 (41.5%) F= 137 (68.5%)	EWGSOP02	14.5										
Johanson, 2020	Cross-sectional	Muscle mass - DXA Muscle Strength - HHD Muscle performance – 4m	2825	Older adults >=60y from Norway	NS	NS	EWGSOP2	2.2										
Jyväkorpi, 2020	Cross-sectional	Muscle mass - DXA Muscle Strength - HHD Muscle performance – SPPB	130	Old men from Finland	87	M= 100%	EWGSOP2	20.8										
Kim, 2020	Cross-sectional	Muscle mass - DXA Muscle Strength - DHD Muscle performance – 4m	2123	Older adults from Korea	M= 76.4 F= 75.5	M= 1070 (50.5%) F= 1053 (49.5%)	AWGS1 AWGS2		M		W							
								AWGS1	10.3		8.1							
								AWGS2	21.3		13.8							
Liu, 2020	Cross-sectional	Muscle mass - BIA Muscle Strength - DHD Muscle performance – 4m	1712	Older adults >=65y from China	62.4	NS	AWGS1	Age(y)										
								65-74			26.5							
								75-84			50.5							
								85+			65.2							
								General			32.5							
Purcell, 2020	Cross-sectional	Muscle mass - DXA Muscle Strength - DHD Muscle performance – 4m	12592	Older adults ≥65y from Canada	NS	M= 6314 (50.1%) F= 6278 (49.9%)	EWGSOP IWGS FNIH		M		W							
								EWGSOP	0.2		0.2							
								IWGS	5.2		7.2							
								FNIH	0.5		0.2							
Shaffie, 2020	Cross-sectional	Muscle mass - DXA Muscle Strength - DHD Muscle performance – 4.57	2426	Older adults > 60y from Iran	69.3	M= 1166 F= 1260	EWGSOP-1(with Iranian cut off) EWGSOP-2(with Iranian cut off)		EWGSOP1			EWGSOP2 (Iranian)			EWGSOP2			
								M	19.7	10.5		12.7						
								W	13.6	7.13		5.42						
								Age (y)	M	W		W	W		M	W		

							EWGSOP-2(with European cut off) definition	60-64	11.8	11.5	6.3	4.9	7.7	4.2
								65-69	21.1	16.1	10.1	8.3	12.3	6.4
								70-74	20	14.8	10	8	13	6.3
								75+	27.5	10	16.3	6.9	19	5.6
Yoshimura, 2020	Cross-sectional	Muscle mass - BIA Muscle Strength - DHD Muscle performance – 6m	963	Older adults >=60y from Japan	72.2	M= 321 F= 642	AWGS1	M				W		
								9.7				8.3		

BIA – bio impedance analysis. DXA – dual x-ray absormetry. M – men. W – women. T – total. GS- Grip strength. HHD – Hydraulic handheld dynamometer. DHD – Digital handheld dynamometer. TUG – time up and go. SPPB – short physical performance battery. SFT – skin fold thickness. ASM – appendicular skeletal mass. ASMI – appendicular skeletal muscle index. RSMI – relative skeletal muscle index. BCM – body cell mass. BCMI – body cell muscle index. TSM – total skeletal muscle mass- TSMI – total skeletal muscle mass index. SMI – skeletal muscle index. FFM – fat free mass. FFMI= fat free muscle mass. SM – skeletal muscle mass. RASM – relative appendicular skeletal muscle. LBM – lean body mass. LBMI – lean body mass index. ALM – appendicular lean mass. LTM_A – appendicular lean tissue mass. ALMI – appendicular lean mass index. MAMC – mid arm muscle circumference. CC – calf circumference. MTH – muscle thickness. A50 – anterior half of the thigh. P50 – posterior half of the thigh. EWGSOP – European working group of sarcopenia in old people. IWGS – International working group in sarcopenia. AWGS – Asian working group in sarcopenia. FNIH – Foundation for the National Institute of Health. NS – not specified. Class I – sarcopenia. Class II – severe sarcopenia.

Appendix 4: Summary table of results and meta-analysis

Sarcopenia Prevalence Stratified by definition and muscle mass measurement tool.

Definition	Tool	Number of Studies*	Participants	Prevalence	95% CI	Heterogeneity
Muscle Mass	DXA	13	13945	11	3.0-20.0	99% (p<0.001)
	BIA	7	4688	14	2.0-27.0	99% (p<0.001)
	Other	2	5412	12	7.0-17.0	99% (p<0.001)
EWGSOP1	DXA	9	11417	11	3.0-20.0	99% (p<0.001)
	BIA	16	16630	11	7.0-16	98% (p<0.001)
	Other	7	7493	9	4.0-14	98% (p<0.001)
EWGSOP2	DXA	3	5124	5	0.0-13.0	99% (p<0.001)
	Other	1	1500	4	3.0-5.0	-
AWGS	DXA	4	7329	5	1.0-10	98% (p<0.001)
	BIA	8	9129	12	3.0-24.0	99% (p<0.001)
	Other	1	612	10	8.0-12	-
IWGS	DXA	4	6771	17	10.0-23.0	96% (p<0.001)
	BIA	1	222	18	13.0-23.0	-
FNIH	DXA	4	12694	15	3.0-29	100% (p<0.001)
	BIA	1	644	16	14.0-19.0	-

*Some studies used more than one definition criteria; due to this reason, the number of studies in the table exceeds the total number of studies in the text.

Sarcopenia Prevalence Stratified by definition and muscle strength measurement tool.

Definition	Tool	Number of Studies*	Participants	Prevalence	95% CI	Heterogeneity
EWGSOP1	Overall	32	35540	11	7.0-14.0	99% (p<0.001)
	HHD	15	15244	10	5.0-16.0	99% (p<0.001)
	DHD	17	20296	11	7.0-16.0	98% (p<0.001)
EWGSOP2	Overall	4	6624	4	1.0-10.0	98% (p<0.001)
	HHD	1	200	15	10.0-20.0	-
	DHD	3	6424	5	1.0-9.0	98% (p<0.001)
AWGS	Overall	13	17070	8	3.0-15.0	99% (p<0.001)
	HHD	5	9877	5	1.0-10.0	98% (p<0.001)
	DHD	8	7193	14	6.0-24.0	99% (p<0.001)
IWGS	Overall	5	6771	16	10.0-23.0	96% (p<0.001)
	HHD	3	6485	18	13.0-23.0	94% (p<0.001)
	DHD	1	286	6	3.0-9.0	-
FNIH	Overall	4	8354	9	3.0-17.0	99% (p<0.001)
	HHD	3	6255	10	0.0-23.0	99% (p<0.001)
	DHD	1	2099	6	5.0-8.0	-

*Some studies used more than one definition criteria; due to this reason, the number of studies in the table exceeds the total number of studies in the text.

Sarcopenia Prevalence Stratified by definition and muscle performance measurement tool.

Definition	Tool	Number of Studies*	Participants	Prevalence	95% CI	Heterogeneity
EWGSOP1	Overall	28	32361	10	6.0-13.0	99 (p<0.01)
	3m	3	4404	13	4.0-24.0	99% (p<0.001)
	4m	8	5858	13	8.0-19.0	96% (p< 0.001)
	4.6	1	1493	7	6.0-9.0	-
	5m	1	4000	2	2.0-2.0	-
	6m	2	1386	14	11.0-18.0	68% (p< 0.001)
	6.4m	1	4811	7	7.0-8.0	-
	7m	1	878	3	2.0-5.0	-
	10m	1	1882	22	20.0-24.0	-
	11m	2	3081	12	9.0-16.0	85% (p= 0.01)
	SPPB	5	2395	9	1.0-19.0	99% (p< 0.01)
	TUG	2	1128	10	0-39.0	99% (p< 0.01)
	SF-36	1	286	0	0-1.0	-
EWGSOP2	Overall	3	6424	4	1.0-9.0	98% (p< 0.01)
	4m	2	4924	5	0.0-13.0	99% (p< 0.001)
	6m	1	1500	4	3.0-5.0	-
AWGS	Overall	12	16426	8	3.0-15.0	99% (p<0.001)
	2.4m	1	3958	6	5.0-6.0	-
	4m	4	5262	17	4.0-33.0	99% (p< 0.001)
	4.57m	1	70	13	6.0-22.0	-
	5m	1	4000	2	1.0-2.0	-
	6m	2	1907	8	6.0-10.0	0% (p= 0.43)
	20m	1	612	9	7.0-11.0	-
	SF-36	1	286	3	1.0-6.0	-
	TUG	1	331	6	3.0-9.0	-
IWGS	Overall	5	6993	17	11.0-23.0	95% (p<0.001)
	4m	2	2321	16	14.0-17.0	0% (p=0.4)
	5m	1	4000	20	19.0-21.0	-
	6m	1	386	11	8.0-14.0	-
	SF-36	1	286	6	3.0-9.0	-
FNIH	Overall	3	7710	7	1.0-17.0	99% (p<0.001)

	3m	1	1611	21	19-23	-
	4m	1	2099	6	5.0-8.0	-
	5m	1	4000	6	5.0-6.0	-

*Some studies used more than one definition criteria; due to this reason, the number of studies in the table exceeds the total number of studies in the text.

Sarcopenia Prevalence in Men stratified by definition and muscle mass measurement tool.

Definition	Tool	Number of Studies*	Participants	Prevalence	95% CI	Heterogeneity
MM	Overall	25	13297	15	10.0-21.0	97% (p< 0.001)
	DXA	16	8242	15	8.0-22.0	97% (p< 0.001)
	BIA	7	2435	11	4.0-19.0	93% (p< 0.001)
	Other	2	2614	23	4.0-41.0	97% (p< 0.001)
EWGSOP1	Overall	36	17846	12	8.0-17.0	98% (p<0.001)
	DXA	15	7491	16	6.0-28.0	99% (p< 0.001)
	BIA	14	7385	10	6.0-14.0	94% (p< 0.001)
	Other	7	2970	9	4.0-15.0	95% (p< 0.001)
EWGSOP2	Overall	6	8839	3	0.0-13.0	99% (p< 0.001)
	DXA	4	8081	2	0.0-15.0	100% (p< 0.001)
	BIA	1	130	21	14.0-28.0	-
	Other	1	628	3	1.0-4.0	-
AWGS	Overall	11	6453	8	4.0-13.0	96% (p< 0.001)
	DXA	5	4721	7	2.0-11.0	96% (p< 0.001)
	BIA	5	1478	14	7.0-23.0	94% (p< 0.001)
	Other	1	254	7	4.0-10.0	96% (p< 0.001)
IWGS	Overall	7	10126	7	1.0-18.0	99% (p< 0.001)
	DXA	5	9059	9	0.0-22.0	99% (p< 0.001)
	BIA	2	1067	4	1.0-7.0	57% (p= 0.13)
FNIH	Overall	6	12755	6	0.0-20.0	100% (p< 0.001)
	DXA	4	9790	6	0.0-31.0	100% (p< 0.001)
	BIA	2	2965	6	2.0-11.0	95% (p< 0.001)

*Some studies used more than one definition criteria; due to this reason, the number of studies in the table exceeds the total number of studies in the text.

Sarcopenia Prevalence in Men stratified by definition and muscle strength measurement tool.

Definition	Tool	Number of Studies*	Participants	Prevalence	95% CI	Heterogeneity
EWGSOP1	Overall	35	17753	12	8.0-17.0	98% (p< 0.001)
	HHD	16	7645	10	4.0-16.0	98% (p< 0.001)
	DHD	19	10108	14	7.0-22.0	98% (p< 0.001)
EWGSOP2	Overall	6	8839	3	0.0-13.0	99% (p< 0.001)
	HHD	2	417	20	17.0-24.0	0% (p< 0.087)
	DHD	4	8422	12	0.0-11.0	99% (p< 0.001)
IWGS	Overall	6	10024	7	1.0-19.0	99% (p< 0.001)
	HHD	3	3188	13	0.0-31.0	99% (p< 0.001)
	DHD	3	6836	7	0.0-17.0	98% (p< 0.001)
FNIH	Overall	5	10031	3	0.0-11.0	99% (p< 0.001)
	HHD	3	3676	8	1.0-18.0	99% (p< 0.001)
	DHD	2	6625	1	0.0-11.0	99% (p< 0.001)

*Some studies used more than one definition criteria; due to this reason, the number of studies in the table exceeds the total number of studies in the text.

Sarcopenia Prevalence in Men stratified by definition and muscle performance measurement tool.

Definition	Tool	Number of Studies*	Participants	Prevalence	95% CI	Heterogeneity
EWGSOP1	Overall	31	16541	12	7.0-18.0	98% (P< 0.001)
	3m	4	1898	13	2.0-27.0	98% (P< 0.001)
	4m	8	2606	21	3.0-41.0	99% (P< 0.001)
	4.57	1	1166	20	17.0-22.0	
	4.6	1	625	8	6.0-11.0	
	5m	1	2000	3	2.0-3.0	
	6m	3	673	18	4.0-35.0	95% (P< 0.001)
	6.4m	1	2343	8	7.0-9.0	
	7m	1	402	0	0.0-.0.0	
	10m	3	1820	11	0.0.-26.0	
	11m	2	1349	14	12.0-16.0	
	SF-36	1	136	1	0.0-3.0	
	SPPB	4	1241	11	2.0-21.0	96% (P< 0.001)
	TUG	1	282	21	16.0-26.0	-
AWGS	Overall	10	6143	8	4.0-13.0	96% (p< 0.001)
	4m	4	2757	11	6.0-18.0	94% (p< 0.001)
	5m	1	2000	3	2.0-3.0	-
	6m	3	996	10	4.0-17.0	91% (p< 0.001)
	20m	1	254	7	4.0-10.0	-
	SF-36	1	136	6	2.0-11.0	-
IWGS	Overall	7	10126	7	1.0-18	99% (p< 0.001)
	4m	3	6802	6	0.0-18.0	98% (p< 0.001)
	5m	1	2000	22	20.0-24.0	-
	6m	1	223	11	7.0-15.0	-
	10m	1	965	4	3.0-5.0	-
	SF-36	1	136	7	3.0-12.0	-
FNIH	Overall	5	10301	3	0.0-11	99% (p< 0.001)
	3m	1	711	21	18.0-24.0	-
	4m	2	6625	1	0.0-11.0	99% (p< 0.001)
	5m	1	2000	8	7.0-9.0	-

	10m	1	965	4	3.0-5.0	-

*Some studies used more than one definition criteria; due to this reason, the number of studies in the table exceeds the total number of studies in the text.

*Some studies used more than one definition criteria; due to this reason, the number of studies in the table exceeds the total number of studies in the text.

Sarcopenia Prevalence in Women stratified by definition and muscle mass measurement tool.

Definition	Tool	Number of Studies*	Participants	Prevalence	95% CI	Heterogeneity
MM	Overall	28	16667	9	5.0-15.0	99% (p< 0.001)
	DXA	19	11616	8	3.0.-14.0	99% (p< 0.001)
	BIA	7	2253	16	0.0-40.0	99% (p< 0.001)
	Other	2	2798	11	10.0-12.0	0% (p= 0.8)
EWGSOP1	Overall	34	22637	10	7.0-13.0	97% (p< 0.001)
	DXA	15	10223	9	5.0-13.0	97% (p< 0.001)
	BIA	14	9721	11	6.0-16.0	98% (p< 0.001)
	Other	5	2693	13	2.0-26.0	97% (p< 0.001)
EWGSOP2	Overall	4	8336	2	8.08.0	99% (p< 0.001)
	DXA	3	7464	1	0.0-8.0	0% (p=0.09)
	Other	1	872	5	4.0-7.0	97% (p< 0.001)
AWGS	Overall	10	6882	6	3.0-11.0	97% (p< 0.001)
	DXA	5	4731	5	1.0-10.0	97% (p< 0.001)
	BIA	4	1793	11	5.0-18.0	94% (p< 0.001)
	Other	1	358	6	3.0-11.0	97% (p< 0.001)
IWGS	Overall	7	9730	9	2.0-19.0	98% (p< 0.001)
	DXA	6	9610	9	2.0-18.0	-
	BIA	1	120	32	24.0-40.0	98% (p< 0.001)
FNIH	Overall	5	11632	5	0.0-17.0	100% (p< 0.001)
	DXA	4	9632	5	0.0-23.0	100% (p< 0.001)
	BIA	1	2000	3	3.0-4.0	-

Sarcopenia Prevalence in Women stratified by definition and muscle strength measurement tool.

Definition	Tool	Number of Studies	Participants	Prevalence	95% CI	Heterogeneity
EWGSOP1	Overall	34	22637	10	7.0-13.0	97% (p< 0.001)
	HHD	17	10023	8	3.0-14.0	98% (p< 0.001)
	DHD	17	12614	11	8.0-15.0	96% (p< 0.001)
AWGS	Overall	10	6882	6	3.0-11.0	97% (p< 0.001
	HHD	3	2816	3	0.0-9.0	92% (p< 0.001
	DHD	7	4066	10	6.0-14.0	97% (p< 0.001
IWGS	Overall	6	9610	9	2.0-19.0	98% (p< 0.001
	HHD	3	2572	15	1.0-33.0	97% (p< 0.001
	DHD	3	7038	8	1.0-17.0	98% (p< 0.001
FNIH	Overall	4	9101	2	0.0-10.0	98% (p< 0.001
	HHD	2	2900	7	0.0-27.0	97% (p< 0.001
	DHD	2	6201	0	0.0-6.0	98% (p< 0.001

*Some studies used more than one definition criteria; due to this reason, the number of studies in the table exceeds the total number of studies in the text.

Sarcopenia Prevalence in Women stratified by definition and muscle performance measurement tool.

Definition	Tool	Number of Studies	Participants	Prevalence	95% CI	Heterogeneity
EWGSOP1	Overall	30	20811	10	7.0-13.0	98% (p< 0.001)
	3m	3	2609	12	7.0-18.0	95% (p< 0.001)
	4m	9	3308	12	8.0-17.0	89% (p< 0.001)
	4.57	1	1260	14	12.0-16.0	-
	4.6	1	868	6	5.0-8.0	-
	5m	1	2000	1	1.0-2.0	-
	6m	2	814	14	8.0-21.0	78% (p= 0.03)
	6.4m	1	2468	7	6.0-8.0	-
	7m	1	476	0	0.0-1.0	-
	10m	2	2639	11	0.0-31.0	100% (p< 0.001)
	11m	2	1732	19	12.0-27.0	93% (p< 0.01)
	SF-36	1	150	0	0.0-1.0	-
	SPPB	5	2050	11	3.0-21.0	97% (p< 0.001)
	TUG	1	437	21	17.0-25.0	-
AWGS	Overall	9	6548	6	3.0-11.0	97% (p< 0.001)
	4m	4	2916	10	5.0-15.0	93% (p< 0.001)
	5m	1	2000	1	1.0-2.0	-
	6m	2	1124	9	7.0-10.0	0% (p< 0.69)
	20m	1	358	12	9.0-16.0	-
	SF-36	1	150	1	0.0-3.0	-
IWGS	Overall	7	9730	9	2.0-19	98% (p< 0.001)
	4m	3	7008	9	0.0-21.0	98% (p< 0.001)
	5m	1	2000	18	17.0-20.0	-
	6m	1	163	12	7.0-17	-
	SF-36	1	150	5	2.0-9.0	-
	TUG	1	409	3	1.0-5.0	-
FNIH	Overall	4	9101	2	0.0-2.0	100% (p< 0.001)
	3m	1	900	20	17.0-23.0	-
	4m	2	6201	0	0.0-6.0	99% (p< 0.001)
	5m	1	2000	3	3.0-4.0	-

*Some studies used more than one definition criteria; due to this reason, the number of studies in the table exceeds the total number of studies in the text.

Appendix 5: Evaluation of risk of bias (Adapted from Hoy et al, 2012)

Author/Year	Was the study's target population a close representation of the national population in relation to relevant variables, e.g. age, sex, occupation?	Was the sampling frame a true or close representation of the target population?	Was some form of random selection used to select the sample, OR, was a census undertaken?	Was the likelihood of non-response bias minimal?	Were data collected directly from the subjects (as opposed to a proxy)?	Was an acceptable case definition used in the study?	Was the study instrument that measured the parameter of interest (e.g. prevalence of sarcopenia) shown to have reliability and validity (if necessary)?	Was the same mode of data collection used for all subjects?	Were the numerator(s) and denominator(s) for the parameter of interest appropriate	Was the length of the shortest prevalence period for the parameter of interest appropriate?	Summary on the overall risk of study bias Low risk ≥8 Moderate risk 6-7 High risk ≤ 5
Baumgartner, 1998	N	N	N	N	Y	Y	Y	Y	Y	Y	MODERATE
Kyle, 2001	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Iannuzzi, 2002	N	N	N	Y	Y	N	Y	Y	Y	Y	MODERATE
Janssem, 2002	N	N	Y	Y	Y	N	Y	Y	Y	Y	MODERATE
Tanko, 2002	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Castillo, 2003	N	Y	N	Y	Y	N	Y	Y	Y	Y	MODERATE
Gillette, 2003	N	Y	N	Y	Y	Y	Y	Y	Y	Y	LOW
Newman, 2003	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	LOW
Rolland, 2003	N	Y	N	Y	Y	N	Y	Y	Y	Y	MODERATE
Lau, 2005	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Chien, 2008	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Tichet, 2008	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Bouchard, 2009	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	LOW
Kim, 2009	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Kirchengast, 2009	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Hairi, 2010	N	Y	N	Y	Y	Y	Y	Y	Y	Y	LOW
Hedayati, 2010	N	N	N	Y	Y	N	Y	Y	Y	Y	MODERATE
Sanada, 2010	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Frisoli, 2011	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	LOW
Wen, 2011	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	LOW
Arango, 2012	N	N	Y	Y	Y	Y	Y	Y	Y	Y	LOW
Kim, 2012	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	LOW
Landi, 2012	N	N	Y	Y	Y	Y	Y	Y	Y	Y	LOW
Lee, 2012	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	LOW

Masanes, 2012	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Bijlsma, 2013	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Coin, 2013	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Domiciano, 2013	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Lee, 2013	N	N	Y	Y	Y	Y	Y	Y	Y	Y	LOW
Legrand, 2013	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Lin, 2013	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Patel, 2013	N	N	Y	Y	Y	Y	Y	Y	Y	Y	LOW
Patil, 2013	N	N	Y	Y	Y	Y	Y	Y	Y	Y	LOW
Pongchaiyakul, 2013	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	LOW
Ryu, 2013	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	LOW
Volpato, 2013	N	N	Y	Y	Y	Y	Y	Y	Y	Y	LOW
Yamada, 2013	N	N	N	Y	Y	Y	Y	Y	Y	Y	LOW
Abe, 2014	N	N	N	Y	Y	N	N	Y	Y	Y	HIGH
Akune, 2014	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Alexandre, 2014	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Batsis, 2014	N	Y	Y	Y	Y	N	Y	Y	Y	Y	LOW
Beaudart, 2014	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Cherin, 2014	N	N	N	Y	Y	N	Y	Y	Y	Y	MODERATE
Figueiredo, 2014	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Ishii, 2014	N	N	Y	Y	Y	Y	Y	Y	Y	Y	LOW
Meng, 2014	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Tanimoto, 2014	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Yoshida, 2014	N	Y	N	Y	Y	Y	Y	Y	Y	Y	LOW
Wu, 2014	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	LOW
Yu, 2014	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	LOW
Beaudart, 2015	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Gao, 2015	N	N	Y	Y	Y	Y	Y	Y	Y	Y	LOW
Han, 2015	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Kemmler, 2015	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	LOW
Wen, 2015	N	N	Y	Y	Y	Y	Y	Y	Y	Y	LOW
Woo, 2015	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Zeng, 2015	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Barbosa-Silva, 2016	N	Y	N	Y	Y	Y	Y	Y	Y	Y	LOW
Batsis, 2016	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	LOW
Bianchi, 2016	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	LOW
Dorosty, 2016	N	N	Y	Y	Y	Y	Y	Y	Y	Y	LOW

Jung, 2016	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Han, 2016	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Spira, 2016	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Wang, 2016	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Dodds, 2017	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Lera, 2017	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Kemmler, 2017	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	LOW
Santos, 2017	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Tramontano, 2017	N	Y	N	Y	Y	Y	Y	Y	Y	Y	LOW
Velazquez, 2017	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Davies, 2018	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Souza-Santos, 2018	N	N	Y	Y	Y	Y	Y	Y	Y	Y	LOW
Uemura, 2018	N	Y	N	Y	Y	Y	Y	Y	Y	Y	LOW
Alexandre, 2019	N	Y	N	Y	Y	Y	Y	Y	Y	Y	LOW
Aryana, 2019	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Du, 2019	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Frazon, 2019	N	Y	N	Y	Y	Y	Y	Y	Y	Y	LOW
Marques, 2019	N	Y	N	Y	Y	Y	Y	Y	Y	Y	LOW
Mori, 2019	Y	Y	N	Y	Y	Y	N	Y	Y	Y	LOW
Kim, 2019	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	LOW
Sousa-Santos, 2019	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	LOW
Badrasawi, 2020	N	N	N	Y	Y	Y	Y	Y	Y	Y	LOW
Chew, 2020	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Johanson, 2020	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	LOW
Jyväkorpi, 2020	N	N	N	Y	Y	Y	Y	Y	Y	Y	MODERATE
Kim, 2020	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	LOW
Liu, 2020	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	LOW
Purcell, 2020	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	LOW
Shaffie, 2020	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	LOW
Yoshimura, 2020	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	LOW

- LOW RISK OF BIAS: Further research is very unlikely to change our confidence in the estimate.
- MODERATE RISK OF BIAS: Further research is likely to have an important impact on our confidence in the estimate and may change the estimate.
- HIGH RISK OF BIAS: Further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate.

N: criterion not met; Y: criterion me

Appendix 6: Supplementary list of References

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Appendices

Ethical approval for Chapter 5

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Affilié à / Affiliated with

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September 11, 2017

Dr. Martin Bilodeau
Associate Professor
School of Rehabilitation Services
University of Ottawa
Scientist, Bruyère Research Institute

Re: **Participation of older adults in clinical trials for management of low back pain: A survey with attendees of the 2017 International Back and Neck Pain Research Forum.**
(M16-17-038)

Final Approval

Dear Dr. Bilodeau,

The Bruyère Continuing Care Research Ethics Board (REB) is pleased to give you ethical approval for the period September 11, 2017 to September 11, 2018.

The following documents have been approved:
- COREB application form, received September 8, 2017
- Consent form, dated September 8, 2017
- Survey questionnaire, received September 8, 2017

The Bruyère Continuing Care REB complies with the membership requirements and operates in compliance with the Tri-Council Policy Statement: Ethics Conduct for Research Involving Humans; the International Conference on Harmonization - Good Clinical Practice: Consolidated Guideline; the provisions of the Personal Health Information Protection Act 2004; and the Food and Drug Act of Health Canada and its applicable Regulations.

Please be advised that any complaints made by participants must be reported to the REB. All changes to the approved protocol must be approved by the REB. Please complete an Annual Project Update/Notification of Termination form by the approval end date as noted above.

We wish you the best of luck with your research endeavors.

Sincerely,

Gordon DuVal, SJD
Chair, Bruyère Research Ethics Board
Bruyère Continuing Care
gduval@bruyere.org

cc: Paulo Nascimento

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October 18, 2017

Dr. Martin Bilodeau
Associate Professor
School of Rehabilitation Services
University of Ottawa
Scientist, Bruyère Research Institute

Re: **Participation of older adults in clinical trials for management of low back pain: A survey with attendees of the 2017 International Back and Neck Pain Research Forum.**
(M16-17-038)

Amendment

Dear Dr. Bilodeau,

Thank you for submitting a request for approval of the item listed below for the above-named study.

☑ Approve the addition of an electronic version of the Survey.

The following document has been approved:

- The addition of an electronic version of the Survey.

The Bruyere Research Institute Research Ethics Board is composed, and acts in compliance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, ICH Guidance E6: Good Clinical Practices, and Part C, Division 5 of the *Food and Drugs Regulations* (Canada).

The information received has been reviewed and I hereby give approval on behalf of the REB. Please note that any future changes to the protocol must be submitted to the Research Ethics Board for approval.

Sincerely,

Gordon DuVal, SJD
Chair, Research Ethics Board
Bruyère Continuing Care
gduval@bruyere.org

cc: Paulo Nascimento

Ethical approval for Chapter 6

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Tél./Tel.: 613-562-6262
Téléc./Fax: 613-562-6367

Hôpital Saint-Vincent Hospital
60, rue Cambridge St. N.
Ottawa ON K1R 7A5
Tél./Tel.: 613-562-6262
Téléc./Fax: 613-782-2785

Résidence Élisabeth-Bruyère Residence
75, rue Bruyère St.
Ottawa ON K1N 5C8
Tél./Tel.: 613-562-6262
Téléc./Fax: 613-562-4223

Résidence Saint-Louis Residence
879, ch. Hiawatha Park Rd.
Ottawa ON K1C 2Z6
Tél./Tel.: 613-562-6262
Téléc./Fax: 613-683-5001

Village Bruyère Village
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Centre de médecine familiale Bruyère
Bruyère Family Medicine Centre
75, rue Bruyère St.
Ottawa ON K1N 5C8
Tél./Tel.: 613-241-3344
Téléc./Fax: 613-241-1971

Centre de médecine familiale Primrose
Primrose Family Medicine Centre
35, rue Primrose St.
Ottawa ON K1R 0A1
Tél./Tel.: 613-230-7788
Téléc./Fax: 613-230-7778

Institut de recherche Bruyère
Bruyère Research Institute
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Ottawa ON K1N 5C8
Tél./Tel.: 613-562-6045
Téléc./Fax: 613-562-4266

Fondation Bruyère Foundation
43, rue Bruyère St.
Ottawa ON K1N 5C8
Tél./Tel.: 613-562-6319
Téléc./Fax: 613-562-6023

Affilié à / Affiliated with
uOttawa

May 16, 2017

Dr. Martin Bilodeau
Associate Professor
School of Rehabilitation Services
University of Ottawa
Scientist, Bruyère Research Institute

Re: **Relationship between sarcopenia and low back pain in older adults. A cross-sectional analysis of the Canadian Longitudinal Study.** (M16-17-028)

Final Approval

Dear Dr. Bilodeau,

The Bruyère Continuing Care Research Ethics Board (REB) is pleased to give you ethical approval for the period May 16, 2017 to May 16, 2018.

The following documents have been approved:
- COREB application form, received May 11, 2017
- CLSA Access agreement, received May 16, 2017

The Bruyère Continuing Care REB complies with the membership requirements and operates in compliance with the Tri-Council Policy Statement: Ethics Conduct for Research Involving Humans; the International Conference on Harmonization - Good Clinical Practice: Consolidated Guideline; the provisions of the Personal Health Information Protection Act 2004; and the Food and Drug Act of Health Canada and its applicable Regulations.

Please be advised that any complaints made by participants must be reported to the REB. All changes to the approved protocol must be approved by the REB. Please complete an Annual Project Update/Notification of Termination form by the approval end date as noted above.

We wish you the best of luck with your research endeavors.

Sincerely,

Gordon DuVal, SJD
Interim Chair, Bruyère Research Ethics Board
Bruyère Continuing Care
gduval@bruyere.org

cc: Paulo Nascimento

Ethical approval for Chapter 7

www.bruyere.org

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Affilié à / Affiliated with

uOttawa

January 3, 2018

Dr. Martin Bilodeau
Associate Professor
School of Rehabilitation Services
University of Ottawa
Scientist, Bruyère Research Institute

Re: "Recruitment of transverse abdominis muscle in older adults with sarcopenia" (Reb Protocol # M16-17-057)

Final Approval

Dear Dr. Bilodeau,

The Bruyère Continuing Care Research Ethics Board (REB) is pleased to give you ethical approval for the above noted study for the period of January 3, 2018 to January 3, 2019.

The following documents have been approved:

- REB Application, received December 19, 2017
- Appendix 1: Recruitment Poster, received December 5, 2017
- Appendix 2: Participant Informed Consent form (version date: December 5, 2017), received December 19, 2017.

The Bruyère Continuing Care REB complies with the membership requirements and operates in compliance with the Tri-Council Policy Statement: Ethics Conduct for Research Involving Humans; the International Conference on Harmonization - Good Clinical Practice: Consolidated Guideline; the provisions of the Personal Health Information Protection Act 2004; and the Food and Drug Act of Health Canada and its applicable Regulations.

Please be advised that any complaints made by participants must be reported to the REB. All changes to the approved protocol must be approved by the REB.

Please complete an Annual Project Update/Notification of Termination form 6 weeks prior to the approval end date as noted above.

We wish you the best of luck with your research endeavors.

Sincerely,

Gordon DuVal, SJD
Chair, Bruyère Research Ethics Board
Bruyère Continuing Care
gduval@bruyere.org

CC. Paulo Nascimento

UNIVERSIDADE FEDERAL DE MINAS GERAIS

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Análise comparativa de medidas ultrassonográficas de função muscular e espessura do músculo transverso abdominal em idosos com e sem dor lombar crônica

Pesquisador: Rafael Zambelli de Almeida Pinto
Área Temática:
Versão: 2
CAAE: 92163218.0.0000.5149
Instituição Proponente: Escola de Educação Física, Fisioterapia e Terapia Ocupacional
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 2.827.200

Apresentação do Projeto:
"Introdução: A perda de massa e função muscular são consequências naturais do envelhecimento. Considerando que os músculos ajudam a sustentar a coluna, o prejuízo nesta estrutura e em sua função pode ser um fator de risco para dor lombar(DL).
Objetivos: O objetivo do presente estudo é comparar a função muscular e a espessura do músculo transverso abdominal (TrA_ de idosos com e sem DL e avaliar a relação da função do músculo TrA com medidas de força de preensão e mobilidade dos idosos de ambos os grupos. Métodos: Ultrassonografia de imagem, dinamometria manual e teste de caminhada de quatro metros serão utilizados para avaliar a espessura muscular, força de preensão manual e velocidade da marcha, respectivamente. A função muscular do transverso abdominal será avaliado por meio do teste de elevação rápida do braço enquanto o início da atividade do músculo transverso do abdome será comparada ao início da contração da motor primário do movimento de elevação do braço (deltoide), medida com eletromiografia de superfície. Estas variáveis serão combinadas com variáveis de confusão em um modelo de regressão logística para verificar a associação da função e quantidade muscular com a dor lombar (variável dependente)."

Objetivo da Pesquisa:
Objetivo Primário:

Endereço: Av. Presidente Antônio Carlos,6627 2º Ad SI 2005
Bairro: Unidade Administrativa II **CEP:** 31.270-901
UF: MG **Município:** BELO HORIZONTE
Telefone: (31)3409-4592 **E-mail:** coep@prpq.ufmg.br

Comparar a função muscular e a espessura do TrA de idosos com e sem DL.
Objetivo Secundário:
Avaliar a relação da função do músculo TrA com medidas de força de preensão e mobilidade entre idosos com e sem dor lombar.

Avaliação dos Riscos e Benefícios:
Segundo os autores:
"Os riscos por participar deste estudo são semelhantes aos presentes nas atividades da vida diária. Os procedimentos serão realizados com você sentado ou deitado em uma maca de tratamento porém, não podemos descartar o risco de queda. Todos os procedimentos são não invasivos, com uma pequena chance de causar algum desconforto. Você não precisa se preocupar com seu desempenho. Nós simplesmente pediremos que você
seja honesto e faça o melhor que puder o que pode resultar em algum grau de cansaço. Para minimizar esses riscos os questionários serão entregues por pesquisadores treinados, os quais irão fornecer todas as instruções necessárias e estarão a disposição para quaisquer esclarecimento.
Benefícios:
Não há benefícios diretos,porém, os dados obditos ajudarão a entender como a função e performance muscular em idosos afeta a atividade dos
músculos localizados na região abdominal. Assim, os resultados podem favorecer o desenvolvimento uma nova teoria para a investigação de estratégias de prevenção e intervenção."

Comentários e Considerações sobre a Pesquisa:
Pesquisa relevante para o corpo de conhecimento.

Considerações sobre os Termos de apresentação obrigatória:
Todos os termos de apresentação obrigatória foram apresentados.

Recomendações:
Sou a favor, S.M.J., de aprovação do projeto.

Conclusões ou Pendências e Lista de Inadequações:
Projeto aprovado.

UNIVERSIDADE FEDERAL DE MINAS GERAIS

Considerações Finais a critério do CEP:

Tendo em vista a legislação vigente (Resolução CNS 466/12), o COEP-UFMG recomenda aos Pesquisadores: comunicar toda e qualquer alteração do projeto e do termo de consentimento via emenda na Plataforma Brasil, informar imediatamente qualquer evento adverso ocorrido durante o desenvolvimento da pesquisa (via documental encaminhada em papel), apresentar na forma de notificação relatórios parciais do andamento do mesmo a cada 06 (seis) meses e ao término da pesquisa encaminhar a este Comitê um sumário dos resultados do projeto (relatório final).

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1157844.pdf	09/08/2018 17:22:28		Aceito
Outros	Carta_Resposta_Parecer_Plataforma_Brasil.docx	09/08/2018 17:15:18	Paulo Roberto Carvalho do Nascimento	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_Analise_comparativa_de_medidas_ultrassonograficas.docx	09/08/2018 17:15:03	Paulo Roberto Carvalho do Nascimento	Aceito
Outros	ParecerCamaraUFMG.jpg	22/06/2018 19:11:04	Paulo Roberto Carvalho do Nascimento	Aceito
Folha de Rosto	Folha_de_rosto_Zambelli.pdf	18/06/2018 01:31:13	Rafael Zambelli de Almeida Pinto	Aceito
Projeto Detalhado / Brochura Investigador	Analise_comparativa_de_medidas_ultrassonograficas_de_funcao_muscular.docx	18/06/2018 01:28:42	Rafael Zambelli de Almeida Pinto	Aceito
Outros	92163218aprovacaoassinada.pdf	17/08/2018 09:27:28	Vivian Resende	Aceito
Outros	92163218parecerassinado.pdf	17/08/2018 09:27:45	Vivian Resende	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

Endereço: Av. Presidente Antônio Carlos,6627 2º Ad SI 2005
Bairro: Unidade Administrativa II **CEP:** 31.270-901
UF: MG **Município:** BELO HORIZONTE
Telefone: (31)3409-4592 **E-mail:** coep@prpq.ufmg.br

UNIVERSIDADE FEDERAL DE MINAS GERAIS

Continuação do Parecer: 2.827.200

BELO HORIZONTE, 17 de Agosto de 2018

Assinado por:
Vivian Resende
(Coordenador)

Endereço: Av. Presidente Antônio Carlos,6627 2º Ad SI 2005
Bairro: Unidade Administrativa II **CEP:** 31.270-901
UF: MG **Município:** BELO HORIZONTE
Telefone: (31)3409-4592 **E-mail:** coep@prpq.ufmg.br

Consent form for Chapter 5

Recruitment of older adults in low back pain clinical trials: a survey with attendees of the 2017 back and neck pain forum

Dear Colleague,

I invite you to participate in a research study entitled: Why are older adults underrepresented in low back pain research? A survey with attendees at the 2017 international back and neck pain research forum. Please consider to answer the questionnaire even if you answered the paper-version during the LBP forum.

I am a PhD candidate in the Rehabilitation Sciences Program at the University of Ottawa, ON, Canada, and am in the process of completing my thesis. As a part of this work, we propose a study which purpose is to investigate the reasons that explain the exclusion/low representativeness of older adults in clinical trials for the management of low back pain.

The enclosed questionnaire has been designed to collect information on: previous, current and future research on LBP; inclusion of older participants, subgroup analysis, reason to not include older participants, demographic information.

Your participation in this research project is completely voluntary. You may decline altogether, or leave blank any questions you do not wish to answer. There are no known risks to participation beyond those encountered in everyday life. Your responses will remain confidential and anonymous. Data from this research will be kept under lock and key and reported only as a collective combined total. No one other than the researchers will know your individual answers to this questionnaire.

If you agree to participate in this project, please answer the questions on the questionnaire as best you can. It should take approximately *03 minutes* to complete. Please complete the questionnaire attached to this letter.

Acceptance: I, _____ *(name of participant),* accept to participate in this research conducted by the research team headed by Dr. Martin Bilodeau from Bruyère Research Institute and the Faculty of Health Sciences of the University of Ottawa.
If you have any questions about this project, feel free to contact *Paulo Nascimento, PhD Candidate or Martin Bilodeau, PhD.* Information on the rights of human subjects in research is available through the Research Ethics Board from the Bruyère Research Institute at 43 Bruyère Street, ON, Canada, K1N5C8 by phone: 613-562-6262 ext. 4003 or email: reb@bruyere.org.
Thank you for your assistance in this important endeavor.
Sincerely,

Paulo Nascimento

Consent form for Chapter 7

Recruiting of Transverse Abdominis Muscle in Older Adults with Sarcopenia

INVESTIGATOR
Martin Bilodeau, Ph.D., PT,
Bruyère Research Institute & School of Rehabilitation Sciences, Faculty of Health Sciences, University of Ottawa

CO-INVESTIGATORS
Paulo Nascimento, MSc, PT,
Bruyère Research Institute & School of Rehabilitation Sciences, Faculty of Health Sciences, University of Ottawa

Stéphane Poitras, Ph.D., PT,
School of Rehabilitation Sciences, Faculty of Health Sciences, University of Ottawa

Rafael Zambelli, Ph.D., PT,
Federal University of Minas Gerais, Belo Horizonte, Brazil

Leani Maximo, Ph.D., PT,
Federal University of Minas Gerais, Belo Horizonte, Brazil

Daysiane Malta, BSc, PT
Federal University of Minas Gerais, Belo Horizonte, Brazil

Invitation to participate

You are invited to participate in a research study investigating the activity and composition of the deep abdominal muscles in older adults (≥ 65 years).

Deep muscles are important to keep the spine stable. A recent study showed that activation of these muscles is delayed in older adults. Our hypothesis is that the musculoskeletal changes due to aging contribute to this delay which may increase the risk for low back pain.

Purpose of the study

This study aims to test whether the muscle loss is associated with low back pain. Also, if there is a relationship between muscle loss and delay in the deep muscle activity.

Participation

To participate, you must have or do not have low back pain and be aged 65 years or older.

To participate, you need to engage in one session of about 1 (one) hour. The session will take place in the Biomechanical Laboratory at the University of Ottawa, Lees Campus, 200 Lees Ave, Ottawa.

Before starting the task, we will confirm your eligibility through some simple health questions. One investigator will record your sex, month and year of birth, height, and weight. Additionally, we will measure the thickness of your abdominal muscles with an ultrasound device.

To measure the muscle thickness, we will ask you to lay down in your back. The assessor will place the scan of the ultrasound machine over your belly to register the thickness of your muscles. To measure the activity of the muscles from your belly, we will move the ultrasound scanner laterally placing it in region between your ribs and pelvis.

Once the initial assessment is completed, we will prepare you for the task. The investigator will attach a pair of surface auto adhesive electrodes over your right shoulder to register the muscular activity. After that, we will help you to lay down resting over your left side. You will need to keep your arm alongside the body while the examiner places the ultrasound transducer to record the recruitment of the TrA. During this procedure, the device will be positioned in the right side of your belly.

Before we start recording the data, you will execute the task to familiarize with the procedure. Then, we will ask you to pay attention and to move your arm towards your head as fast as you can when you when the examiner say to you “GO”.

Risks

The risks of participating in this study are similar to those present in daily living activities. The procedures will be performed with you seated or lying in a treatment bed. All procedures are non-invasive with a small chance to cause any discomfort. You do not have to worry about your performance. We will simply ask you to be honest and do your best.

Benefits

Although there is no direct benefit, your participation will provide data that will help to understand how loss of muscle mass in in older adults affects the activity of the muscles located in the deep layer of the bely.

Confidentiality and anonymity

We will assign you a code so that your name will remain confidential to the extent permitted by law. Any document with your personal information will only be accessed by the investigators.

All data will be kept in a file cabinet (in the research office) or in Bruyère computer server, which is password-protected. You will not be identified in any publication or presentation related to this study. After the publication of the results all the raw data will be deleted when digital and shredded when in paper form.

Voluntary Participation

I understand that taking part in this research study is completely voluntary. I may choose not to take part at all. If I decide to be in this study, I may stop participating at any time. If I decide not to be in this study, or if I stop participating at any time, I will not be penalized.

Consent

I, _____ *(name of participant)*, accept to participate in this research conducted by the research team headed by Dr. Martin Bilodeau from the Bruyère Research Institute and the Faculty of Health Sciences of the University of Ottawa.

Questions

You are encouraged to ask questions. If you have any questions about the research study itself, you can contact: Dr. Martin Bilodeau at the Bruyère Research Institute, 43 Bruyère Street, Ottawa, Ontario, K1N 5C8.

If you have questions about the rights of research subjects or have ethical concerns about this study, you can contact the chair of the Bruyère Continuing Care Research Ethics Board at (613) 562-6262 x4003 or at REB@ bruyere.org.

There are two copies of this form, one of which is for you to keep.

_____ _____ / ____ / ____
Signature of participant yyyy mm dd

_____ _____ / ____ / ____
Signature of the researcher yyyy mm dd

Research instrument(s) (e.g., questionnaire, interview guide, research protocol, etc.) as well as the tables, figures, and other materials necessary but not contained in the articles or previous chapters.