Understanding the link between physical capability markers, sarcopenia and frailty and adverse health outcomes

Fanny Emily Petermann Rocha

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Institute of Health and Wellbeing

College of Medical, Veterinary & Life Sciences

University of Glasgow

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Abstract

Although chronological age is the main determinant of ageing, physical and social environment factors play a crucial role in healthy ageing, even in earlier stages of life. Physical and biological limitations are not, necessarily, restricted to older ages. Therefore, considering the predicted rapid increase in the number of older people worldwide along with its individual and societal burden, research into healthy ageing – including middle-aged and older individuals – is a priority.

Physical capability is the ability to perform the basic and instrumental activities of daily living. As the decline in physical function occurs progressively with age, the study of this process should start earlier in life and not only during older age. Low levels of physical capability markers (such as grip strength, muscle mass and physical performance [gait speed]) are strong predictors of future health, including premature mortality, cardiovascular and neurodegenerative diseases in middle-aged and old-aged populations. With age, the decline in physical function could occur in more than one marker. Consequently, the study of combined physical capability markers and their clinical combinations 'sarcopenia' and 'frailty' needs to be further explored using prospective data with common and non-common adverse health outcomes.

Considering the associations of physical capability, sarcopenia, and frailty with adverse health outcomes are not fully understood (both investigated in isolation and as the combined effect), the main aim of this thesis was to determine the associations between measures of physical capability, sarcopenia, and frailty and a range of health outcomes, including mortality, cardiovascular (CVD) and respiratory diseases.

To achieve this general aim, seven papers were completed and included in this thesis. Since the overall prevalence of frailty was already estimated using different classifications, the first paper included in this thesis systematically reports and summarises the overall prevalence of sarcopenia (and severe sarcopenia) using different global classifications. Using 6 main classifications, I estimated that the overall prevalence of sarcopenia ranges from 10% to 27% according to the classification used while the prevalence of severe sarcopenia

ranges to 2 to 9%. Then, data from the UK Biobank study was used to investigate the association between the exposures and health outcomes. UK Biobank is a general cohort study that recruited over 500,000 participants between 2006 and 2010. Participants aged 37-73 years attended one of the 22 assessment research centres across Scotland, England and Wales at baseline.

Using the UK Biobank data, the other six studies were carried out. Across these manuscripts, the associations between different exposures - combinations of sarcopenia, frailty, and individual physical capabilities – and adverse outcomes were determined in each manuscript included: incident and mortality for CVD, respiratory diseases, osteoporosis, cancer, COVID-19, dementia as well as all-cause mortality.

In terms of individuals physical capability markers, the strongest association was identified between slow gait speed and incident COPD and respiratory disease as well as all-cause, respiratory and CVD. For incident osteoporosis instead, low muscle mass, followed by slow gait speed, were associated with a higher risk in both sexes. Regarding combinations of physical capability markers, slow gait speed plus low muscle mass, followed for severe sarcopenia, demonstrated the strongest association with incident respiratory disease and all-cause mortality. In terms of osteoporosis, pre-sarcopenic men and sarcopenic women showed a stronger association with incident osteoporosis. The study of the combination between frailty and sarcopenia categories identified that the highest CVD and respiratory risk was identified among frail and sarcopenic individuals. In addition, individuals with more than one clinical condition (frailty, sarcopenia, cachexia, and malnutrition) had almost five times higher risk of dying than those with none (hazard ratio (HR): 4.96 [95% CI: 2.73 to 9.01]). Finally, when frailty was investigated in isolation, I demonstrated that, independently of the frailty classification used, those with pre-frail or frail had a higher risk of severe covid-19. Moreover, pre-frail and frail individuals had an increased risk of all-cause dementia independently of confounder factors such as morbidity (HR pre-frail: 1.21 [95% CI: 1.04 to 1.42] and HR frail: 1.98 [95% CI: 1.47 to 2.67]).

Therefore, this thesis demonstrated that individuals with lower physical capability, sarcopenia and/or frailty had a higher risk of adverse health outcomes, including: incidence and mortality for osteoporosis, CVD, respiratory

disease, cancer, COVID-19, dementia, and all-cause mortality. These associations remained even after adjustment for a large range of potential confounders and existed both in middle-aged and older adult sub-groups.

Considering that the age-related decline in physical capability markers, and therefore sarcopenia and frailty, could be delay and prevented, health interventions to improve physical capability that may reduce the risk of these outcomes are more urgent than ever.

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Publications

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Petermann-Rocha, F. *et al. (February 2019).* **Research Away Day Institute of Health and Wellbeing, University of Glasgow 2019** – 'Association of Sarcopenia with disease incidence and mortality'. Oral presentation.

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Author's Declaration

I declare that this thesis is the result of my own work. In those cases that a contribution of others was used, explicit reference was included. Five out of seven of the manuscripts included are open access; therefore, they can be openly shared in this thesis. For the other two, permission was requested to the editor in chief, or the embargo period was honoured.

The contents of this thesis have not been submitted for any other degree at the University of Glasgow or any other institution.

Fanny Emily Petermann Rocha

December 2021

Main Abbreviations

BIA	: Bioimpedance
CHI	: Community Health Index
COPD	: Chronic obstructive pulmonary disease
CVD	: Cardiovascular disease
DXA	: Dual-energy x-ray absorptiometry
EAC	: Ethics Advisory Committee
FEV1	: Forced expiratory volume in one second
HES	: Health Episode Statistics
HR	: Hazard ratio
MRC	: Medical Research Council
NHS	: National Health Service
OR	: Odds ratio
RR	: Risk Ratio
SD	: Standard deviation
SMR01	: Scottish Morbidity Records
WHO	: World Health Organisation

Chapter 1 Introduction

1.1 Ageing beyond biological changes

The global population is ageing quickly. In 2019, the number of older adults (>60 years) across the globe was 1 billion (WHO); accounting for 12% of the population. Yet, by the year 2050, the World Health Organisation (WHO) has projected that this will double to over 2,000 million individuals; or 22% of the population (WHO, 2018). Whilst extended life expectancy might represent a success story, additional years that are affected by major diseases and severely limited functionality will result in poor quality of life for the individual and place a heavy burden on carers and the health and social care systems.

Ageing is a complex age-progressive process characterised by a decline in several physiological functions that affect most body systems, resulting in a gradual loss of function and potential disability in later life (Lara et al., 2016). The latter contributes to worse mental and physical capacity, hearing, vision and movement, increased vulnerability to non-communicable diseases, and, finally, death. Although chronological age is the main determinant of ageing, physical and social environment factors play a crucial role in healthy behaviour and healthy ageing opportunities from the early stages of life. As a result, health in older individuals is determined by the combined effects of biological and lifestyle factors influenced by wider environmental factors.

In spite of the above, physical and biological limitations are not, necessarily, restricted to older ages. Evidence suggests that physical and mental capacities start to decline at younger ages in some individuals. Therefore, considering the predicted rapid increase in the number of older people worldwide along with its individual and societal burden, research into ageing – including middle-aged and older individuals – is a priority.

1.1.1 Challenges for an ageing society

As society ages, the incidence of physical limitations to perform activities of daily living along with the burden of non-communicable diseases is likely to rise as well. For the first time, people older than 60 years have exceeded those

younger than 15 years in many countries (Rowe, 2019). This transformation represents major obstacles in the way societies are organised. Particularly, it will require innovative initiatives in the public and private sectors to improve the health and social care systems, transportation, housing and urban planning, and economic security for the current and future generations (Rowe, 2019). Therefore, although ageing could be considered an achievement of public policies, it is still a large and growing problem for governments, which have to promote healthy ageing and health for older individuals.

Healthy ageing, or ageing well, defined as "the process of developing and maintaining the functional ability that enables wellbeing in older age", has been established as a health priority and focus of the WHO between 2015 and 2030 (WHO, 2020). Achieving an age-friendly environment, combating ageism, integrating care and improving access to long-term care are part of the main actions proposed by the United Nations to foster healthy ageing during the coming decade (Decade of Healthy Ageing (2021-2030) (WHO).

If health in older adults is seen beyond the absence of disease, ageing well might be achievable for each older adult (WHO, 2020). Yet, are the systems and societies prepared for this challenge? How is it possible to age well with the growing burden of non-communicable diseases and clinical syndromes worldwide? Promoting psychological, social, and physical functionality might be one of the strategies to confront these obstacles.

1.1.2 Physical capability markers and their associations with adverse health outcomes

Physical capability is the ability to perform the basic and instrumental activities of daily living. As the decline in physical function occurs progressively, the study of this process should start earlier in life and not only during older age (Garber et al., 2010, Tomey and Sowers, 2009). In this context, low levels of physical capability markers (such as grip strength, muscle mass and physical performance [gait speed]) are strong predictors of future health, including premature mortality, cardiovascular and neurodegenerative diseases in middle-aged and old-aged populations (Celis-Morales et al., 2018, White et al., 2013, Veronese et al., 2018, Li et al., 2018). These markers of physical capability are all known to

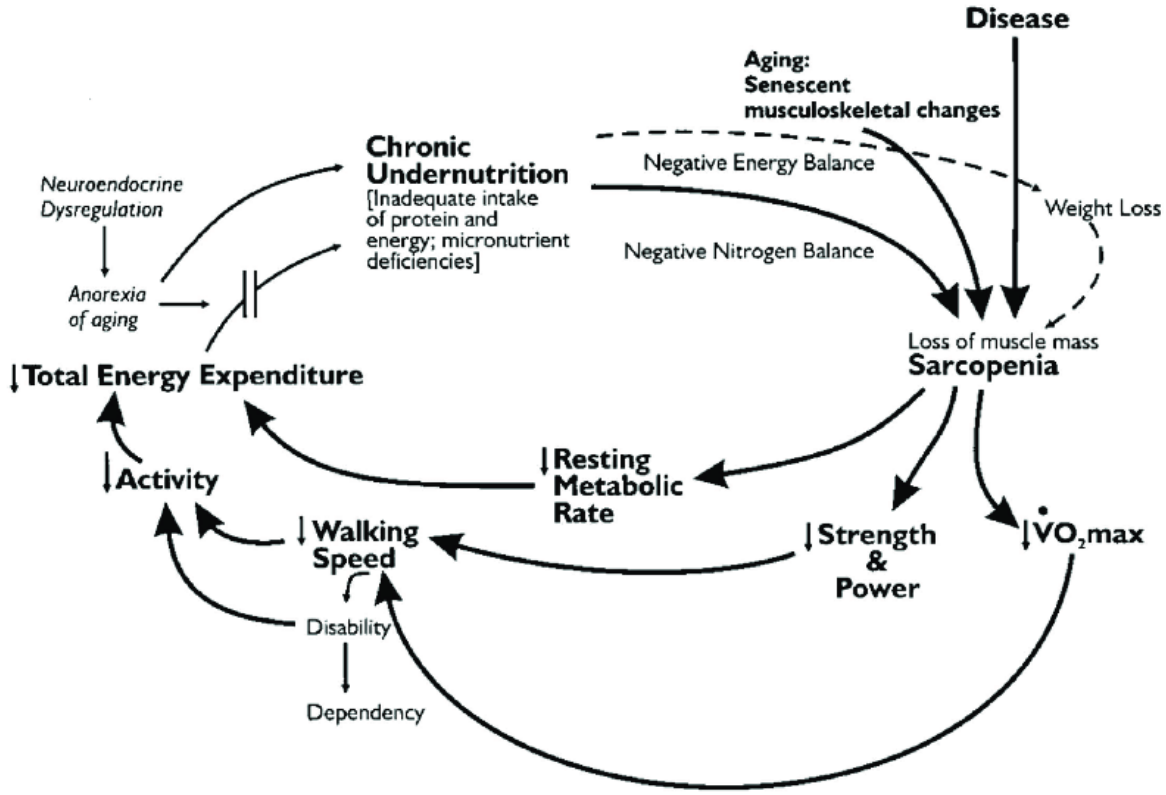
decline after ~35 years of age. With the rapid growth in the number of older adults, the number of individuals with low physical capability levels is expected to increase. This, in turn, will also increase the number of people who are at higher risk of developing non-communicable diseases (WHO, 2018).

With age, the decline in physical function could occur in more than one marker. Consequently, the study of combined physical capability markers and their clinical combinations 'sarcopenia' and 'frailty' needs to be further explored using prospective data with common and non-common adverse health outcomes. Although the association of each individual physical marker with adverse health outcomes is often studied in isolation (Welsh et al., 2020, Celis-Morales et al., 2018, White et al., 2013, Veronese et al., 2018, Li et al., 2018), a further investigation needs to be carried out to investigate combined physical capability markers (i.e., sarcopenia and/or frailty) with mortality, cardiovascular disease (CVD), or cancer in prospective studies both in middle-aged and older adults.

1.1.3 Sarcopenia and frailty

Of the many harmful conditions that occur with ageing, particular emphasis has been placed on sarcopenia and frailty as both are multifactorial syndromes associated with falls, hospitalisations, disability, and worse quality of life. Both conditions can co-exist (Figure 1.1), but the severity of each may vary, independently of each other, between individuals (Cesari et al., 2014, Dodds and Sayer, 2016).

Figure 1-1 Continuous cycle between frailty and sarcopenia



Cycle between frailty and sarcopenia. Figure extracted from '*Frailty in Older Adults: Evidence for a Phenotype'* (Fried et al., 2001).

1.2 Sarcopenia

1.2.1 Definition

Sarcopenia is one of the muscular syndromes related to ageing and one of the 150 musculoskeletal conditions that contribute to disability worldwide (WHO, 2021). A decline in muscle mass and function is probably one of the most dramatic and important processes during ageing (Larsson et al., 2019). As a result, investigations to understand the mechanisms associated with sarcopenia have increased through the scientific community. Despite the progress in this field, there are still many gaps which are a high priority to our society, such as when sarcopenia starts, how to identify an early diagnostic or what should be its operational definition (and associated cut-off points).

The concept of sarcopenia was first reported 30 years ago. In 1989, Irwin Rosenberg was the first person to introduce the "sarcopenia concept" (from the Greek 'sarx' or flesh + 'penia' or loss) after he concluded that with age-decline

the most significant deterioration was in lean body mass (Rosenberg, 1989, Rosenberg, 1997). Nowadays, sarcopenia is recognised as a complex syndrome characterised by a progressive loss of muscle strength along with a higher risk of disability and reduction in quality of life that begins early in life (Marty et al., 2017, Dennison et al., 2017, Cruz-Jentoft et al., 2019b).

1.2.2 Evolution of sarcopenia classification

Between 5% and 50% is the estimated prevalence of sarcopenia among adults 60-years-old and above (Shafiee et al., 2017, von Haehling et al., 2010). These large differences in prevalence are explained by the different criteria employed to estimate it. Different operational definitions have been proposed based on combining the three main physical capability markers mentioned before: low muscle mass, low muscle strength (grip strength) and low physical performance (gait speed). Various working groups have proposed different cut-off points and operational classifications to estimate sarcopenia (Cruz-Jentoft et al., 2010, Fielding et al., 2011, Studenski et al., 2014, Chen et al., 2014a, Cruz-Jentoft et al., 2014, Cruz-Jentoft et al., 2019b, Chen et al., 2020). Most of them have defined sarcopenia as the combination of low muscle mass plus low muscle strength or low muscle mass plus slow gait speed (Table 1-1). In 2019, the EWGSOP established a new operational definition and new cut-off points for sarcopenia (EWGSOP2) (Cruz-Jentoft et al., 2019b). These new guidelines suggest that low muscle strength - more than low muscle mass - is the principal determinant of sarcopenia. Thereby, low muscle strength plus low muscle mass should be established as criteria to confirm sarcopenia, whereas the sum of these criteria plus a slow gait speed has been defined as severe sarcopenia (Cruz-Jentoft et al., 2019b).

Table 1-1 Evolution of operational classification and cut-off points for sarcopenia

Working group	Definition of sarcopenia	Cut-off points
European Working Group on Sarcopenia in Older People (EWGSOP, 2010) (Cruz-Jentoft et al., 2010)	Low muscle mass plus low muscle function or Low muscle mass plus low physical performance.	Muscle mass: DXA, <7.23 kg/m^2 (men) and <5.67 kg/m^2 (women). BIA, <8.87 kg/m^2 (men) and <6.42 kg/m^2 (women) Grip strength (muscle function): <30 kg in men and <20 kg in women.

		Gait speed (performance): ≤0.8 m/s
International working group on Sarcopenia (IWGS, (2011) (Fielding et al., 2011)	Low muscle mass plus low muscle physical performance.	Muscle mass: <7.23 kg/m^2 in men and <5.67 in women. Gait speed (performance): <1m/s
Asian Working group for Sarcopenia (AWGS, 2014) (Studenski et al., 2014)	Low skeletal muscle mass plus low muscle function or Both low skeletal muscle mass and low physical performance.	Muscle mass: DXA, <7.0 kg/m^2 (men) and <5.4 kg/m^2 (women). BIA, <7.0 kg/m^2 (men) and <5.7 kg/m^2 (women) Grip strength (muscle function): <26 kg in men and <18 kg in women. Gait speed (performance): ≤0.8 m/s
Foundation for the National Institutes of Health (FNIH, 2014) (Chen et al., 2014a)	Low muscle mass plus low muscle function.	Muscle mass adjusted by the body mass index: < 0.789 kg/m^2 men and < 0.512 kg/m^2 women Grip strength: <26 kg men and < 16 kg women
International Sarcopenia Initiative (ISI, 2014) (Cruz-Jentoft et al., 2014)	The same definition of EWGOSP but no cut-off points defined.	None
European Working Group on Sarcopenia in Older People 2 (EWGSOP2, 2019) (Cruz-Jentoft et al., 2019b).	Low muscle mass plus low muscle function.	Muscle mass: <7.0 kg/m^2 in men and <5.5 kg/m^2 in women. Grip strength (function): <27 kg in men and <16 kg in women.
Asian Working group for Sarcopenia (AWGS, 2020)(Chen et al., 2020)	The same definition of sarcopenia as AWGS 2014, but new cut-off points defined. The guideline introduces the concept of “possible sarcopenia”, defined as either low grip strength or low physical performance.	Muscle mass: DXA, <7.0 kg/m^2 (men) and <5.4 kg/m^2 (women). BIA, <7.0 kg/m^2 (men) and <5.7 kg/m^2 (women) Grip strength (function): <28 kg in men and <18 kg in women. Gait speed (performance): <1 m/s or

		5-time chair stand test: ≥12 s or Short physical performance battery: ≤9

1.2.3 Sarcopenia and health outcomes – current evidence

Sarcopenia is associated with worse outcomes. Studies have shown that sarcopenic people have a higher risk of morbidity and mortality compared with non-sarcopenic people (Liu et al., 2017, Li et al., 2019, Hanlon et al., 2018b). For instance, Zhang et al. showed that sarcopenia was associated with an increased risk for all-cause mortality among older nursing home residents (HR: 1.86 [95% CI: 1.42 to 2.45]) (Zhang et al., 2018), while Jones et al. determined that sarcopenia, defined by EWGSOP criteria, impacts the functional and health status in COPD patients, specifically those with reduced functional performance, exercise capacity and quality of life (Jones et al., 2015). The associations between the previous classification of sarcopenia and all-cause mortality, respiratory disease and CVD have been widely studied (Zhang et al., 2018, Kim and Choi, 2015, Bone et al., 2017). However, the evidence using the latest classification needs to be further elucidated. In fact, Bachettini et al. showed that gait speed was the only criterion independently associated with mortality in the definition of sarcopenia using the latest classification (76% higher risk of mortality) (Bachettini et al., 2020).

Moreover, the contributions of lifestyle factors to age-related changes in physical capability and sarcopenia are not fully understood. It is also unknown whether sarcopenia measured in the middle-aged predict worse or better health outcomes. Furthermore, it is unclear whether the associations of physical capability and sarcopenia with adverse health outcomes are similar across sociodemographic sub-groups; or whether these measures add predictive utility over and above conventional risk factors for adverse health outcomes such as CVD and respiratory diseases. Therefore, the translation of the research evidence into clinical practice could help to reduce sarcopenia, fall, functional limitations, cognitive impairments, CVD, and mortality (Kelley and Kelley, 2017, Marty et al., 2017, Dennison et al., 2017, Cruz-Jentoft et al., 2019b).

1.3 Frailty

1.3.1 Definition

Frailty is recognised as a multifactorial clinical state that places individuals at a high risk of morbidity, hospital admission, and vulnerability when exposed to a stressor (Fried et al., 2001a). Different operational definitions have been established based on reductions in physical function (mainly strength), reserve, resistance to stressors, psychosocial risk factors and/or multimorbidity (Fried et al., 2001a, Mitnitski et al., 2001, Rockwood and Mitnitski, 2007). Frailty also has a negative impact on instrumental and activities of daily living due to the decline in function from multisystem dysregulation (Gale et al., 2015). This decline in the physiological reserve and function leads to a loss of dynamic homeostasis and is often associated with age (Chen et al., 2014b). Thus, frailty is usually acknowledged as a geriatric syndrome. However, as per sarcopenia, frailty should not be only associated with older generations. Hanlon et al. demonstrated that frailty and pre-frailty are identified both in middle-age (31.6% and 2.7%, respectively) and adults 65 years and above (6.0% and 0.6%, respectively) (Hanlon et al., 2018a). Hence, frailty is a useful risk assessment tool to proactively identify middle-aged individuals at high risk.

In 1998, Fried and Walston suggested that frailty is a vicious cycle of energy dysregulation of many factors interacting with each other (Fried and Walston, 1998). From that moment on, the biological basis and complexity of the frailty definition have tried to be explained deeper (WHO, 2017).

1.3.2 Evolution of frailty classifications

Different operational classification tools for frailty have been proposed since its establishment as a clinical phenotype and a predictor of worse health outcomes (Bouillon et al., 2013). Nonetheless, there is not a unique definition for frailty. The most common definitions are the Frailty Phenotype - also known as the Fried Frailty Score - and the Frailty Index (the Frailty Index of Deficit Accumulation (Fried et al., 2001a, Mitnitski et al., 2001, Rockwood and Mitnitski, 2007). Using data from the Cardiovascular Health Study, Fried et al. defined frailty in 2001 as *“a clinical syndrome in which three or more of the following criteria are*

present": unintentional weight loss, self-reported exhaustion, low grip strength, slow walking speed and low physical activity. Intermediate or pre-frail was defined as 1 or 2 of the criteria mentioned above, while robust or non-frail was defined for those with any criteria (Fried et al., 2001a). The Frailty Index is a more complex score established in 2002 by Mitnitski et al. as a proportion of deficit accumulated by an individual that increased with age in a log-linear relationship (Mitnitski et al., 2002). Later, in 2007, Rockwood & Mitnitski verified that the Frailty Index summarises vulnerability through the proportion of potential deficits present in a person as the sum of symptoms, signs, diseases and disabilities (Rockwood and Mitnitski, 2007). Despite the massive use of the previous index, the National Institute for Health and Care Excellence has recommended using the Clinical Frailty Score in clinical practice. This scale was first introduced by Rockwood et al. in 2005 as a proxy of the Frailty Index (correlation r=0.80) and summarises the overall level of frailty in a short time (Rockwood et al., 2005). In 2020, this scale was reviewed and updated to a 9-point scale (Rockwood and Theou, 2020). An overview of these three different frailty classifications is shown in Table 1-2.

Table 1-2 Frailty classifications

Classification	Criteria and definition
Frailty Phenotype (Fried et al., 2001a)	**Robust (or non-frail):** does not fulfil any criterion. **Pre-frail:** fulfils one or two criteria. **Frail:** fulfils three or more criteria. **Unintentional weight loss:** more than 10 pounds in the previous years. **Weakness:** grip strength in the lowest 20% by gender and body mass index. **Exhaustion:** felt exhausted ≥3 days in last week **Slow walking speed:** walking time/15 feet in the lowest 20% by gender and height. **Low physical activity:** men <383 kcal/per week women <270 kcal/per week
Frailty Index (Rockwood and Mitnitski, 2007)	Initial score based on the proportion of 70 possible deficits presents using data from the existing clinical record. The deficits included long-term conditions, physical, cognitive,

	or sensory impairments, and psychosocial factors. The classifications follow Clegg's criteria (Clegg et al., 2016): **No frailty**: score <0.12. **Mild frailty:** score 0.12 to 0.24. **Moderate frailty:** score 0.25 to 0.36. **Severe frailty:** score >0.36
Clinical Frailty Score – version 2.0 (Rockwood and Theou, 2020)	**Very fit**: people who are robust, active, energetic, and motived. **Well:** people who have no active disease symptoms, but are less fit than category 1. **Managing well:** people whose medical problems are well controlled, but are not regularly active beyond routine walking. **Vulnerable:** while not dependent on others for daily help, often symptoms limit activities. **Mildly frail:** these people often have more evident slowing, and need help in high order IADLs. **Moderately frail:** people who need help with all outside activities and with keeping house. **Severely frail:** people who are completely dependent on personal care. **Very severely frail:** people who are completely dependent and approaching the end of life. **Terminally ill:** in this category is found people with a life expectancy <6 months and who are evidently frail.

Due to these differences in screening tools, the prevalence of frailty ranges from 4% to 59.1%, according to the classification used for its definition (Rohrmann, 2020). The latest systematic review and meta-analysis of population-level studies - from 62 countries and representing 1,755,497 individuals older than 50 years - showed that the prevalence of frailty was 12% (95% CI: 11% to 13%) using the Frailty Phenotype and 24% (95% CI: 22% to 26%) using the Frailty Index. In turn, pre-frail was identified in 46% and 49% of the participants included in this meta-analysis using the Frailty Phenotype and the Frailty Index, respectively (O'Caoimh et al., 2020). Due to these large differences, the WHO has made an

urgent call to develop a global consensus on the operational definition of frailty (WHO, 2017).

1.3.3 Frailty and health outcomes – current evidence

Frailty is a predictor of disability, morbidity, and mortality, which increases the burden on public health care systems (Fried et al., 2001a). Frailty also has a negative impact on activities of daily life and instrumental activities of daily life with approximately 60% of those with frailty being negatively impacted compared to approximately 14% of non-frail older adults (Gale et al., 2015). Studies have shown that frail people have a higher risk of all-cause mortality (Li et al., 2019), CVD (Veronese et al., 2017), respiratory disease (Lahousse et al., 2016), and cancer outcomes (Brown et al., 2015) compared with those non-frail. For instance, Gray et al. – following 2 619 adults older than 65 years – demonstrated that frailty was associated with 1.78 and 4.46-times higher risk of incident dementia and non-Alzheimer dementia, respectively, compared with non-frail individuals (Gray et al., 2013) while Li et al identified that an increased frailty index was associated with 1.28-times (95% CI: 1.24 to 1.32), 1.31-times (95% CI: 1.23 to 1.40) and 1.23-times (95% CI: 1.11 to 1.38) higher risk of all-cause mortality, CVD and respiratory-related mortality, respectively. As frailty is often recognised as a geriatric syndrome, its association with adverse health outcomes is rarely investigated in younger people (Hanlon et al., 2018a). Yet, the decline in the physiological reserve and function might start earlier in life. Additionally, the joint association of frailty with other clinical conditions, such as sarcopenia, needs to be elucidated. Therefore, further studies of this syndrome both in middle-aged and older adults are still needed.

1.4 Thesis overview

1.4.1 Motivation

Considering the associations of physical capability, sarcopenia, and frailty with adverse health outcomes are not fully understood (both investigated in isolation and as the combined effect), this thesis attempts to address some of the current gaps in the literature as well as the contributions of lifestyle factors to age-related changes in these exposures in middle-aged and older adults.

1.4.2 Aim

To determine the associations between measures of physical capability, sarcopenia, and frailty and a range of health outcomes, including mortality, cardiovascular and respiratory diseases.

1.4.3 Objectives

I. To pool the results of existing studies to determine the global prevalence of sarcopenia and severe sarcopenia using different criteria assessments.

II. To compare the associations of different combinations of physical capability markers used to define sarcopenia and health outcomes, using data from the UK Biobank cohort.

III. To investigate the associations between sarcopenia categories – along with its individual components – and incident osteoporosis in both middle-aged and older aged men and women, using data from the UK Biobank cohort.

IV. To investigate the associations of combinations of sarcopenia and frailty with CVD, respiratory disease and cancer outcomes as well as all-cause mortality in middle-aged and older-aged adults, using data from the UK Biobank.

V. To investigate the clustering and mortality risk among these clinical conditions in the middle-aged and older-aged adults, using data from the UK Biobank cohort.

VI. To compare the association between frailty and severe COVID-19 infection resulting in hospital admission or death using two different approaches to measuring frailty, using data from the UK Biobank cohort.

VII. To investigate the association of the frailty phenotype – along with its individual components – with all-cause dementia incidence, using data from the UK Biobank cohort.

1.4.4 Structure of the thesis: paper connection

Throughout this thesis, each objective mentioned above will be systematically covered across seven published papers. **Chapter 2, paper 1** - "*Global prevalence of sarcopenia and severe sarcopenia: a systematic review and meta-analysis*" - systematically reports and summarises the prevalence of sarcopenia (and severe sarcopenia) using different classifications and by sociodemographic factors across the globe. Since six out of the seven papers used UK Biobank data, **Chapter 3** summarises this prospective cohort study's design and general methodology. The other six published papers are included in **Chapter 4**. In this chapter, the individual and combined associations of physical capability markers, sarcopenia and frailty with incidence and mortality outcomes will be covered. **Paper 2** - "*Physical capability markers used to define sarcopenia and their association with cardiovascular and respiratory outcomes and all-cause mortality: A prospective study from UK Biobank"* - identifies whether a different combination of physical capability markers used to define sarcopenia results in a stronger association with incidence and mortality from CVD and respiratory disease as well as all-cause mortality. The association between sarcopenia and osteoporosis has rarely been studied in prospective studies. Therefore, **paper 3** - *"Association of sarcopenia with incident osteoporosis: A prospective study of 168,682 UK Biobank participants*" - reviews this association. Sarcopenia and frailty are associated with each other and often co-exist; however, they are usually investigated in isolation. **Paper 4** - *"The joint association of sarcopenia and frailty with incidence and mortality health outcomes: A prospective study*" - investigates this combined association with CVD, respiratory disease, cancer outcomes, as well as all-cause mortality. Likewise, sarcopenia and frailty share similar diagnostic criteria with other clinical conditions such as malnutrition and cachexia. **Paper 5** - *"Frailty, sarcopenia, cachexia and malnutrition as comorbid conditions and their associations with mortality: a prospective study from UK Biobank"* - reports the clustering and mortality risk among these clinical conditions in the middle- and older-aged adults. In terms of the individual association of frailty, the literature has reported its association with adverse health outcomes, as was mentioned above. However, its association with other emerging outcomes - such as COVID-19 and dementia risk - has been less investigated. **Paper 6,** "*Comparison of two different frailty measurements and*

risk of hospitalisation or death from COVID-19: findings from UK Biobank", and **paper 7**, "Associations between physical frailty and dementia incidence: a prospective study from UK Biobank", summarises these individual associations. Finally, **Chapter 5** provides a general summary of the key findings obtained in the aforementioned manuscripts, the studies' strengths and limitations, the implications of the findings for future research and practice and the main skill and techniques learnt throughout the PhD process.

Chapter 2 Global prevalence of sarcopenia and severe sarcopenia: a systematic review and meta-analysis (Paper 1)

REVIEW

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Global prevalence of sarcopenia and severe sarcopenia: a systematic review and meta-analysis

Fanny Petermann-Rocha[1,2,3†], Viktoria Balntzi[2†], Stuart R. Gray[2], Jose Lara[4], Frederick K. Ho[1‡], Jill P. Pell[1‡] & Carlos Celis-Morales[2,5,6*‡]

[1]*Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK;* [2]*British Heart Foundation Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK;* [3]*Facultad de Medicina, Universidad Diego Portales, Santiago, Chile,* [4]*Department of Applied Sciences, Faculty of Health and Life Sciences, Northumbria University, Newcastle, UK,* [5]*Centre of Exercise Physiology Research (CIFE), Universidad Mayor, Santiago, Chile,* [6]*Laboratorio de Rendimiento Humano, Grupo de Estudio en Educación, Actividad Física y Salud (GEEAFyS), Universidad Católica del Maule, Talca, Chile*

Abstract

Background Sarcopenia is defined as the loss of muscle mass and strength. Despite the seriousness of this disease, a single diagnostic criterion has not yet been established. Few studies have reported the prevalence of sarcopenia globally, and there is a high level of heterogeneity between studies, stemmed from the diagnostic criteria of sarcopenia and the target population. The aims of this systematic review and meta-analysis were (i) to identify and summarize the diagnostic criteria used to define sarcopenia and severe sarcopenia and (ii) to estimate the global and region-specific prevalence of sarcopenia and severe sarcopenia by sociodemographic factors.

Methods Embase, MEDLINE, and Web of Science Core Collections were searched using relevant MeSH terms. The inclusion criteria were cross-sectional or cohort studies in individuals aged ≥18 years, published in English, and with muscle mass measured using dual-energy x-ray absorptiometry, bioelectrical impedance, or computed tomography (CT) scan. For the meta-analysis, studies were stratified by diagnostic criteria (classifications), cut-off points, and instruments to assess muscle mass. If at least three studies reported the same classification, cut-off points, and instrument to measure muscle mass, they were considered suitable for meta-analysis. Following this approach, 6 classifications and 23 subgroups were created. Overall pooled estimates with inverse-variance weights obtained from a random-effects model were estimated using the *metaprop* command in Stata.

Results Out of 19 320 studies, 263 were eligible for the narrative synthesis and 151 for meta-analysis (total $n = 692\,056$, mean age: 68.5 years). Using different classifications and cut-off points, the prevalence of sarcopenia varied between 10% and 27% in the studies included for meta-analysis. The highest and lowest prevalence were observed in Oceania and Europe using the European Working Group on Sarcopenia in Older People (EWGSOP) and EWGSOP2, respectively. The prevalence ranged from 8% to 36% in individuals <60 years and from 10% to 27% in ≥60 years. Men had a higher prevalence of sarcopenia using the EWGSOP2 (11% vs. 2%) while it was higher in women using the International Working Group on Sarcopenia (17% vs. 12%). Finally, the prevalence of severe sarcopenia ranged from 2% to 9%.

Conclusions The prevalence of sarcopenia and severe sarcopenia varied considerably according to the classification and cut-off point used. Considering the lack of a single diagnostic for sarcopenia, future studies should adhere to current guidelines, which would facilitate the comparison of results between studies and populations across the globe.

Keywords Sarcopenia; Prevalence; Systematic review; Meta-analysis

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**Correspondence to: Dr Carlos Celis-Morales, British Heart Foundation Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow G12 8TA, UK. Phone: + 44 141 3304201, Email: carlos.celis@glasgow.ac.uk*
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†These authors are first joint authors.
‡These authors are joint senior authors.

Introduction

Sarcopenia refers to the gradual loss of skeletal muscle mass and strength that, although it is usually associated with advanced ageing, is now recognized to start before 60 years.[1,2] In 1989, Rosenberg defined sarcopenia as loss of muscle mass, from the Greek words sarx (flesh) and penia (loss) after comparing the lean body mass of the thigh of an older woman to a younger woman.[3] Three decades later, sarcopenia is defined as the loss of both muscle mass and strength[1] and has been formally recognized as a muscle disease in the International Classification of Disease (ICD-10: M62 [84]).[4]

Sarcopenia is known to be more prevalent in older populations,[5] but the decline in muscle mass starts from ~40 years onwards.[1] Therefore, the adverse effects of sarcopenia on quality of life, health care demand, morbidity, and mortality can affect both middle-aged and older-aged adults.[1,2,6] The pathophysiology of sarcopenia is complex and results from biological alterations in the structure of the muscles, hormonal imbalances, and external influences such as energy intake deficiencies.[7] In addition to older-aged adults, underweight people, women, and people with other chronic conditions are more likely to develop sarcopenia and the adverse health outcomes associated with this condition.[8]

Despite the seriousness of this disease, a single diagnostic criterion has not yet been established. Several attempts to standardize the operational diagnostic criterion and cut-off points for sarcopenia have been proposed, most of which have used combinations of measures of muscle mass, muscle strength, and gait speed. Among them, the most used definitions are the European Working Group on Sarcopenia in Older People [EWGSOP (2010)],[5] the revised EWGSOP2 (2019),[1] the Asian Working Group for Sarcopenia (AWGS),[9] the International Working Group on Sarcopenia (IWGS),[10] the Foundation for the National Institute of Health (FNIH),[11] as well as definitions using muscle mass only as a single criterion (e.g. Newman and Baumgartner definitions).[12,13] However, within these definitions, the cut-off values applied along with the method used to estimate those values —bioelectrical impedance (BIA) or dual-energy x-ray absorptiometry (DXA)—differ between diagnostic criteria and are highly conditional on the researcher's available resources. This makes it harder to reach a standardized and homogeneous estimate of disease prevalence. To our knowledge, an estimation of the global prevalence is lacking. Some previous systematic reviews and meta-analyses estimated the prevalence of sarcopenia; nevertheless, this prevalence was estimated in healthy older adults only,[14] or community-dwelling older people,[15,16] or only using two diagnostic criteria for sarcopenia.[17] Additionally, there are no studies that have specifically reported the prevalence of severe sarcopenia.

Here, we report the results of a systematic review and meta-analysis to determine the prevalence of sarcopenia addressing the limitations of previous studies. Therefore, the aims of this study were (i) to identify and summarize the diagnostic criteria used to define sarcopenia and severe sarcopenia and (ii) to estimate the global and region-specific prevalence of sarcopenia and severe sarcopenia by sociodemographic factors.

Methods

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines 2020.[18] The protocol is available on PROSPERO (ID protocol: CRD42019141290).

Data sources and search strategy

A systematic search was undertaken in August 2019 using the following databases: MEDLINE, Embase, CENTRAL, and Web of Science Core Collections. Relevant MeSH terms and Boolean phases were used for the search: sarcopenia, muscle mass, grip strength, and gait speed without time restriction and in humans only. The complete search strategy for each database is shown in the Supporting Information.

Study selection

Cross-sectional or cohort studies that included individuals aged ≥18 years with data available on sarcopenia, severe sarcopenia, or other combinations of physical capability markers called sarcopenia, published in English, and those in which muscle mass was measured using DXA, BIA, or computed tomography (CT) scan were included. Studies reporting only incidence rather than the prevalence (e.g. follow-up studies not reporting baseline data), using other study designs (e.g. randomized control trials), using other instruments to measure muscle mass (e.g. calf circumference, SARC-F, or mid-upper arm circumference), conducted in hospitalized people (or undergoing surgery or recovering from a fall), receiving cancer treatment (chemotherapy or radiotherapy), or with a particular disease (e.g. Alzheimer's disease, HIV, cognitive impairment, sclerosis, or rheumatoid arthritis) were excluded (*Figure* 1).

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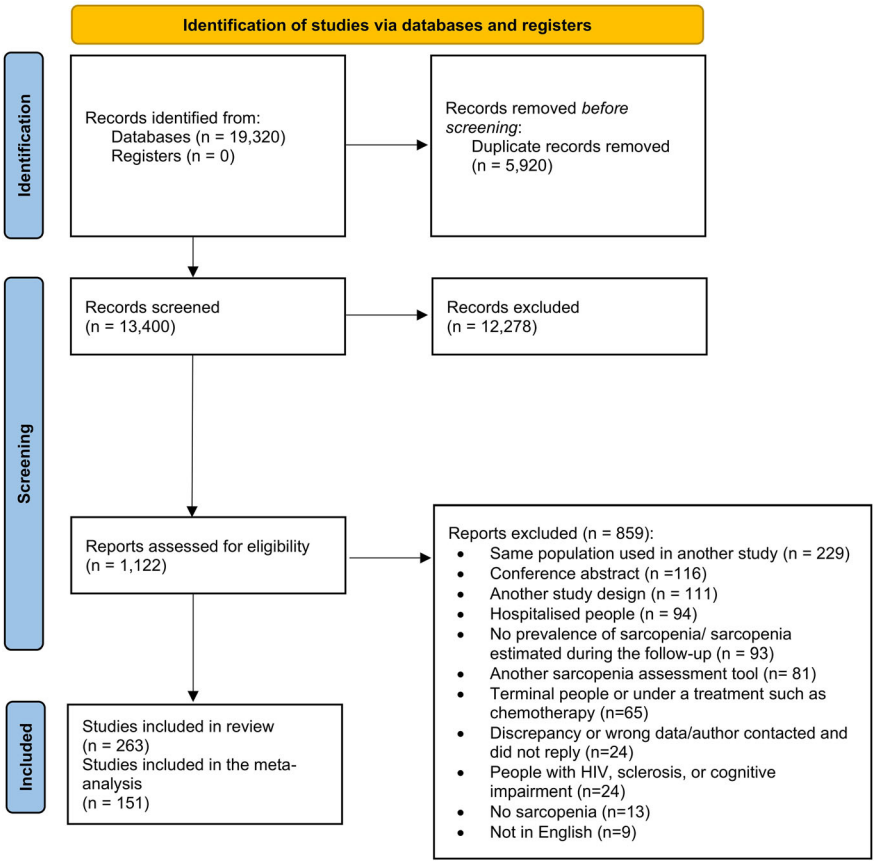

Figure 1 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow diagram.

Data extraction

All titles and abstracts were screened for suitability by two reviewers (F. P.-R. and V. B.) according to the inclusion and exclusion criteria using Covidence.[19] If the study was deemed suitable, it progressed to the retrieval of the full text. If, after a review of the full text, the article was still considered suitable for the analysis, then it progressed to data extraction. These processes were conducted by the same researchers (F. P.-R. and V. B.). Studies with multiple reports were linked, and the larger cohort was used. Additionally, if some information was missing (e.g. cut-off points used) or there was ambiguity (e.g. different numbers reported throughout the text and tables), the lead author was contacted for clarification. If the lead authors did not reply after three attempts over the period of 8 weeks, the article was removed from the analyses (*Figure* 1).

Data from eligible articles were extracted using a standardized form. The form included lead author, year of publication, study design, country, sample size, age, sex, the diagnostic criterion of sarcopenia and severe sarcopenia (if any) used (criteria and cut-off points used to define it), and the prevalence of sarcopenia and/or severe sarcopenia (if any).

Methodological quality assessment

All studies included were further assessed using the risk of bias tool for prevalence studies. This instrument was created by Hoy *et al*. to assess population-based prevalence studies.[20] The tool has 10 questions and evaluates both external (Questions 1 to 4) and internal (Questions 5 to 10) validity. Hoy *et al*. designed two answers: 'yes', to indicate low risk; and 'no', to indicate high risk. For the current systematic review, we additionally included an 'unclear' option when the information was not available to make a judgement for a particular item. Additionally, each study was assigned an overall risk of study bias as 'low', 'moderate', or 'high' (Question 11 in the Hoy *et al*. assessment tool). Studies with $\geq$8 questions scored as low risk were considered to be of 'low risk', those with 6–7 questions scored as low risk were considered to be of 'moderate risk', and those with $\leq$5 questions scored as low risk were considered to be of 'high risk'. This method has been used in previous systematic reviews.[21,22] Each article was scored independently by two reviewers (F. P.-R. and V. B.), and scores were compared. When there was a disagreement, a consensus was achieved.

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Meta-analysis

All studies were stratified by the sarcopenia diagnostic criteria (classifications) as well as by the cut-off points and instrument used to measure muscle mass (subgroups). If a subgroup contained at least three studies that applied the same cut-off for all physical capability markers and used the same instrument to measure muscle mass, these were considered suitable for meta-analysis. In total, 6 sarcopenia classifications and 23 subgroups were identified according to their cut-off points. The classifications and subgroups within classifications are shown in *Table* 1.

The *metaprop* command in Stata was used to calculate the overall pooled estimates with inverse-variance weights obtained from random-effect meta-analysis models.[23] For subgroup analyses, heterogeneity was assessed using the I^2 statistic (which ranges from 0% to 100%). When one study reported more than one cut-off point to define sarcopenia based on the same classification (e.g. two different cut-off points to define muscle mass in the EWGSOP), only one of the studies was kept to estimate the overall prevalence of that classification. The latter was carried out only for the subgroups within the EWGSOP and muscle mass classifications. Finally, the prevalence was estimated by region (Europe, Asia, Africa, North America, South America, and Oceania) and, where possible, by sex. Following the World Health Organization (WHO) definition of ageing, studies were also meta-analysed based on age categories ($\geq$60 and $<$60 years). A meta-regression analysis by age was also performed for all studies and by classification. Stata 16 statistical software (StataCorp LP) was used to perform all analyses.

Results

Search results

The initial search identified 19 320 records. After removing duplicates (n = 5920), 13 400 titles and abstracts were screened. Of these, 1122 were selected for a full-text review for the eligibility assessment (*Figure* 1). Following the application of the inclusion and exclusion criteria, 859 further studies were removed. Therefore, 263 studies were finally included in this systematic review for narrative synthesis (*Figure* 1).

Quality assessment

Using the modified version of the Hoy *et al*. quality assessment tool,[20] the higher or unclear risks were observed in Questions 1 to 4, that is, those relating to the external validity of the study. Question 1—which refers to the representativeness of the sample to the national population in relation to relevant variables such as age or sex—had the highest proportion of 'higher risk' studies with only 3.4% of studies graded 'low risk' for this item (*Figure* 2). On the other hand, questions regarding internal validity (Questions 5 to 10) showed lower risk of bias; 89.4–100% of the studies were graded 'low risk' for these questions. Because of these discrepancies between external and internal validity, we identified that 75.7% of the studies had a moderate (67.3%) or high (8.4%) overall risk of bias (*Figure* 2). Therefore, according to Hoy *et al*., 'further research is likely to have an important impact on our confidence in the estimate and may change the estimate'.[20] Studies were not excluded due to their quality assessment score. More information on each study according to their quality assessment is available in Supporting Information, *Table* S1.

Characteristics of studies—narrative synthesis

A total of 263 studies were included in this systematic review, corresponding to 692 056 individuals (there were also data available on 317 578 women and 319 184 men) with a mean age of 68.5 years (references 1 to 263 in the Supporting Information). Overall, 207 studies were cross-sectional, 53 were cohort studies, and 3 used both designs. Studies were conducted between 2000 and 2019. Most of the studies were carried out in Europe or Asia, while only four studies originated from Africa. BIA was the instrument most often used to assess muscle mass (137 studies), followed by DXA (121 studies) and CT scan (11 studies). In six studies, more than one method to assess muscle mass was used. Height was the principal method used to correct muscle mass while weight was used in 23 studies only. The overall prevalence of sarcopenia ranged from 0.2% to 86.5% according to the classification used (0.3–91.2% in women and 0.4–87.7% in men). The most commonly used classifications were the EWGSOP (prevalence range: 0.4–57.4%) and AWGS (prevalence range: 0.3–53.0%), used in 95 and 55 studies, respectively. Among measures of muscle mass only, skeletal muscle mass corrected for height squared was the most frequently reported approach (79 studies). The prevalence using this approach ranged from 0.2% to 86.5%. Severe sarcopenia was estimated in 34 studies only, with prevalence ranging from 0.2% to 45.0% in women and from 0.2% to 17.1% in men (overall prevalence range: 0.2–34.4%). More information for each study and the cut-off points used is available in *Tables* S2 and S3, respectively.

Meta-analysis

A total of 151 of the 263 studies were suitable for meta-analysis. The average age in these studies was 71.5 years

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Table 1 Classifications and cut-off points used to define sarcopenia in meta-analysis

Classification	Sarcopenia				Severe sarcopenia
	Definition	Muscle mass (instrument)	Grip strength	Gait speed	
EWGSOP2	Sarcopenia was defined as low grip strength and a low muscle mass.	Men <7.0 kg/m^2 Women <6.0 kg/m^{2a} (DXA)	Men <27 kg Women <16 kg	Men and women <0.8 m/s	Was defined as the combination of sarcopenia plus slow gait speed.
EWGSOP	Sarcopenia was defined as the combination of low muscle mass plus low grip strength or slow gait speed.	Men <8.87 kg/m^2 Women <6.42 kg/m^2 (BIA) Men <7.26 kg/m^2 Women <5.5 kg/m^2 (DXA) Men <7.26 kg/m^2 Women <5.45 kg/m^2 (DXA) Men <7.23 kg/m^2 Women <5.67 kg/m^2 (DXA) Men <8.31 kg/m^2 Women <6.68 kg/m^2 (BIA) Men <10.75 kg/m^2 Women <6.75 kg/m^2 (BIA)	Men <30 kg Women <20 kg	Men and women <0.8 m/s	In some studies, when the three physical capabilities were together, the reviewers defined the combination as severe sarcopenia while in other, it was defined as per sarcopenia but with a lower cut-off point for muscle mass.
AWGS	Sarcopenia was defined following the same approach of the EWGSOP.	Men 7.0 kg/m^2 Women <5.4 kg/m^2 (DXA) Men <7.0 kg/m^2 Women <5.7 kg/m^2 (BIA)	Men <26 kg Women <18 kg	Men and women <0.8 m/s	Similar than the EWGSOP.
IWGS	Sarcopenia was defined as the combination of low muscle mass and slow gait speed.	Men <7.23 kg/m^2 Women <5.67 kg/m^2 (DXA) Men <7.23 kg/m^2 Women <5.67 kg^2 (BIA)	—	Men and women <1.0 m/s	—
FNIH	Sarcopenia was defined as low muscle mass and low grip strength.	Men <0.789 or <19.75 kg Women <0.512 or <15.02 kg (DXA) Men <0.789 or <19.75 kg Women <0.512 or <15.02 kg (BIA)	Men <26 kg Women <16 kg	Men and women <0.8 m/s	Was defined as the combination of sarcopenia plus slow gait speed.
Muscle mass	Sarcopenia was defined as low muscle mass only.	Men <7.26 kg/m^2 Women <5.45 kg/m^2 (DXA) Men <7.25 kg/m^2 Women <5.67 kg/m^2 (DXA) Men <10.75 kg/m^2 Women <6.75 kg/m^2 (BIA) Men <8.87 kg/m^2 Women <6.42 kg/m^2 (BIA) Men <0.789 Women <0.512 (DXA) Men <0.789 Women <0.512 (BIA) Men <37% Women <27.6% (BIA) Men <6.87 kg/m^2 Women <5.46 kg/m^2 (DXA) Men <7.23 kg/m^2 Women <5.67 kg/m^2 (DXA) Men <7.26 kg/m^2 Women <5.5 kg/m^2 (DXA)	—	—	Severe sarcopenia as defined using the same approach, but employing a lower cut-off point for muscle mass.

AWGS, Asian Working Group for Sarcopenia; BIA, bioelectrical impedance; DXA, dual-energy x-ray absorptiometry; EWGSOP, European Working Group on Sarcopenia in Older People; EWGSOP2, European Working Group on Sarcopenia in Older People 2; FNIH, Foundation for the National Institute of Health; IWGS, International Working Group on Sarcopenia.
[a]At the time of the search, these studies did not have the newly updated cut-off of 5.5 kg/m^2 for women for the EWGSOP2.

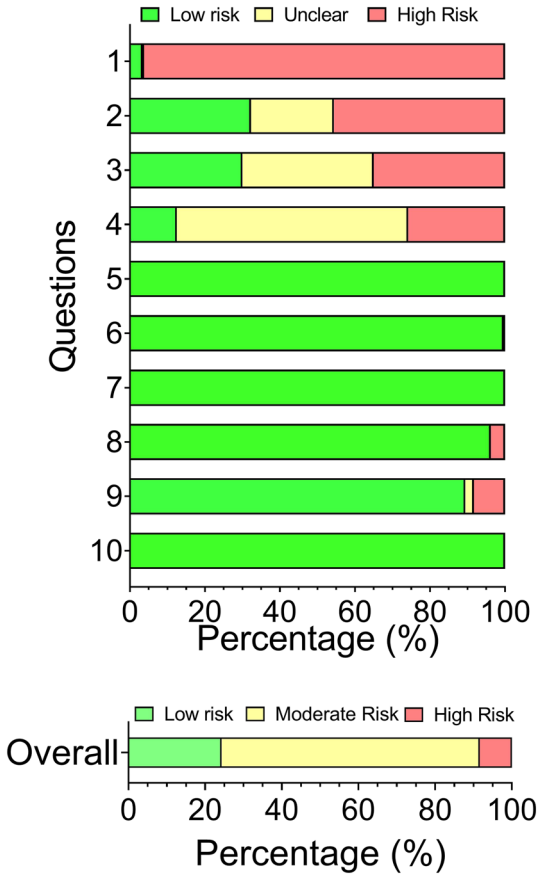

Figure 2 Overall quality assessment of studies included. Studies were assessed using a modified version of Hoy *et al*. The questions were as follows: (1) Was the study's target population a close representation of the national population in relation to relevant variables, for example, age, sex, and occupation? (2) Was the sampling frame a true or close representation of the target population? (3) Was some form of random selection used to select the sample, OR was a census undertaken? (4) Was the likelihood of non-response bias minimal? (5) Were data collected directly from the subjects (as opposed to proxy)? (6) Was an acceptable case definition used in the study? (7) Was the study instrument that measured the parameter of interest (e.g. prevalence of low back pain) shown to have reliability and validity (if necessary)? (8) Was the same mode of data collection used for all subjects? (9) Was the length of the shortest prevalence period for the parameter of interest appropriate? (10) Were the numerator(s) and denominator(s) for the parameter of interest appropriate? Summary item on the overall risk of study bias (overall).

(10% of the population was younger than 60 years and 10% older than 80 years). The individual prevalence by classification and subgroups within the classifications is available in Supporting Information, *Figures* S1–S12, while a summary of the prevalence of these classifications by different sociodemographic characteristics is shown in *Figures* 3–7. The overall prevalence of sarcopenia ranged from 10% [95% confidence interval (CI): 2.0–17.0%] using the EWGSOP2 to 27% (95% CI: 23.0–31.0%) using the overall muscle mass definition (*Figure* 3). The prevalence for each classification was as follows: EWGSOP2: 10% (95% CI: 2.0–17%); AWGS: 18% (95% CI: 14–23%) using DXA and 14% (95% CI: 11–16%) using BIA; IWGS: 11% (95% CI: 6.0–16.0%) using DXA and 20% (4.0–37.0%) using BIA; and FNIH: 10% (95% CI: 7.0–12.0%) using DXA and 15% (8.0–22.0%) using BIA (*Figures* S1a–S6a). For the EWGSOP and muscle mass, two prevalence figures are reported. The first includes all studies grouped by different cut-off points and the second excluding studies that reported more than one cut-off point to define sarcopenia (for that classification). Using the first approach, the prevalence of sarcopenia ranged from 15% (95% CI: 7.0–24%) to 29% (95% CI: 21–36%) for the EWGSOP and from 9% (95% CI: 4.0–14.0%) to 45% (95% CI: 3.0–86.0%) for muscle mass (*Figures* S1a.2 and S6a.2). Excluding these studies, the overall prevalence did not change (*Figures* S2a.1 and S6a.1). The latter approach was kept for the other analyses (prevalence by region, age, and sex).

When the analyses were stratified by region and type of classification or sarcopenia (*Figure* 4), the highest prevalence was observed in Oceania using the EWGSOP (40%) followed by South America using muscle mass (35%) while the lowest prevalence was observed in Europe using the EWGSOP2 (1%) and Oceania using the FNIH (5%). Europe and Asia were the regions with more information available regarding prevalence by classification, while in Africa, the prevalence was estimated only using FNIH (13%). More information regarding each classification by region is available in *Figures* S1b–S6b.

Studies were also classified according to the mean age of the participants as $\geq$60 and $<$60 years. Only four classifications of sarcopenia (EWGSOP, AWGS, FNIH, and muscle mass) contributed to estimate the prevalence in individuals younger than 60 years, which ranged from 8% to 36%. The prevalence for individuals older than 60 years was estimated from studies using all six classifications for sarcopenia, producing a range from 10% to 27% (*Figure* 5). More information regarding the prevalence of sarcopenia by age categories according to each classification and subgroup is available in *Figures* S1c–S6c. Meta-regression analysis showed that the overall prevalence increased by increasing age in years; however, this was not statistically significant (P = 0.718, *Figure* S7). More information for each classification is available in *Figure* S7a–S7f.

Those studies that reported subgroup analyses by sex contributed to pooled estimates derived in women and men. The overall prevalence by sex according to each classification is shown in *Figure* 6, while the individual prevalence for each classification and subgroup is available in *Figures* S1d–S6d for women and S1e–S6e for men. In brief, the prevalence of sarcopenia was higher in men compared with women when the EWGSOP2 (11.0% vs. 2%) and muscle mass (35% vs. 27%) were used for classification. Women classified using the IWGS had a higher prevalence of sarcopenia than men (17% vs. 12%) while the prevalence by sex was similar using the EWGSOP, AWGS, and FNIH.

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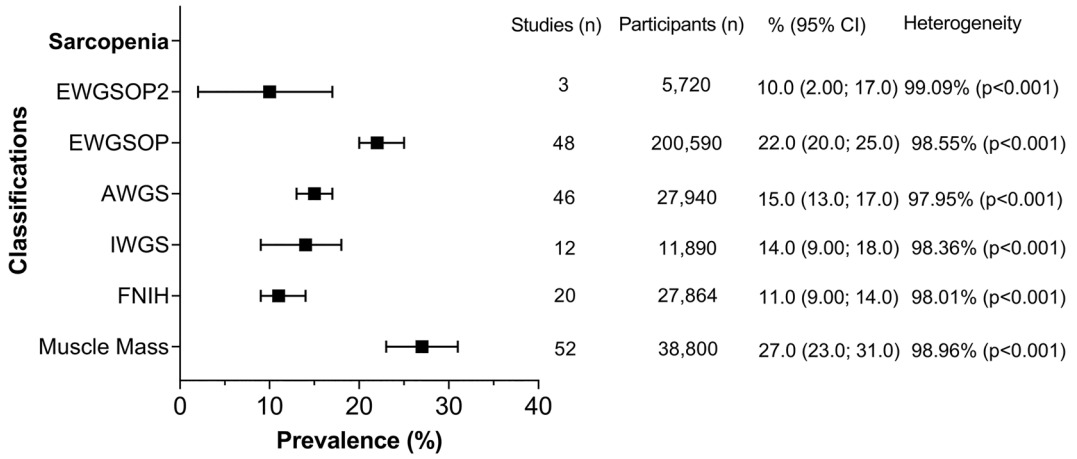

Figure 3 Overall prevalence of sarcopenia according to the classification used. Data presented as prevalence (%) with their respectively 95% confidence intervals (CIs) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects model were estimated for the analyses using *metaprop* in Stata. Heterogeneity was assessed using the I^2 statistic (ranged from 0% to 100%). %, estimated prevalence; AWGS, Asian Working Group for Sarcopenia; EWGSOP, European Working Group on Sarcopenia in Older People; EWGSOP2, European Working Group on Sarcopenia in Older People 2; FNIH, Foundation for the National Institute of Health; IWGS, International Working Group on Sarcopenia.

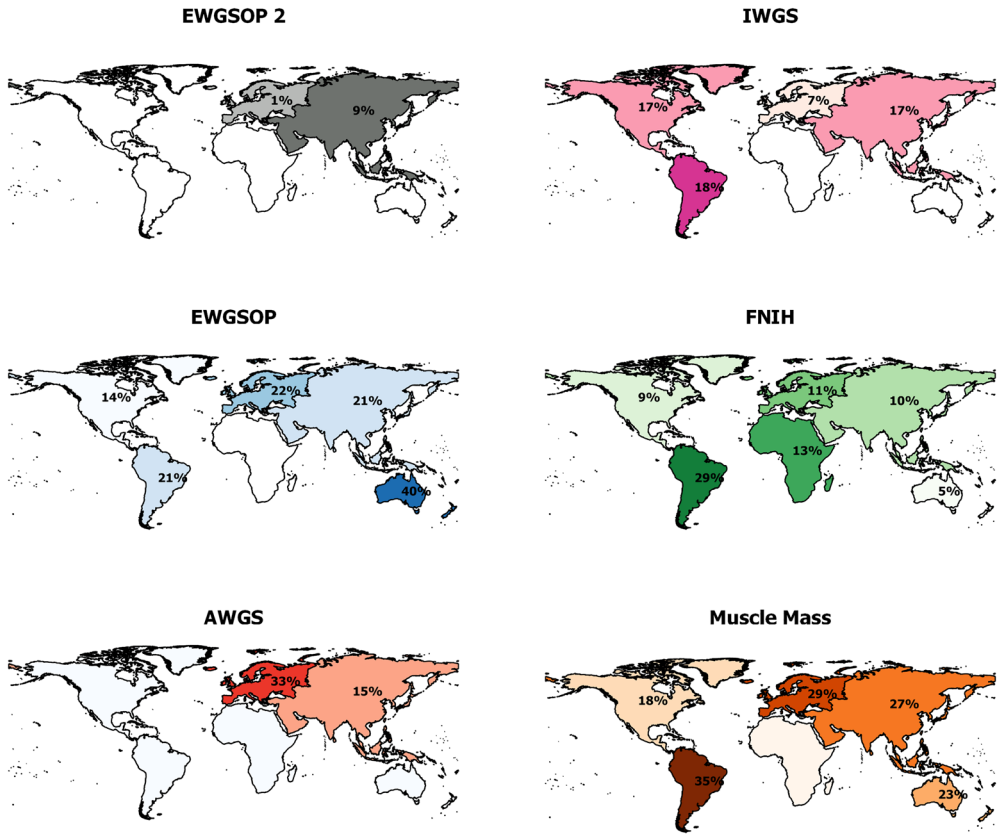

Figure 4 Overall prevalence of sarcopenia by classification and region of origin. Data presented as prevalence (%) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects model were estimated for the analyses using *metaprop* in Stata. AWGS, Asian Working Group for Sarcopenia; EWGSOP, European Working Group on Sarcopenia in Older People; EWGSOP2, European Working Group on Sarcopenia in Older People 2; FNIH, Foundation for the National Institute of Health; IWGS, International Working Group on Sarcopenia.

Finally, 24 studies included in the meta-analysis also reported results for severe sarcopenia using five out of the six main classifications (there were no published estimates using IWGS). According to the classification used, the prevalence of severe sarcopenia ranged from 2% to 9% (*Figure* 7). When the studies were stratified by region and classification, the

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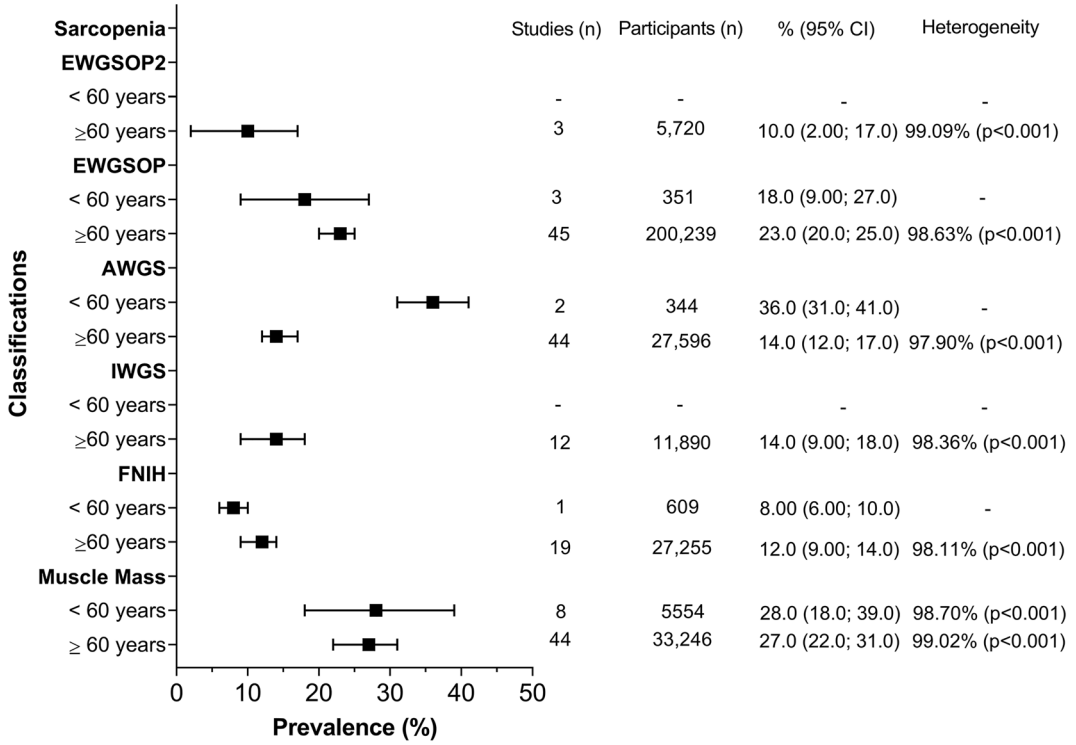

Figure 5 Overall prevalence of sarcopenia by classification and age. Data presented as prevalence (%) with their respectively 95% confidence intervals (CIs) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects model were estimated for the analyses using *metaprop* in Stata. Heterogeneity was assessed using the I^2 statistic (ranged from 0% to 100%). Due to the low numbers of studies with people younger than 60 years, it was impossible to estimate heterogeneity for the EWGSOP, AWGS, and FNIH classifications. %, estimated prevalence; AWGS, Asian Working Group for Sarcopenia; EWGSOP, European Working Group on Sarcopenia in Older People; EWGSOP2, European Working Group on Sarcopenia in Older People 2; FNIH, Foundation for the National Institute of Health; IWGS, International Working Group on Sarcopenia.

prevalence was higher in European studies using the EWGSOP (12%) while Asian and Oceanic studies reported the lowest overall prevalence using the AWGS, FNIH, and EWGSOP (3%) (*Figure* S9a–S9d). In terms of sex, severe sarcopenia was measured using four out of the five classifications. Women reported a higher prevalence compared with men using the EWGSOP and muscle mass, while, using the AWGS and EWGSOP2, the prevalence was similar (*Figure* 7). Finally, the prevalence by age categories was estimated only for muscle mass as studies using the other classifications reported for people older than 60 years only (*Figure* S12). More information about severe sarcopenia by classification and subgroup analysis is available in *Figures* S8–S12.

Discussion

Sarcopenia is a progressive and complex disease associated with a higher burden of morbidity and mortality.[1,2,6] In this study, a comprehensive systematic review of the published literature was performed, and data were extracted for the estimation of the overall prevalence of sarcopenia and severe sarcopenia. Including 263 studies that met the inclusion criteria, the narrative synthesis highlighted that the overall prevalence of sarcopenia ranged between 0.2% and 86.5% according to the classification used. This review revealed that the two most commonly reported classifications were the EWGSOP and the AWGS. Additionally, many studies estimated sarcopenia solely by muscle mass adjusted for height squared. The meta-analysis included six major classifications of sarcopenia—within 23 subgroups with different cut-off points and instrument to assess muscle mass—and estimated that the overall prevalence of sarcopenia ranged from 10%, using the EWGSOP2, to 27%, using the overall muscle mass definition. Moreover, even though previous systematic reviews and meta-analysis have reported the prevalence of sarcopenia in specific regions or communities,[14–16,24,25] this is the first study that reports the prevalence of severe sarcopenia. From 34 studies with severe sarcopenia data, the prevalence of severe sarcopenia ranged from 0.2% to 34.4% in the narrative review while the pooled estimate from the meta-analysis ranged from 2.0% to 9.0%. The revised EWGSOP2 emphasizes that severe sarcopenia should be based on the combination of sarcopenia plus a low physical performance, such as slow gait speed.[1] Therefore, considering that slow gait speed has been identified as an independent risk factor for all-cause mortality[26,27] and that a

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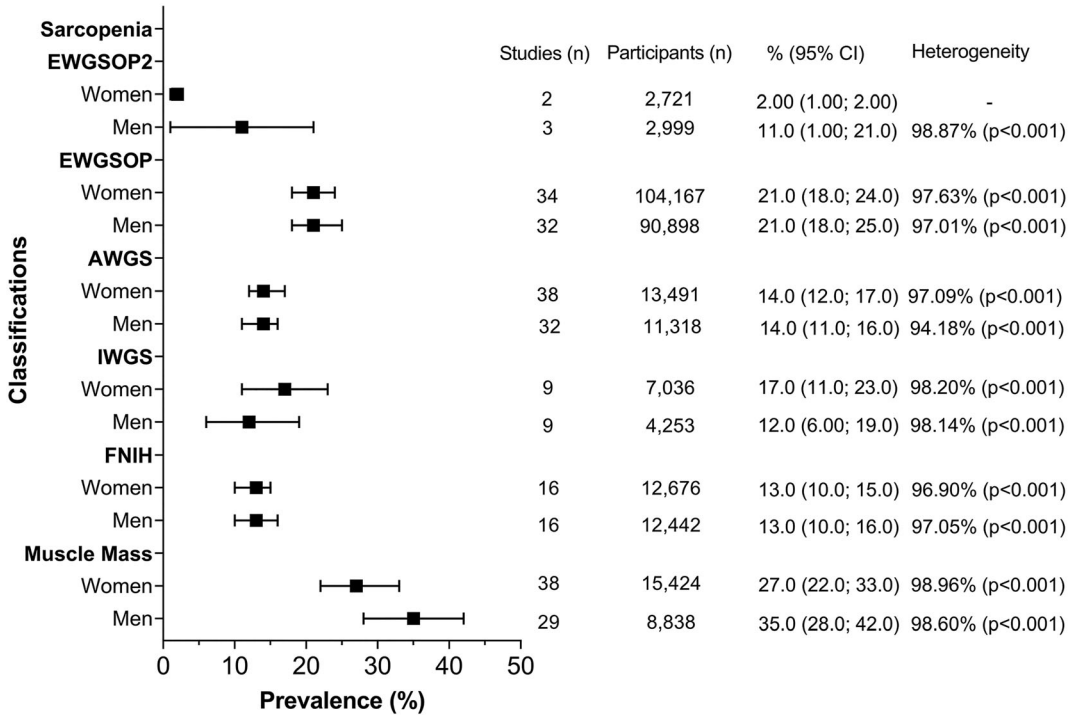

Figure 6 Overall prevalence of sarcopenia by classification and sex. Data presented as prevalence (%) with their respectively 95% confidence intervals (CIs) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects model were estimated for the analyses using *metaprop* in Stata. Heterogeneity was assessed using the I^2 statistic (ranged from 0% to 100%). Due to the low numbers of studies with data available for women, it was impossible to estimate heterogeneity for the EWGSOP2. %, estimated prevalence; AWGS, Asian Working Group for Sarcopenia; EWGSOP, European Working Group on Sarcopenia in Older People; EWGSOP2, European Working Group on Sarcopenia in Older People 2; FNIH, Foundation for the National Institute of Health; IWGS, International Working Group on Sarcopenia.

previous work demonstrated that the combination of slow gait speed and low grip strength, followed by severe sarcopenia, had the highest risk effect over all-cause mortality, cardiovascular disease, and respiratory disease,[6] further study of severe sarcopenia should be encouraged.

Sarcopenia used to be recognized as an ageing-related disease.[5] Nowadays, it is known that the decrease in muscle mass function and quality start at ~40 years and that sarcopenia often appears earlier in life.[1,2] However, studies in this field still tend to focus on older people. In fact, only 10% of the studies included in the meta-analysis estimated the prevalence in people younger than 60 years. Considering that previous research has demonstrated a higher risk of adverse health outcome in middle-aged individuals with sarcopenia,[6] this age group merits further research. This systematic review and meta-analysis also revealed that research on sarcopenia in Africa is very limited. Because 16% of the world's population lives in Africa (more than 1.4 billion)[28] and many Africans have poor access to good nutrition and health care,[29] future studies on sarcopenia are required in order to fully understand the burden of disease in this region.

Across the available studies, there are wide variations in the estimated prevalence of sarcopenia due to the different diagnostic criteria used, differences in the methods used to measure muscle mass, differences in the cut-off points applied, and heterogeneous study populations. These could all contribute to the vast amount of heterogeneity identified among studies. Few systematic reviews and meta-analyses have been attempted to investigate the prevalence of sarcopenia across the globe.[14–16] Shafiee *et al*. reported the overall prevalence in healthy older adults only. Based on 35 studies, the overall prevalence of sarcopenia was 10% in both sexes.[14] Our meta-analysis did not estimate the overall prevalence due to the difference in the cut-off points and instruments within classifications. Moreover, we did not limit our inclusion criteria to healthy adults only as people with sarcopenia often suffer from other chronic conditions. Recently, Papadopoulou *et al*. estimated the worldwide prevalence of sarcopenia, but the study focused on different environmental settings—community, nursing homes, and hospitalized people.[15] Based on 41 studies in total, the authors found that nursing homes residents and hospitalized patients were more likely to be sarcopenic. The prevalence of sarcopenia was 11% and 9% in community-dwelling men and women, respectively; 51% and 31% in men and women in nursing homes, respectively; and 23% and 24% in hospitalized men and women, respectively.[15] However, for that meta-analysis, only three diagnostic tools were applied for the diagnosis of sarcopenia. In the same line, Mayhew *et al*. reported the prevalence of sarcopenia only in

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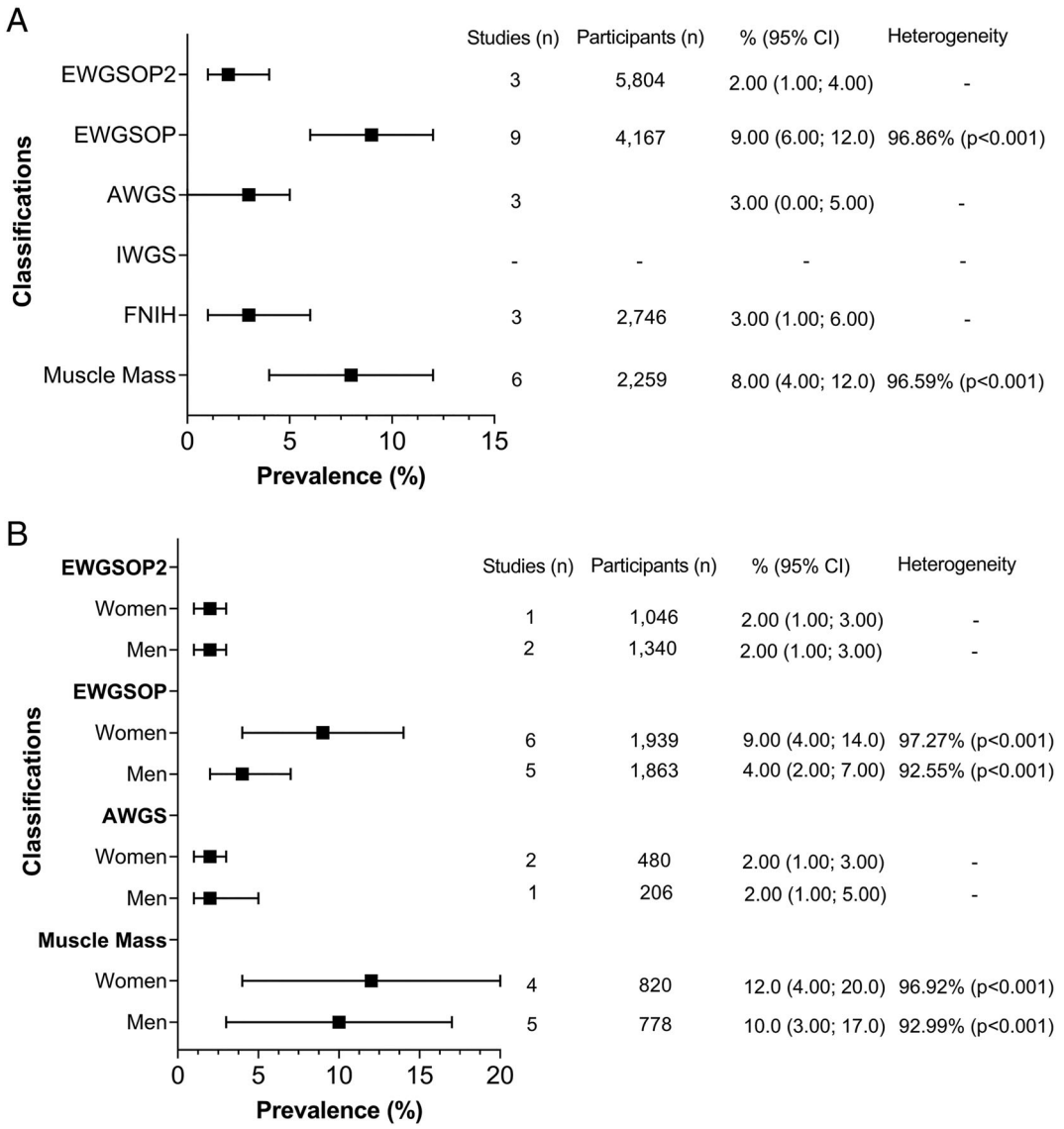

Figure 7 Overall prevalence of severe sarcopenia. Data presented as prevalence (%) with their respectively 95% confidence intervals (CIs) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects model were estimated for the analyses using *metaprop* in Stata. Heterogeneity was assessed using the I^2 statistic (ranged from 0% to 100%). Due to the low numbers of studies, it was impossible to estimate heterogeneity in some cases. Panel (*A*) shows the overall prevalence of severe sarcopenia by classification, while panel (*B*) the overall prevalence by classification and sex. %, estimated prevalence; AWGS, Asian Working Group for Sarcopenia; EWGSOP, European Working Group on Sarcopenia in Older People; EWGSOP2, European Working Group on Sarcopenia in Older People 2; FNIH, Foundation for the National Institute of Health; IWGS, International Working Group on Sarcopenia.

community-dwelling older adults.[16] Reviewing 109 studies, they identified that the prevalence of sarcopenia in this population ranged from 9.9% to 40.4% depending on the diagnostic criterion used. In contrast to Mayhew *et al.*, we did not restrict our inclusion criteria to only community-dwelling older adults because sarcopenia is documented to begin earlier in life.

Sarcopenia leads to a worse quality of life and higher economic burden and health care cost.[30] Although sarcopenia has been recognized as a disease in the ICD since 2016,[4] few studies have examined the overall prevalence in representative samples of the populations, such as National Health Surveys. As a result, the quality assessment in this systematic review and meta-analysis concluded that 'further work is likely to have an important impact on our confidence in the estimate'. Nevertheless, even if more studies become available for inclusion in this meta-analysis, the external validity will not improve unless they are conducted on a representative sample of the population. Furthermore, the lack of a universal and standardized diagnostic criterion for sarcopenia

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still remains one of the main challenges and priorities. The latter has made it difficult to conduct robust studies on sarcopenia, but it is even more difficult to compare or harmonize the results across studies. It also impacts on the ability to produce uniform guidelines for the prevention and treatment of sarcopenia. Sarcopenia can be partially reversed with the correct intervention and treatment.[31] Therefore, even if different cut-off points exist across the globe due to differences in ethnicity or sex, definitions should use the same physical capability markers to diagnose sarcopenia. Achieving a consensual diagnostic criterion would facilitate the comparison of results across studies and help translate the results into clinical practice beyond the research field.

Strengths and limitations

This work was conducted in accordance with the PRISMA guidelines 2020.[18] Study selection, data extraction, and the assessment of quality were carried out by two independent reviewers.[32] In addition, articles included for meta-analysis, and then classified by classification and subgroups, were comparable or identical in terms of the definition of sarcopenia used, the instrument to measure muscle mass, the methods used for the adjustment of muscle mass, and the cut-off points for each criterion. In fact, each subgroup had to have at least three articles using the same methodology—both in the instrument used to measure muscle mass, the adjustment, and cut-off point—for a pooled estimate to be derived. Moreover, if one study reported more than one prevalence using different cut-off points for the same main classification (different subgroups), only one prevalence was kept to avoid having the same population in the analyses more than one.

However, there are some limitations. Firstly, the search included all studies published up to August 2019. More recent studies have not been included. While this might impact the overall prevalence of all classifications and subgroups by cut-off points, the biggest impact is likely to be on prevalence estimated using EWGSWOP2[1] as well as the AWGS that updated its sarcopenia definition and its cut-off points in March 2020.[33] Secondly, although our systematic review and meta-analysis included populations from different regions, the restriction to English articles may have systematically excluded studies conducted in regions such as Latin America, Asia, Africa, and Oceania, generating a potential language selection bias. Moreover, we could not reliably assess publication bias because of the small number of studies per sarcopenia classification and the high heterogeneity among studies. Based on current recommendations, at least 10 studies are needed to examine reporting bias using funnel plots and, if the heterogeneity is high, the minimum number of studies may be substantially more than 10.[34] As for many of our analyses, the number of studies included was below 10, and the heterogeneity was high; we did not perform funnel plots. Thirdly, other sociodemographic characteristics such as ethnicity or area of residence were not assessed due to the lack of information in the majority of the studies. Fourthly, receiving no reponses from the corresponding authors, 24 articles were removed due to missing information or ambiguities in reporting the main study findings. The inclusion of those studies might change the prevalence of some classifications. However, as the corresponding authors did not provide the requested data, more bias could be introduced by including them in our study. Finally, the heterogeneity among studies was higher than 90%; therefore, pooled estimates should be interpreted with caution. While this represents 'considerable heterogeneity', previous meta-analyses of prevalence have reported similar results,[35] mainly due to the variability of the results among studies. The wide variety among classifications and cut-off points used to define sarcopenia may explain the huge heterogeneity identified. Yet, our meta-analysis still provides relevant information regarding the burden of sarcopenia, providing a summarized estimate that can be used to calculate baseline risk for the total population as well as by sex and region.[35]

In conclusion, we found that using different classification systems and cut-off points, the prevalence of sarcopenia ranged from 0.2% to 86.5% in the narrative review and from 10% to 27% in the meta-analysis. The prevalence of severe sarcopenia was estimated, but fewer studies could be included. Similarly, few studies reported prevalence in individuals younger than 60 years. The prevalence by sex was different according to the classification used. EWGSOP and AWGS were the classification systems most commonly used, and muscle mass was most commonly reported as muscle mass adjusted for height squared. Most information was available on European and Asian populations, and least on African. Deriving robust pooled estimates is hindered by the lack of a single classification system. Reaching a consensual diagnostic criterion would facilitate not only research but also the translation of research findings into clinical practice.

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The authors of this manuscript certify that they comply with the ethical guidelines for editorship and publishing in the *Journal of Cachexia, Sarcopenia and Muscle*.[36]

Online supplementary material

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

Figure S1a. Prevalence of sarcopenia using the EWGSOP2.
Figure S1b. Prevalence of sarcopenia using the EWGSOP2 by region of origin.
Figure S1c. Prevalence of sarcopenia using the EWGSOP2 by age categories.
Figure S1d. Prevalence of sarcopenia using the EWGSOP2 in women.
Figure S1e. Prevalence of sarcopenia using the EWGSOP2 in men.
Figure S2a.1. Prevalence of sarcopenia using the EWGSOP (excluding those who reported the prevalence more than once using different cut-off points).
Figure S2a.2. Prevalence of sarcopenia using the EWGSOP (all cut-off points).
Figure S2b. Prevalence of sarcopenia using the EWGSOP by region of origin (excluding those who reported the prevalence more than once using different cut-off points).
Figure S2c. Prevalence of sarcopenia using the EWGSOP by age categories (excluding those who reported the prevalence more than once using different cut-off points).
Figure S2d.1. Prevalence of sarcopenia using the EWGSOP in women (excluding those who reported the prevalence more than once using different cut-off points).
Figure S2d.2. Prevalence of sarcopenia using the EWGSOP in women (all cut-off points).
Figure S2e.1. Prevalence of sarcopenia using the EWGSOP in men (excluding those who reported the prevalence more than once using different cut-off points).
Figure S2e.2. Prevalence of sarcopenia using the EWGSOP in men (all cut-off points).
Figure S3a. Prevalence of sarcopenia using the AWGS.
Figure S3b. Prevalence of sarcopenia using the AWGS by region of origin.
Figure S3c. Prevalence of sarcopenia using the AWGS by age categories.
Figure S3d. Prevalence of sarcopenia using the AWGS in women.
Figure S3e. Prevalence of sarcopenia using the AWGS in men.
Figure S4a. Prevalence of sarcopenia using the IWGS.
Figure S4b. Prevalence of sarcopenia using the IWGS by region of origin.
Figure S4c. Prevalence of sarcopenia using the IWGS by age categories.
Figure S4d. Prevalence of sarcopenia using the IWGS in women.
Figure S4e. Prevalence of sarcopenia using the IWGS in men.
Figure S5a. Prevalence of sarcopenia using the FNIH.
Figure S5b. Prevalence of sarcopenia using the FNIH by region of origin.
Figure S5c. Prevalence of sarcopenia using the FNIH by age categories.
Figure S5d. Prevalence of sarcopenia using the FNIH in women.
Figure S5e. Prevalence of sarcopenia using the FNIH in men.
Figure S6.a.1. Prevalence of sarcopenia using muscle mass (excluding those who reported the prevalence more than once using different cut-off points).
Figure S6.a.2. Prevalence of sarcopenia using muscle mass (all cut-off points).
Figure S6b. Prevalence of sarcopenia using muscle mass by region of origin (excluding those who reported the prevalence more than once using different cut-off points).
Figure S6c. Prevalence of sarcopenia using muscle mass by age categories (excluding those who reported the prevalence more than once using different cut-off points).
Figure S6d.1 Prevalence of sarcopenia using muscle mass in women (excluding those who reported the prevalence more than once using different cut-off points)
Figure S6d.2 Prevalence of sarcopenia using muscle mass in women (all cut-off points).
Figure S6e.1 Prevalence of sarcopenia using muscle mass in men (excluding those who reported the prevalence more than once using different cut-off points)
Figure S6e.2. Prevalence of sarcopenia using muscle mass in men (all cut-off points).
Figure S7. Overall meta-regression by age.
Figure S7a. Meta-regression by age using the EWGSOP2.
Figure S7b. Meta-regression by age using the EWGSOP.
Figure S7c. Meta-regression by age using the AWGS.
Figure S7d. Meta-regression by age using the IWGS.
Figure S7e. Meta-regression by age using the FNIH.
Figure S7f. Meta-regression by age using muscle mass.
Figure S8. Prevalence of severe sarcopenia using different classifications.
Figure 9a. Prevalence of severe sarcopenia using the EWGSOP2.
Figure S9b. Prevalence of severe sarcopenia using the EWGSOP.
Figure S9c. Prevalence of severe sarcopenia using the AWGS.
Figure S9d. Prevalence of severe sarcopenia using the FNIH.
Figure S9e. Prevalence of severe sarcopenia using muscle mass.
Figure S10. Prevalence of severe sarcopenia in women.
Figure S11. Prevalence of severe sarcopenia using in men.
Figure S12. Prevalence of severe sarcopenia by age categories and muscle mass.
Table S1. Supporting Information

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Conflict of interest

None to declare.

Copyright

Transparency

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained

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2.1.1 Appendix A

2.1.2 Search strategy (13.08.2019)

EMBASE	8,308
1 sarcopenia/	
2 sarcopenia.tw.	9,931
3 1 or 2	11,444
4 muscle mass/	24,084
5 muscle mass.tw.	23,559
6 4 or 5	32,972
7 exp hand strength/	24,068
8 hand strength.tw.	518
9 7 or 8	24,246
10 walking speed/	13,286
11 walking speed.tw.	8,294
12 10 or 11	15,401
13 6 and 12	2,269
14 6 and 9	727
15 6 and 9 and 12	424
16 severe sarcopenia.tw.	139
17 3 or 13 or 14 or 15 or 16	12,682
18 limit 17 to (human and English language)	10,638
19 limit 18 to (adult <18 to 64 years> or aged <65 + years>)	**6,475**

MEDLINE	
1 sarcopenia/	3,373
2 sarcopenia.tw.	5,837
3 1 or 2	6,565
4 Muscle, Skeletal/	135,472
5 muscle mass.tw.	15,577
6 4 or 5	145,178
7 exp hand strength/	13,784
8 hand strength.tw.	0
9 7 or 8	13,784
10 walking speed/	849
11 walking speed.tw.	5,654
12 10 or 11	6,150
13 6 and 12	637
14 6 and 9	2,240
15 6 and 9 and 12	81
16 severe sarcopenia.tw.	56
17 3 or 13 or 14 or 15 or 16	8,960
18 limit 17 to (human and English language)	6,467
19 limit 18 to “all adult (19 plus years)”	**4,900**

CENTRAL	
1 sarcopenia OR (muscle mass and hand strength) OR (muscle mass and walking speed) OR (muscle mass and hand strength and walking speed) OR Severe sarcopenia	1434
2 1 and excluded trials	0
WEB OF SCIENCE	
1 TS=(sarcopenia OR severe sarcopenia)	14,479
2 TS=(((muscle) (mass)) AND ((hand) (strength)))	2,625
3 TS = (((muscle) (mass)) AND ((walking) (speed)))	1,350
4 TS = (((muscle) (mass)) AND ((hand) (strength)) AND ((walking) (speed)))	211
5 #4 OR #3 OR #2 OR #1	17,329
6 #5 and excluded CLINICAL TRIAL OR REFERENCE MATERIAL OR EDITORIAL OR CASE REPORT OR RETRACTED PUBLICATION OR REVIEW OR LETTER OR CORRECTION OR RETRACTION OR ABSTRACT OR DATA SET OR EARLY ACCESS OR BIBLIOGRAPHY OR MEETING OR BOOK OR NEWS OR DATA PAPER OR PATENT OR DATA STUDY	8,799
7 #6 AND excluded PORTUGUESE OR TURKISH OR ITALIAN OR KOREAN OR GERMAN OR POLISH OR INDONESIAN OR UNSPECIFIED OR FRENCH OR PERSIAN OR MALAY OR JAPANESE OR RUSSIAN OR HUNGARIAN OR SLOVENIAN OR SPANISH OR CHINESE	8,158
8 #7 AND excluded VETERINARY SCIENCES OR ZOOLOGY OR MICROBIOLOGY OR PARASITOLOGY	7,945

2.1.3 Supplementary Table 1. Quality assessment of studies included

	1	2	3	4	5	6	7	8	9	10	11
Adebusoye 2018	HR	HR	LR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Aibar-Almazan 2018	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Akune 2014	HR	HR	LR	HR	LR	LR	LR	LR	HR	LR	Moderate risk
Alkahtani 2017	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Anastacio 2019	HR	U	U	U	LR	HR	LR	LR	LR	LR	High risk
Androga 2017	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	Low risk
As'Habi 2018	HR	LR	LR	U	LR	LR	LR	LR	LR	LR	Low risk
AtesBuluts 2018	HR	HR	U	U	LR	LR	LR	HR	HR	LR	High risk
Bahat 2018	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Barbosa-Silva 2016	HR	HR	HR	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Bataille 2017	HR	LR	LR	U	LR	LR	LR	LR	LR	LR	Low risk
Beaudart 2015	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Bellanti 2018	HR	HR	HR	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Benavides-Rodriguez 2017	HR	U	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Bering 2018	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Bijlsma 2013	LR	LR	HR	U	LR	LR	LR	LR	LR	LR	Low risk
Boetto 2019	HR	HR	HR	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Bouchard 2009	HR	LR	LR	HR	LR	LR	LR	HR	LR	LR	Moderate risk
Bravo-Jose 2018	HR	U	LR	LR	LR	LR	LR	LR	LR	LR	Low risk
Buckinx 2017	HR	U	U	U	LR	LR	LR	LR	U	LR	High risk
Buehring 2013	HR	HR	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Buehring 2013	HR	U	HR	U	LR	LR	LR	LR	HR	LR	High risk
Bunout 2018	HR	HR	U	U	LR	LR	LR	LR	U	LR	High risk
Byun 2017	HR	HR	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Caan 2018	HR	HR	LR	U	LR	LR	LR	LR	HR	LR	Moderate risk
Caan 2017	HR	LR	LR	HR	LR	LR	LR	LR	HR	LR	Moderate risk
Castillo 2003	HR	LR	U	LR	LR	LR	LR	LR	LR	LR	Low risk
Chalhoub 2015	HR	LR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
chang 2015	HR	LR	HR	LR	LR	LR	LR	LR	HR	LR	Moderate risk
Chang 2017	HR	HR	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Chaput 2007	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Chen 2017	HR	HR	HR	HR	LR	LR	LR	LR	U	LR	High risk
Cheng 2014	HR	LR	HR	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Cherin 2014	HR	HR	HR	U	LR	LR	LR	HR	LR	LR	High risk
Chien 2008	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Chien 2015	HR	U	HR	U	LR	LR	LR	LR	U	LR	High risk
Choe 2018	HR	U	HR	U	LR	LR	LR	LR	HR	LR	High risk
Choe 2017	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Chistensen 2018	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Clynes 2015	HR	LR	LR	HR	LR	LR	LR	LR	LR	LR	Low risk
Coin 2008	HR	HR	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Conzade 2019	HR	LR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Costa 2015	HR	U	U	U	LR	LR	LR	HR	LR	LR	High risk

CotoMontes 2017	HR	LR	LR	HR	LR	LR	LR	LR	LR	LR	Low risk
Cravo 2017	HR	HR	LR	U	LR	LR	LR	LR	HR	LR	Moderate risk
Cuesta 2015	HR	U	LR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Davies 2018	HR	LR	LR	U	LR	LR	LR	LR	LR	LR	Low risk
deRosa 2015	HR	U	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
De Souza 2015	HR	HR	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Delmonico 2007	HR	LR	LR	LR	LR	LR	LR	LR	LR	LR	Low risk
Dodds 2017	HR	LR	LR	U	LR	LR	LR	LR	LR	LR	Low risk
Domiciano 2013	HR	U	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Dorosty 2016	HR	LR	LR	HR	LR	LR	LR	LR	LR	LR	Low risk
dosSantos 2014	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Dufour 2013	HR	HR	HR	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Dupuy 2015	HR	HR	HR	HR	LR	LR	LR	HR	LR	LR	High risk
Dutra 2019	HR	U	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Eguchi 2017	HR	U	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Emami 2018	HR	HR	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
FanelliKuczmarski 2013	HR	LR	LR	U	LR	LR	LR	LR	LR	LR	Low risk
Fonseca 2019	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Franzon 2019	HR	LR	LR	HR	LR	LR	LR	LR	LR	LR	Low risk
Frisoli 2018	HR	U	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Fukuoka 2019	HR	HR	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Fung 2019	HR	LR	LR	HR	LR	LR	LR	LR	LR	LR	Low risk
Gan 2019	HR	LR	LR	U	LR	LR	LR	LR	LR	LR	Low risk
Gielen 2015	HR	HR	LR	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Giglio 2018	HR	HR	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Giusto 2015	HR	HR	U	LR	LR	LR	LR	LR	LR	LR	Moderate risk
Glenn 2017	HR	U	U	U	LR	LR	LR	HR	LR	LR	High risk
Gray 2016	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Greenhall 2017	HR	U	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Gu 2018	HR	U	LR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Hai 2017	HR	U	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Han 2018	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	Low risk
Han 2016	HR	HR	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Han 2017	HR	U	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Han 2016	HR	U	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Harita 2019	HR	HR	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Hars 2016	HR	HR	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Hashemi 2016	HR	LR	LR	U	LR	LR	LR	LR	LR	LR	Low risk
Hayashi 2013	HR	U	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Hayashi 2018	HR	HR	LR	U	LR	LR	LR	LR	HR	LR	Moderate risk
He 2016	HR	U	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
He 2018	HR	U	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Hedayati 2010	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Hida 2018	HR	LR	HR	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Hirai 2019	HR	LR	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Hirani 2015	HR	LR	LR	HR	LR	LR	LR	LR	LR	LR	Low risk
Hiraoka 2016	HR	HR	U	U	LR	LR	LR	LR	LR	LR	Moderate risk

Hoffmann 2016	HR	LR	LR	U	LR	LR	LR	LR	LR	LR	Low risk
Hong 2019	HR	U	U	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Hsu 2014	HR	LR	LR	LR	LR	LR	LR	LR	LR	LR	Low risk
Hu 2017	HR	LR	LR	HR	LR	LR	LR	LR	LR	LR	Low risk
Ilhan 2019	HR	HR	U	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Ishii 2014	HR	LR	LR	HR	LR	LR	LR	LR	LR	LR	Low risk
Isoyama 2014	HR	HR	U	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Ishikawa 2018	HR	U	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Iwasaki 2017	HR	LR	LR	HR	LR	LR	LR	LR	LR	LR	Low risk
Jang 2018	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	Low risk
Janssen 2006	HR	LR	LR	HR	LR	LR	LR	LR	HR	LR	Moderate risk
Jones 2019	HR	LR	HR	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Kamijo 2018	HR	HR	U	LR	LR	LR	LR	LR	LR	LR	Moderate risk
Kera 2017	HR	HR	U	LR	LR	LR	LR	LR	LR	LR	Moderate risk
Kim 2018	HR	LR	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Kim 2016	HR	LR	LR	U	LR	LR	LR	LR	LR	LR	Low risk
Kim 2018	HR	LR	LR	HR	LR	LR	LR	LR	LR	LR	Low risk
Kim 2016	HR	LR	LR	HR	LR	LR	LR	LR	LR	LR	Low risk
Kim 2019	HR	LR	U	LR	LR	LR	LR	LR	HR	LR	Moderate risk
Kim 2019	HR	LR	LR	HR	LR	LR	LR	LR	HR	LR	Moderate risk
Kim 2018	HR	HR	U	LR	LR	LR	LR	LR	LR	LR	Moderate risk
Kim 2009	HR	HR	HR	LR	LR	LR	LR	LR	LR	LR	Moderate risk
Kirchengast 2009	HR	LR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Kobayashi 2019	HR	U	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Koo 2017	HR	HR	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Kruger 2016	HR	LR	LR	LR	LR	LR	LR	LR	LR	LR	Low risk
Kruger 2015	HR	LR	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Krzyminska-Siemaszko 2019	HR	U	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Kusaka 2017	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Kuyumcu 2016	HR	U	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Kyle 2001	HR	LR	HR	LR	LR	LR	LR	LR	LR	LR	Low risk
Lamarca 2014	HR	LR	U	HR	LR	LR	LR	HR	LR	LR	Moderate risk
Landi 2012	HR	LR	LR	LR	LR	LR	LR	LR	LR	LR	Low risk
Lardies-Sanchez 2017	HR	HR	LR	LR	LR	LR	LR	LR	LR	LR	Low risk
Lau 2005	HR	U	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Lee 2015	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Legrand 2013	HR	LR	LR	HR	LR	LR	LR	LR	LR	LR	Low risk
Lera 2017	HR	LR	LR	U	LR	LR	LR	LR	LR	LR	Low risk
Liguori 2018	HR	U	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Lim 2010	HR	LR	LR	HR	LR	LR	LR	LR	LR	LR	Low risk
Lima 2009	HR	U	HR	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Lima 2019	HR	HR	HR	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Lin 2018	HR	HR	HR	LR	LR	LR	LR	LR	LR	LR	Moderate risk
Lu 2013	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Lu 2019	HR	LR	U	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Lucassen 2017	HR	LR	HR	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Marini 2012	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk

Maruya 2019	HR	U	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Marzetti 2014	HR	HR	LR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Masanes 2012	HR	HR	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Matsumoto 2019	HR	HR	HR	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Mazocco 2019	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Melton 2000	HR	LR	LR	HR	LR	LR	LR	LR	LR	LR	Low risk
Menant 2017	HR	LR	LR	HR	LR	LR	LR	LR	LR	LR	Low risk
Mesinovic 2019	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Mesquita 2017	HR	LR	LR	HR	LR	LR	LR	LR	LR	LR	Low risk
Mienche 2019	HR	U	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Mijinarends 2016	HR	LR	LR	HR	LR	LR	LR	HR	HR	LR	Moderate risk
Mijinarends 2016	HR	LR	LR	U	LR	LR	LR	LR	LR	LR	Low risk
Misra 2019	HR	LR	U	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Miyakoshi 2013	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Mohseni 2017	HR	LR	LR	U	LR	LR	LR	LR	LR	LR	Low risk
Momoki 2017	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Montano-Loza 2016	HR	HR	U	U	LR	LR	LR	LR	U	LR	High risk
Moreira 2016	LR	LR	HR	LR	LR	LR	LR	LR	LR	LR	Low risk
Mori 2017	HR	HR	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Mori 2019	HR	U	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Mori 2019	HR	U	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Mori 2019	HR	U	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Murakami 2015	HR	HR	U	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Murata 2018	HR	HR	HR	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Nascimento 2018	HR	HR	HR	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Nasimi 2019	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	Low risk
Nishiguchi 2015	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Nishimura 2019	HR	LR	LR	LR	LR	LR	LR	LR	LR	LR	Low risk
Norshafarina 2013	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Ohashi 2018	HR	U	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Ohyama 2019	HR	HR	HR	U	LR	LR	LR	LR	HR	LR	High risk
Okamura 2019	HR	LR	U	LR	LR	LR	LR	LR	LR	LR	Low risk
Olesen 2019	HR	HR	U	HR	LR	LR	LR	LR	LR	LR	Moderate risk
OliveraNeta 2018	HR	HR	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Ottestad 2018	HR	LR	LR	HR	LR	LR	LR	LR	LR	LR	Low risk
Ozturk 2018	HR	HR	U	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Pagotto 2014	HR	LR	LR	HR	LR	LR	LR	LR	LR	LR	Low risk
Papachristou 2015	HR	LR	HR	LR	LR	LR	LR	LR	LR	LR	Low risk
Park 2018	HR	U	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Park 2010	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Park 2017	HR	HR	U	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Pedrero-Chamizo 2015	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	Low risk
Pereira 2015	HR	HR	U	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Petta 2017	HR	HR	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Poggiogalle 2019	HR	LR	LR	LR	LR	LR	LR	LR	LR	LR	Low risk
Poggiogalle 2019	HR	HR	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Rasaei 2019	HR	U	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Rathnayake 2019	HR	LR	LR	U	LR	LR	LR	LR	LR	LR	Low risk

Reid 2018	HR	LR	LR	HR	LR	LR	LR	LR	LR	LR	Low risk
Reijnierse 2015	HR	U	HR	U	LR	LR	LR	HR	LR	LR	High risk
Ren 2016	HR	HR	HR	LR	LR	LR	LR	LR	LR	LR	Moderate risk
Rodondi 2012	HR	HR	U	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Rodríguez-García 2018	HR	HR	HR	LR	LR	LR	LR	LR	LR	LR	Moderate risk
Rodriguez-Rejon2019	HR	LR	LR	U	LR	LR	LR	LR	LR	LR	Low risk
Rossi 2017	HR	LR	LR	U	LR	LR	LR	LR	LR	LR	Low risk
Roth 2004	HR	U	HR	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Ryan 2017	HR	HR	HR	U	LR	LR	LR	HR	LR	LR	High risk
Sanada 2010	HR	U	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Sanchez-Rodriguez 2019	HR	LR	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Santos 2017	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Schaap 2018	LR	LR	LR	HR ?	LR	LR	LR	LR	HR	LR	Low risk
Scott 2016	HR	LR	LR	HR	LR	LR	LR	LR	LR	LR	Low risk
Scott 2019	HR	LR	LR	HR	LR	LR	LR	LR	LR	LR	Low risk
Senior 2015	HR	HR	LR	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Sheng 2019	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Sherk 2009	HR	U	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Silva 2013	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
SilvaNeto 2016	HR	U	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Singh 2014	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Singhal 2019	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Sjoblom 2013	HR	LR	LR	HR	LR	LR	LR	LR	LR	LR	Low risk
Souza 2017	HR	HR	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Soysal 2019	HR	U	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Spira 2016	HR	HR	HR	LR	LR	LR	LR	LR	LR	LR	Moderate risk
Steffl 2016	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Stoever 2017	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Su 2019	HR	U	LR	LR	LR	LR	LR	LR	LR	LR	Low risk
Sugie 2017	HR	HR	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Sugimoto 2019	HR	HR	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Suzuki 2018	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Tabibi 2018	HR	HR	LR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Tanaka 2018	HR	HR	LR	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Tang 2018	HR	HR	LR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Tanimoto 2012	HR	HR	HR	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Tasar 2015	HR	U	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Tay 2015	U	U	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Tessier 2019	LR	LR	LR	U	LR	LR	LR	LR	LR	LR	Low risk
Tichet 2008	HR	LR	HR	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Trajanoska 2018	HR	LR	LR	HR	LR	LR	LR	LR	HR	LR	Moderate risk
Tramontano 2017	HR	HR	LR	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Tuzun 2018	HR	U	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Tuzun 2019	HR	U	U	U	LR	LR	LR	LR	HR	LR	High risk
Urzi 2017	HR	HR	HR	LR	LR	LR	LR	LR	LR	LR	Moderate risk
VanDeBool 2015	HR	HR	U	U	LR	LR	LR	LR	HR	LR	High risk
VelazquezAlva 2017	HR	HR	LR	LR	LR	LR	LR	LR	LR	LR	Low risk

Vermeiren 2019	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Walsh 2006	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Wang 2019	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Wang 2018	HR	HR	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Wang 2016	HR	HR	U	U	LR	LR	LR	LR	HR	LR	High risk
Wen 2015	HR	LR	LR	U	LR	LR	LR	LR	LR	LR	Low risk
Westbury 2018	HR	LR	U	HR	LR	LR	LR	LR	HR	LR	Moderate risk
Wiriya 2019	HR	U	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Woo 2015	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Wu 2013	HR	HR	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Wu 2014	HR	U	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Xiao 2018	HR	HR	U	U	LR	LR	LR	LR	HR	LR	High risk
Xu 2018	HR	LR	LR	LR	LR	LR	LR	LR	LR	LR	Low risk
Yadigar 2016	HR	U	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Yalcin 2016	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Yamada 2019	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Yamada 2013	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Yang 2015	HR	HR	HR	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Yang 2018	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Yang 2016	HR	U	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Yasemin 2019	HR	HR	HR	U	LR	LR	LR	LR	HR	LR	High risk
Yazar 2019	HR	U	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Yoowannakul 2018	HR	U	U	U	LR	LR	LR	LR	U	LR	High risk
Yoshida 2014	HR	LR	U	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Yu 2014	HR	HR	HR	HR	LR	LR	LR	LR	LR	LR	Moderate risk
Yuki 2017	HR	LR	LR	U	LR	LR	LR	LR	LR	LR	Low risk
Zambrano 2019	HR	HR	LR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Zeng 2018	HR	U	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk
Zenging 2018	HR	LR	LR	U	LR	LR	LR	LR	LR	LR	Low risk
Zhang 2019	HR	U	U	U	LR	LR	LR	LR	LR	LR	Moderate risk
Zoico 2004	HR	HR	HR	U	LR	LR	LR	LR	LR	LR	Moderate risk

Studies were assessed using a modified version of Hoy et al. The questions were:

1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. age, sex, occupation?
2. Was the sampling frame a true or close representation of the target population?
3. Was some form of random selection used to select the sample, OR, was a census undertaken?
4. Was the likelihood of non-response bias minimal?
5. Were data collected directly from the subjects (as opposed to proxy)?
6. Was an acceptable case definition used in the study?
7. Was the study instrument that measured the parameter of interest (e.g. prevalence of low back pain) shown to have reliability and validity (if necessary)?
8. Was the same mode of data collection used for all subjects?
9. Was the length of the shortest prevalence period for the parameter of interest appropriate?
10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?
11. Summary item on the overall risk of study bias (overall).

HR: higher risk, U: unclear; LR: low risk.

2.1.4 Supplementary Table 2. Characteristics of the studies included in the systematic review

Study	Country/ Region	Age	Type of study	Classification used	Assessment method for muscle mass	Correction method for muscle mass	Sample (n) (total-women-men	Total prevalence			Sarcopenia Only			Severe sarcopenia only		
								T n (%)	W n (%)	M n (%)	T n (%)	W n (%)	M n (%)	T n (%)	W n (%)	M n(%)
(Adebusoye et al., 2018)	Nigeria/ Africa	69.1 (7.2)	CS	EWGSOP	BIA	Height	624-378-246	-	-	-	34 (5.4)	27 (7.1)	7 (2.8)	-	-	-
(Aibar-Almazán et al., 2018)	Spain/Europe	69.2 (7.6)	CS	EWGSOP	BIA	Height	,-235-,	-	84 (35.7)	-	-	64 (27.2)	-	-	20 (8.5)	-
(Akune et al., 2014)	Japan/ Asia	77.3 (5.6)	CS	EWGSOP	BIA	Height	1000-651-349	-	-	-	129 (12.9)	81 (12.4)	48 (13.8)	-	-	-
(Alkahtani, 2017)	Saudi Arabia /Asia	27.1 (4.2)	CS	MM	BIA (inbody) BIA (tanita) DXA	Height	-,-,232	-	-	-	-	-	2 (0.9) 4 (1.7) 2 (0.9)	-	-	-
(Anastácio et al., 2019)	Brazil / South America	52.6 (13.3)	PP	MM	BIA	FFMI	100-43-57	-	-	-	19 (19)	12 (27.9)	7 (12.3)	-	-	-
(Androga et al., 2017)	USA/North America	50.8 (0.5)	PP	MM	DXA	Height	11616	-	-	-	1661 (14.3)	-	-	-	-	-
(As'habi et al., 2018)	Iran/Asia	≥18	CS	Other	BIA	Height	79-44-35	-	-	-	9 (11.4)	1 (2.3)	8 (22.8)	-	-	-
(Ates Bulut et al., 2018)	Turkey/Europe ¥	75.6 (8.2)	CS	EWGSOP	BIA	Height	2816-,-,	-	-	-	993 (35.3)	-	-	-	-	-
(Bahat et al., 2018)	Turkey /Asia and Europe¥	74.6 (6.7)	CS	EWGSOP IWGS FNIH	BIA	Height Height Height	207-140-67	-	-	-	8 (3.9) 4 (1.9) 19 (9.2)	1 (0.7) 1 (0.7) 13 (9.3)	7 (10.4) 3 (4.5) 6 (9.0)	-	-	-
(Barbosa-Silva et al., 2016)	Brazil/South America	≥60	CS	EWGSOP	DXA	Height	179,-,-	15 (8.4)	-	-	9 (5.0)	-	-	6 (3.3)	-	-
Bataille 2017 (Bataille et al., 2017)	France/Europe	77.5 (70.8 - 84.8)	CS	EWGSOP	BIA	Height	111-46-65	-	-	-	35 (31.5)	10 (21.7)	25 (38.5)	-	-	-
(Beaudart et al., 2015)	Belgium/ Europe	73.5 (6.2)	CS	EWGSOP	DXA	Height	534-322-212	-	-	-	73 (13.7)	48 (14.4)	22 (11.8)	-	-	-
(Bellanti et al., 2018)	Italy/Europe	77.2 (6.6)	CS	MM	DXA	Height	115-64-61	-	-	-	48 (41,7)	20 (37.0)	28 (45.9)	-	-	-
(Benavides-Rodríguez et al., 2017)	Colombia/ South America	63.5 (5.9)	CS	EWGSOP	BIA	Height	98,-,-	29 (29.6)	-	-	22 (22.5)	-	-	7 (7.1)	-	-
(Bering et al., 2018)	Brazil/South America	50.5 (11.3)	CS	EWGSOP	DXA	Height	104,-,-	-	-	-	13 (12.5)	-	-	-	-	-

(Bijlsma et al., 2013)	Netherlands/ Europe	63.2 (38-82)	PP	MM	BIA DXA	Height Height	654-329-325	-	-	-	22(3.4) 25(3.8)	7 (2.1) 10 (3.0)	15(4.6) 15(4.6)	-	-	-
(Boetto et al., 2019)	Italy/Europe	83.2 (9.4)	CS	EWGSOP FNIH	BIA	Height BMI	97-71-26				13 (13.4) 13 (13.4)	6 (8.4) 5 (2.1)	7 (26.9) 8 (30.8)	-	-	-
(Bouchard et al., 2009)	Canada/North America	74.0 (0.2)	PP	MM	DXA	Height	897-462-432	-	-	-	250 (27.9)	82 (18.9)	168 (38.9)	-	-	-
(Bravo-José et al., 2018)	Spain/Europe	81.7 (8.0)	CS	EWGSOP	BIA	Height	285-199-86	118 (41.4)	96 (48.2)	22 (25.6)	40 (14.0)	-	-	78 (27.4)	-	-
(Buckinx et al., 2017)	Belgium/ Europe	83.2 (8.9)	CS	EWGSOP	BIA	Height	662,-,-	-	-	-	250 (37.6)	-	-	-	-	-
(Buehring et al., 2013a)	USA/North America	80.7 (5.9)	CS	MM	DXA	Height	97-49-48	-	-	-	23 (23.7)	9 (18.4)	14 (29.2)	-	-	-
(Buehring et al., 2013b)	USA/North America	75.5 (7.5)	CS	MM	DXA	Height	304,-,-	-	-	-	46 (15.0)	-	-	-	-	-
(Bunout et al., 2018)	Chile / South America	53.1 (7.2)	CS	Other	DXA	Height	192-106-86	-	-	-	16 (8.3)	5 (4.7)	11 (2.8)	-	-	-
(Byun et al., 2017)	South Korea/ Asia	68.4 (8.9)	CS	EWGSOP	BIA	Height	80-13-67	-	-	-	20 (25.0)	3 (23.1)	17 (25.3)	-	-	-
(Caan et al., 2018)	USA/North America	54 (18-80)	RP	MM	CT scan	Height	3241,-,-	-	-	-	1086 (33.5)	-	-	-	-	-
(Caan et al., 2017)	USA/North America	62.6 (11.4)	RP	MM	CT scan	Height	3262-1628-1634	-	-	-	1383 (42.4)	643 (39.5)	740 (45.3)	-	-	-
(Castillo et al., 2003)	USA/North America	75.1 (0.8)	CS	MM	BIA	Height	1700-1006-694	-	-	-	102 (6.0)	59 (6.2)	43 (6.2)	-	-	-
(Chalhoub et al., 2015)	USA/ North America	77.5 (4.0)	PP	EWGSOP*	DXA	Residual	6658-1114-5544	-	-	-	371 (5.6)	180 (16.2)	191 (3.4)	-	-	-
(Chang et al., 2015)	South Korea/ Asia	47.6 (12.0)	RP	MM	BIA	Height Weight	3902-1701-2201	507 (13.0) 1339 (80.0)	33 (1.9) 738 (43.4)	474 (21.5) 601 (27.3)	426 (10.9) 1071 (27.4)	29 (1.7) 547 (32.2)	397 (18.0) 524 (23.8)	81 (2.0) 268 (6.9)	4 (0.2) 191 (11.2)	77 (3.5) 77 (3.5)
(Chang et al., 2017)	Korea/ Asia	66.5 (19.6)	CS	AWGS	BIA	Height	715-390-325	-	-	-	31 (4.3)	19 (4.9)	12 (3.7)	-	-	-
(Chaput et al., 2007)	Canada/North America	66.5 (5.3)	CS	MM	DXA	Height	50-34-16	-	-	-	12 (24.0)	8 (23.5)	4 (25.0)	-	-	-
(Chen et al., 2017)	China/Asia	53.5 (5.8)	CS	MM	DXA	Regression Height	-,177,-	-	-	-	-	12(6.8) 7(3.9)	-	-	-	-
(Cheng et al., 2014)	China/Asia	78.7 (7.4)	CS	MM	DXA	Height	2679-1336-1343	-	-	-	244 (9.1)	67 (5.0)	177 (13.2)	-	-	-
(Cherin et al., 2014)	France/Europe	63.1 (10.2)	CS	EWGSOP	DXA	Height	1421-868-553	-	-	-	221 (15.6)	135 (15.5)	86 (15.6)	-	-	-
(Chien et al., 2008)	Taiwan/Asia	75.5 (6.7)	CS	MM	BIA	Height	302-145-157	-	-	-	66 (21.8)	28 (19.0)	38 (24.0)	-	-	-

(Chien et al., 2015)	Taiwan/Asia	76.8 (6.9)	CS	MM	BIA	Height	488-264-224	-	-	-	92 (18.8)	38 (14.4)	54 (24.1)	-	-	-
(Choe et al., 2018)	South Korea/ Asia	54.9 (9.5)	RP	MM	CT scan	BMI	1828-707-1121	-	-	-	454 (24.8)	228 (32.2)	226 (20.2)	-	-	-
(Choe et al., 2017)	South Korea / Asia	72.4 (4.4)	CS	FNIH AWGS	BIA	BMI Height	916-487-429	-	-	-	63 (6.9) 94 (10.3)	25 (5.0) 44 (9)	38 (8.9) 50(11.7)	-	-	-
(Christensen et al., 2018)	Denmark/ Europe	79 (6.6)	CS	EWGSOP	DXA	Height	80-52-28	21 (26.2)	13 (25.0)	8 (28.6)	12 (15.0)	-	-	9 (11.2)	-	-
(Clynes et al., 2015)	UK /Europe	76.1 (2.6)	CS	EWGSOP IWGS FNIH	DXA	Height Height BMI	298-142-156	-	-	-	10 (3.4) 25 (8.4) 6 (2.0)	3 (2.1) 12 (8.4) 3 (2.1)	7 (4.5) 13 (8.3) 3 (1.9)	-	-	-
(Coin et al., 2008)	Italy/Europe	73.7 (5.4)	CS	MM	DXA	Height	352-216-136	-	-	-	175 (49.6)	106 (49.1)	69 (50.4)	-	-	-
(Conzade et al., 2019)	Germany/ Europe	75.7 (6.5)	CS-PP	EWGSOP	DXA	Height	975-480-495	-	-	-	65 (6.7)	43 (9.0)	22 (4.4)	-	-	-
(Costa et al., 2015)	Brazil/ Europe	67.4 (8.7)	CS	MM	DXA	Height Newman	91-50-41	-	-	-	37 (40.6) 19 (21.0)	-	-	-	-	-
(Coto Montes et al., 2017)	Spain/Europe	77.2 (0.5)	CS	EWGSOP	BIA	Height	200-116-84	-	-	-	52 (26.0)	41 (35.3)	11 (13.1)	-	-	-
(Cravo et al., 2017)	Portugal/ Europe	>40	RP	MM	CT scan	Height	71-36-35	-	-	-	22 (31.0)	-	-	-	-	-
(Cuesta et al., 2015)	Spain/ Europe	83.2 (78.7-87.5)	PP	EWGSOP	BIA	Height	298-188-110	57 (19.1)	43 (22.9)	14 (12.07)	21 (7.1)	13 (6.9)	8 (7.3)	36 (12.0)	30 (16.0)	6 (5.4)
(Davies et al., 2018)	Spain /Europe	75.4 (5.9)	CS	EWGSOP* FNIH	DXA	Height BMI	1611-900-711	-	-	-	352 (21.8) 332 (20.6)	131 (14.6) 180 (20.0)	221 (31.1) 152 (21.4)	-	-	-
(De Rosa et al., 2015)	Italy/Europe	50 (5.0)	RP	MM	BIA	Height Weight	131-80-51	- 131 (100)	- 80 (100)	- 51 (100)	5 (3.8) 86 (65.6)	0 44 (55.0)	5 (9.8%) 42 (52.4)	- 45(34.4)	- 36 (45.0)	- 9 (17.6)
(de Souza Genaro et al., 2015)	Brazil/South America	70.6 (5.2)	CS	EWGSOP	DXA	Height	-,105,-	-	-	-	35 (33.3)	-	-	-	-	-
(Delmonico et al., 2007)	USA/North America	73.6 (2.9)	PP	MM	DXA	Height Regression	2976-1546-1433	-	-	-	603 (20.3) 603 (20.3)	314 (20.4) 312 (20.2)	289 (20.2) 291 (20.3)	-	-	-
(Dodds et al., 2017)	UK/ Europe	85.0	PP	EWGSOP*	BIA	Height	719-437-282	-	-	-	149 (20.7)	90 (20.6)	59 (20.9)	-	-	-
(Domiciano et al., 2013)	Brazil/South America	73.2 (5.2)	CS	MM	DXA	Height Newman	611,-,-	-	-	-	23 (3.8) 122 (20.0)	-	-	-	-	-
(Dorosty et al., 2016)	Iran/Asia	67.2 (6.1)	CS	EWGSOP	BIA	Height	644,-,-	-	-	-	220 (34.1)	-	-	-	-	-
(dos Santos et al., 2014)	Brazil/South America	67.2 (6.1)	CS	MM	DXA	Height Newman	149,-,-	-	-	-	25 (16.8) 32 (21.5)	-	-	-	-	-
(Dufour et al., 2013)	USA/North America	78.4 (4.4)	PP	MM	DXA	Height Newman	767-493-274	-	-	-	115 (15.0) 166 (21.6)	62 (12.6) 114 (23.7)	53 (19.3) 52 (19.0)	-	-	-
(Dupuy et al., 2015)	France/Europe	80.5 (3.9)	CS	EWGSOP IWGS MM	DXA	Height Height Height	,-3025-,	-	-	-	-	390 (12.9) 142 (4.7) 283 (9.4)	-	-	-	-

				MM MM Other		Newman Delmonico Height						541 (17.9) 511 (16.9) 89 (2.9)				
(Dutra et al., 2019)	Brazil/South America	46.3 (15.6)	CS	MM	BIA	Fat mass	-,118,-					51 (43.2)				
(Eguchi et al., 2017)	Japan/ Asia	74.0 (1.0)	CS	MM	DXA	Height	40,-,-	-	-	-	11 (27.5)	-	-	-	-	-
(Emami et al., 2018)	Germany/ Europe	67.3 (10.1)	PP	MM	DXA	Height	207,-,-	-	-	-	44 (21.3)	-	-	-	-	-
(Fanelli Kuczmarski et al., 2013)	USA/North America	47.8 (0.2)	CS	EWGSOP	DXA	Percentile	2176,-,-	-	-	-	139 (6.4)	-	-	-	-	-
(Fonseca et al., 2019)	Brazil/South America	55 (9.0)	PP	EWGSOP	DXA	Height	116,-,-	-	-	-	33 (28.5)	-	-	-	-	-
(Franzon et al., 2019)	Sweden/Europe	86.6 (1.0)	CS	EWGSOP2 EWGSOP	DXA	Height	-,-,287	- -	- -	63 (22.0) -	- -	- -	58 (20) 60 (20.9)	- -	- -	5 (1.7) -
(Frisoli et al., 2018)	Brazil/South America	78.44 (7.16)	CS	EWGSOP	DXA	Height	332,191-141	-	-	-	64 (19.3)	28 (14.7)	36 (25.5)	-	-	-
(Fukuoka et al., 2019)	Japan/ Asia	73.7 (6.3)	CS	AWGS	BIA	Height	267-108-159	-	-	-	50 (18.7)	24 (22.2)	26 (16.4)	-	-	-
(Fung et al., 2019)	Singapore/Asia	68.3 (5.7)	CS	AWGS	BIA	Height	387-181-206	106 (27.4)	61 (33.7)	45 (21.8)	91 (23.5)	50 (27.6)	41 (19.9)	15 (3.9)	11 (6.0)	4 (1.9)
(Gan et al., 2020)	China/ Asia	53.5 (12.6)	CS	Other*	DXA	Weight	3536-,-,	-	-	-	-	-	365 (10.3)	-	-	-
(Gielen et al., 2015)	UK & Belgium / Europe	60.0 (10.3)	PP	EWGSOP IWGS MM	DXA	Height	,-,-433 ,-,-506 ,-,-518	-	-	7 (1.6) - -	-	-	6 (1.4) 12 (2.4) 81 (15.7)	-	-	1 (0.2)
(Giglio et al., 2018)	Brazil/South America	70 (7.0)	PP	EWGSOP	DXA	Height	170-59-111			62 (36.5)	10 (16.9)	52 (46.8)				
(Giusto et al., 2015)	Italy/Europe	59 (26-68)	CS	Other*	DXA	Height	59-13-46				45 (76.3)	9 (69.2)	36 (78.3)			
(Glenn et al., 2017)	USA/North America	78.2 (6.6)	CS	MM	DXA	BMI	57-41-16	-	-	-	15 (10.6)	-	-	-	-	-
(Gray et al., 2016)	USA/North America	77.2 (6.2)	CS	MM	DXA	BMI	43-32-11	-	-	-	4 (9.3)	4 (12.5)	0 (0.0)	-	-	-
(Greenhall and Davenport, 2017)	UK/Europe	55.3 (16.4)	CS	MM	BIA	Height	490-230-260	172 (35.1)	7 (16.1)	165 (63.5)	141 (28.8)	7 (16.1)	134 (51.3)	31 (6.3)	0	31 (11.9)
(Gu et al., 2018)	South Korea/Asia	53.6 (10.2)	RP	MM	CT scan	Height	653-154-499	-	-	-	241 (36.9)	16 (10.4)	225 (45.0)	-	-	-
(Hai et al., 2017)	China/Asia	68.6 (6.5)	CS	AWGS	BIA	Height	836-421-415	-	-	-	88 (10.5)	41 (9.7)	47 (11.3)	-	-	-
(Han and Chung, 2018)	China/Asia	69.5 (6.6)	CS	AWGS	BIA	Height	711-362-349	-	-	-	77 (10.8)	48 (13.2)	29 (8.3)	-	-	-

(Han et al., 2016a)	China/Asia	69.8 (5.4)	PP	AWGS	BIA	Height	657,-,-	-	-	-	64 (9.7)	-	-	-	-	-
(Han et al., 2017)	South Korea/Asia	69.5 (6.6)	CS	MM	DXA	Height	18782-10729-8053	-	-	-	5857(31.2)	3085(28.8)	2772(34.4)	-	-	-
(Han et al., 2016b)	Taiwan/Asia	72.7 (5.7)	CS	EWGSOP	BIA	Height Weight	878-476-402	- 67(7.6)	2(0.4) 51(10.7)	27(6.7) 16(4.0)	29 (3.3) 48 (5.5)	2(0.4) 34(7.1)	22(5.5) 14(3.5)	- 19 (2.2)	17(3.6)	2(0.5)
(Harita et al., 2019)	Japan/Asia	73.0 (5.0)	CS	AWGS	BIA	Height	141-72-69	-	-	-	12(8.5)	10 (13.9)	2 (4.3)	-	-	-
(Hars et al., 2016)	Switzerland/Europe	65.0 (1.4)	PP	MM Delmonico Delmonico EWGSOP2 FNIH	DXA	Height Height Percentile Height BMI	913-729-184				102 (11.2) 157 (17.2) 184 (20.2) 156 (17.0) 32 (3.5)	82 (11.3) -	20(10.9) -			
(Hashemi et al., 2016)	Iran/Asia	66.8 (7.7)	CS	EWGSOP	DXA	Height	300-154-146	54 (18.0)	23(14.9)	31(21.2)	37(12.3)	15(9.7)	22(15.0)	17(5.7)	8(5.2)	9(6.1)
(Hayashi et al., 2013)	Japan/Asia	69.5 (50-78)	CS	Other*	BIA	Height	50-31-19				20 (40)	13 (41.9)	7 (36.8)			
(Hayashi et al., 2018)	Japan/Asia	>41	RP	Other*	BIA	Height	112-55-57	-	-	-	14 (12.5)	9 (16.4)	5 (8.8)	-	-	-
He 2016 (He et al., 2016b)	USA -China / North America-Asia	43.4 (14.9)	CS	EWGSOP* MM	DXA	Height	17891-,-,	-	-	-	78 (0.4) 456 (2.5)	-	-	-	-	-
(He et al., 2018)	China/Asia	71.4 (5.8)	CS	EWGSOP IWGS FNIH AWGS	BIA	Height Height BMI Height	371-219-152	-	-	-	42 (11.3) 91 (24.5) 55 (14.8) 57 (15.4)	26 (11.9) 54 (24.7) 33 (15.1) 39 (17.8)	16 (10.5) 37 (24.3) 22 (14.5) 18 (11.8)	-	-	-
(Hedayati and Dittmar, 2010)	Germany/Europe	68.1(4.8)	CS	MM	BIA	Weight	110-55-55	-	-	-	8 (7.3)	6 (11.0)	2 (4.0)	-	-	-
(Hida et al., 2018)	Japan/Asia	64.9 (9.3)	CS	MM	BIA	Height	335-189-146	-	-	-	89 (26.6)	58 (30.7)	31 (21.2)	-	-	-
(Hirai et al., 2019)	Japan/Asia	76 (70-81)	CS	AWGS	BIA	Height	201,-,-	-	-	-	59 (29.3)	-	-	-	-	-
(Hirani et al., 2015)	Australia/ Oceania	80.6 (6.0)	PP	FNIH	DXA	ALM	,-,-1819	-	-	141 (7.8)	-	-	84 (5.8)	-	-	57 (3.1)
(Hiraoka et al., 2016)	Japan/Asia	67.1 (10.0)	CS	EWGSOP* AWGS*	CT scan	Height	807-,-,	-	-	-	84 (10.4) 54 (6.9)					
(Hoffmann et al., 2016)	Canada/North America	62.6 (10.1)	PP	MM	DXA	Height	60,-,-	-	-	-	6 (10.0)	-	-	-	-	-
(Hong et al., 2019)	South Korea/Asia	56.5 (5.6)	CS	MM	BIA	Weight	14024-6016-8008	-	-	-	1676 (12.0)	434 (7.2)	1242 (15.5)	-	-	-
(Hsu et al., 2014)	Taiwan/Asia	83.0 (5.4)	CS	EWGSOP	BIA	Height	-,-,353	-	-	-	-	-	109 (30.9)	-	-	-
(Hu et al., 2017)	China/Asia	71.2 (6.7)	CS	AWGS	DXA	Height	607-356-251	112 (18.4)	71 (19.9)	41 (16.3)	-	-	-	-	-	-

(İlhan et al., 2019)	Turkey/Asia and Europe*	77.1 (6.8)	CS	EWGSOP	BIA	Height	442,-,-				11 (2.5)					
(Ishii et al., 2014)	Japan/Asia	74.6 (5.3)	PP	EWGSOP	BIA	Height	1971-994-977				359 (18.2)	220 (22.1)	139 (14.2)			
(Isoyama et al., 2014)	Sweden/ Europe	56 (32-69)	CS	EWGSOP	DXA	Height	330-				66 (20.0)					
(Ishikawa et al., 2018)	Japan/Asia	76 (69-80)	CS	AWGS	DXA	Height	260-91-169				65 (25.0)	17 (18.7)	48 (28.4)			
(Iwasaki et al., 2017)	Japan/Asia	82 (79-85)	CS	AWGS	BIA	Height	272,-,-				70 (25.7)					
(Jang et al., 2018)	South Korea/Asia	78.0 (6.2)	PP	AWGS Kim 2016 FNIH	BIA	Height Weight BMI	1343-741-602				221 (16.4) 209 (15.6) 215 (16.0)	137 (18.5) 127 (17.7) 133 (19.7)	84 (14.0) 82 (13.6) 82 (13.6)			
(Janssen, 2006)	USA/ North America	>65	PP	MM	BIA	Height	5036-2840-2196	3421 (67.9)	1494 (52.6)	3421 (87.8)	2743 (54.4)	1190 (41.9)	1553 (70.7)	679 (13.5)	304 (10.7)	375 (17.1)
(Jones et al., 2020)	UK/Europe	64.1 (2.8)	PP	EWGSOP	BIA	Height	181301-95340-85961				15050 (8.3)	11540 (12.1)	3510 (4.1)			
(Kamijo et al., 2018)	Japan/Asia	65.3 (12.9)	PP	AWGS	BIA	Height	119,-,-				13 (10.9)					
(Kera et al., 2017)	Japan/Asia	73.8 (5.8)	CS	AWGS	BIA	Height	1283-800-483				234 (18.2)	192 (24.0)	42 (8.7)			
(Kim et al., 2018a)	USA/North America	67.7 (10.8)	CS	MM	CT scan	Height	778-209-569				375 (48.2)	32 (15.3)	343 (60.3)			
(Kim et al., 2016a)	South Korea/ Asia	47.8 (11.5)	CS	MM	BIA	Weight	23473-10467-13006				4578 (19.5)	2737 (16.2)	1841 (14.2)			
(Kim et al., 2018b)	South Korea/ Asia	64 (48-78)	CS	FNIH AWGS Other	DXA	BMI Height	2828-1627-1201	-	-	-	136 (4.8) 456 (16.1) 548 (16.4)	88 (4.0) 389 (23.9) 314 (19.5)	48 (5.4) 67 (5.6) 324 (19.3)	-	-	-
(Kim et al., 2016b)	South Korea/ Asia	75.3 (5.1)	CS	Other	DXA	Weight	302-,-,				27 (8.9)					
(Hyun Kim et al., 2020)	South Korea/ Asia	75.9 (4.0)	CS	EWGSOP EWGSOP2 AWGS IWGS FNIH	DXA	Height Height Height BMI	2099-1046-1053	489(23.3) 233 (11.1) - -	192(18.4) 88 (8.4) - -	297(28.2) 145 (13.8) - -	438(20.9) 195 (9.3) 191 (9.1) 325 (15.5) 137 (6.5)	169(16.2) 70 (6.7) 84 (8.0) 164 (15.7) 49 (4.7)	269(25.5) 125 (11.9) 107 (10.2) 161 (15.3) 88 (8.4)	51(2.4) 38 (1.8) - - -	23(2.2) 18 (1.7) - - -	28(2.7) 20 (1.9) - - -
(Kim and Won, 2019)	South Korea/ Asia	54.4(12.7)	RP	MM	BIA	BMI	2168-839-1329				218(10.0)	69 (8.2)	149 (11.2)			
(Kim et al., 2018c)	South Korea/ Asia	76.7 (5.7)	CS	AWGS	BIA	Weight	194,-,-				16 (8.3)					
(Kim et al., 2009)	South Korea/ Asia	51.7 (14.6)	PP	MM	DXA	Height Weight	526-328-198				15 (2.8) 71 (13.5)	8 (2.4) 45 (13.7)	7 (3.5) 26 (13.1)			
(Kirchengast and Huber, 2009)	Austria/ Europe	71.5 (7.8)	CS	MM	DXA	Height	139-76-63				87 (62.3)	46 (60.5)	41 (65.0)			

(Kobayashi et al., 2020)	Japan/Asia	71.4 (5.3)	CS	MM	BIA	Height	427-222-205				91 (21.3)	57 (25.7)	34 (16.6)			
(Koo et al., 2017)	Japan/Asia	53.1 (14.2)	CS	MM	BIA	Weight BMI	309-164-145	-	-	-	70 (22.7) 56 (18.1)	39 (23.8) -	31 (21.4) -			
(Kruger et al., 2016)	South Africa/Africa	57.0 (10.2)	CS	MM	DXA	Height	-,247,-					22 (8.9)				
(Kruger et al., 2015)	South Africa/ Africa	18-40	CS	EWGSOP FNIH	DXA	Height BMI	,-609-,	-	-	-	-	37 (6.1) 47 (7.7)	-	-	-	-
(Krzymińska-Siemaszko et al., 2019)	Poland/ Europe	74.2 (6.1)	CS	EWGSOP	BIA	Height	468-382-86				21 (4.5)	8 (2.0)	13 (15.1)			
(Kusaka et al., 2017)	Japan/Asia	74 (65-86)	CS	AWGS	BIA	Height	-,116,-					10 (6.2)				
(Kuyumcu et al., 2016)	Turkey/Asia	73.1 (6.2)	CS	Other	BIA	Height	100-59-41	-	-	-	16 (16.0)	8 (13.6)	8 (19.5)	-	-	-
(Kyle et al., 2001)	Switzerland/ Europe	≥60	CS	MM	DXA	Height	191-100-91	-	-	-	21 (11.0)	11 (11.0)	10 (9.1)	-	-	-
(Lamarca et al., 2014)	Brazil/ South America	70.7 (7.0)	CS	MM MM Other Other	DXA BIA DXA BIA	Height	49-,-, 102-,-, 49-,-, 102-,-,	-	-	-	36 (73.5) 52 (51.0) 31 (63.3) 46 (45.1)	-	-	-	-	-
(Landi et al., 2012)	Italy/Europe	84.1 (6.9)	CS	EWGSOP	BIA	Height	122-91-31				40 (32.8)	19 (20.9)	21 (67.7)			
(Lardiés-Sánchez et al., 2017)	Spain/ Europe	84.9 (7.6)	CS	EWGSOP	BIA	Height	339-218-121	237 (69.9)	154(70.4)	83 (68.6)	183 (54.0)	120(55.0)	63(52.0)	54 (15.9)	34 (15.6)	20 (16.5)
(Lau et al., 2005)	China/Asia	≥70	CS	MM	DXA	Height	525-264-261	-	-	-	51 (9.7)	19 (7.2)	32 (12.3)	-	-	-
(Lee and Park, 2015)	Korea/Asia	71.2 (4.6)	CS	AWGS	DXA	Height	196,-,-	-	-	-	15 (7.7)	-	-	-	-	-
(Legrand et al., 2013)	Belgium/ Europe	84.8 (3.6)	PP	EWGSOP	BIA	Height	288-185-103	-	-	-	36 (12.5)	23 (12.4)	13 (12.6)	-	-	-
(Lera et al., 2017)	Chile/ South America	67.6 (5.9)	CS	EWGSOP	DXA	Height	1006-687-319	192 (19.0)	160(18.9)	32(19.4)	170 (16.9)	119 (17.3)	51(15.9)	22 (2.2)	11 (1.6)	11 (3.5)
(Liguori et al., 2018)	Italy /Europe	80.9 (6.6)	CS	EWGSOP*	BIA	Height	473-288-185	-	-	-	62 (13.1)	23 (8.0)	39 (211)	-	-	-
(Lim et al., 2010)	South Korea/ Asia	74.3 (7.5)	CS	MM MM	DXA	Height Weight	386-158-228	-	-	-	101 (26.2) 190 (49.2)	23 (14.6) 101 (63.9)	78 (34.2) 89 (39.0)	-	-	-
(Lima et al., 2009)	Brazil/ South America	66.7 (5.5)	CS	MM	DXA	Height	-,246,-	-	-	-	-	42 (17.0)	-	-	-	-
(Lima et al., 2019)	Japan/Asia	68.3 (6.3)	CS	EWGSOP*	DXA	FFM	,-234-,	-	31 (13.3)	-	-	17 (7.3)	-	-	14 (6.0)	-
(Lin et al., 2018)	Taiwan/ Asia	63.3(13.2)	CS	EWGSOP	BIA	Height	120-57-63	-	-	-	20 (16.7)	10 (17.5)	10 (15.9)	-	-	-
(Lu et al., 2013)	Taiwan/ Asia	63.6 (10.1)	CS	MM	BIA	Weight	600-456-144				251 (41.8)	200 (43.8)	51 (35.4)			

(Lu et al., 2020)	Singapore/Asia	73.2 (5.3)	CS	AWGS	DXA	Height	189-119-70				87 (46.0)	55(46.2)	32(45.7)			
(Lucassen et al., 2017)	Netherlands/ Europe	59 (4)	CS	MM	DXA	Weight	915-512-404	-	-	-	174(19.0)	138(26.9)	36(8.9)	-	-	-
(Marini et al., 2012)	Italy/Europe	70.8 (4.0)	CS	MM	DXA	Height	207-132-75	-	-	-	23 (11.1)	5 (3.8)	18 (24.0)	-	-	-
(Maruya et al., 2019)	Japan/Asia	71.0 (5.1)	CS	AWGS	BIA	Height	759-410-349	-	-	-	25 (3.3)	13 (3.2)	12 (3.4)	-	-	-
(Marzetti et al., 2014)	Italy/Europe	74.9 (6.5)	CS	MM	BIA	Height	142-84-58	-	-	-	23 (16.2)	-	-	-	-	-
(Masanes et al., 2012)	Spain/Europe	75.0 (3.4)	PP	MM	BIA	Height	200-110-90	-	-	-	45 (22.5)	36 (32.7)	9 (10.0)	-	-	-
(Matsumoto et al., 2019)	Japan/Asia	72.6 (9.1)	CS	AWGS	BIA	Height	467-285-182	-	-	-	26 (5.6)	15 (5.4)	11 (6.2)	-	-	-
(Mazocco et al., 2019)	Brazil/South America	63.7 (5.9)	CS	EWGSOP	DXA	Height	-,205,-	-	-	-	-	5 (2.4)	-	-	-	-
(Melton et al., 2000)	USA/North America	≥65	CS	MM	DXA	Height	694-349-345	-	-	-	29 (4.2)	13 (3.8)	16 (4.7)	-	-	-
(Menant et al., 2017)	Australia/ Oceania	81.2 (4.5)	CS	EWGSOP Baumgartner Bouchard	DXA	Height Height Height	419,-,-	-	-	-	88 (21.0) 97 (23.1) 306(73.0)	-	-	-	-	-
(Mesinovic et al., 2019)	Australia/ Oceania	61.6 (8.5)	CS	EWGSOP2	DXA	Height	84-,-,	-	-	-	-	-	-	7 (8.3)	-	-
(Mesquita et al., 2017)	Brazil/South America	77.0 (8.6)	CS	MM	BIA	Height	216-159-57	-	-	-	156 (72.2)	106 (66.7)	50 (87.7)	-	-	-
(Mienche et al., 2019)	Indonesia/Asia	71.8(6.11)	CS	AWGS	DXA	Height	120-74-46	-	-	-	19 (15.8)	5 (6.8)	14 (30.4)	-	-	-
(Mijnarends et al., 2016a)	Iceland/ Europe	74.7 (4.7)	PP	EWGSOP	CT scan	Percentile	2309-1335-974				169 (7.3)	125 (9.4)	44 (4.5)			
(Mijnarends et al., 2016b)	Netherlands/ Europe	74.9 (7.2)	CS	EWGSOP	BIA	Height	227-110-117				53 (23.3)	25 (22.7)	28 (23.9)			
(Misra et al., 2019)	USA/America	62.5 (8.0)	PP	MM	DXA	Quartiles	1696-1035-561				345 (20.3)	211 (20.4)	134 (23.9)			
(Miyakoshi et al., 2013)	Japan/Asia	66.3 (9.2)	CS	MM	DXA	Height	-,2400,-					387 (16.1)				
(Mohseni et al., 2017)	Iran/Asia	57.6 (6.2)	CS	EWGSOP	BIA	Height	-,250,-					55 (22.0)				
(Momoki et al., 2017)	Japan/Asia	77.7 (6.8)	CS	AWGS	DXA	Height	-,186,-					39 (20.9)				
(Montano-Loza et al., 2016)	Canada/North America	57.2 (1.0)	PP	MM	CT scan	Height	678-221-457				427 (62.9)	81 (36.6)	345 (75.5)			
(Moreira et al., 2016)	Brazil/South America	49.9(5.5)	CS	MM	BIA	Height	-,491,-					96 (20.0)				

(Mori et al., 2017)	Japan/Asia	55.7 (10.3)	CS	AWGS	BIA	Height	36-27-9				6 (16.6)	6 (22.0)	0			
(Mori et al., 2019a)	Japan/Asia	71.5 (5.1)	CS	AWGS	BIA	Height	331,-,-				31 (9.4)					
(Mori and Tokuda, 2019)	Japan/Asia	68.2 (10.7)	CS	AWGS	BIA	Height	166-67-99				12 (7.2)	4 (6.0)	8 (8.0)			
(Mori et al., 2019b)	Japan/Asia	59.0 (11.0)	PP	AWGS	DXA	Height	-,-,308						124 (40.0)			
(Murakami et al., 2015)	Japan/Asia	73.0 (5.1)	CS	AWGS	BIA	Height	761-447-314				116 (15.2)	72 (16.1)	44 (14.0)			
(Murata et al., 2018)	Japan/Asia	75.6 (6.1)	CS	AWGS	BIA	Height	288-137-151				88 (30.6)	42 (30.7)	46 (30.5)			
(Nascimento et al., 2018)	Brazil/South America	68.3(6.0)	CS	MM	DXA	BMI	-,64,-					31 (48.4)				
(Nasimi et al., 2019)	Iran/Asia	70.3 (4.6)	CS	AWGS	BIA	Height	501-247-254				104 (20.8)	34 (13.8)	70 (27.6)			
(Nishiguchi et al., 2015)	Japan/Asia	73.0 (5.4)	CS	AWGS	BIA	Height	-,273,-					22 (8.0)				
N(Nishimura et al., 2019)	Japan/Asia	70.4 (5.6)	CS	AWGS	BIA	Height	213-105-108				41 (19.2)	19 (18.2)	22 (20.4)			
(Norshafarina et al., 2013)	Malaysia/ Asia	66.4(5.7)	CS	MM	BIA	Height	388-233-155	232 (59.8)	94 (40.3)	138 (89.0)	178 (45.9)	65 (27.9)	113 (72.9)	54 (13.9)	29 (12.4)	25 (16.1)
(Ohashi et al., 2018)	Japan/Asia	68.2(11.2)	CS	Other	CT scan	Height	214-92-122	-	-	-	27 (12.6)	14 (15.2)	13 (10.6)	-	-	-
(Ohyama et al., 2019)	Japan/Asia	78.8 (5.7)	CS	AWGS	BIA	Height	126-55-71				27 (21.4)	16 (29.0)	11 (15.5)			
(Okamura et al., 2019)	Japan/Asia	65.4(11.1)	CS	AWGS	BIA	Height	433-197-236				32 (7.4)	16 (8.1)	16 (6.8)			
(Olesen et al., 2019)	Denmark/ Europe	57.4(12.9)	PP	EWGSOP	BIA	Height	182,-,-				31 (17.0)					
(Oliveira Neta et al., 2018)	Brazil/South America	67.0 (8.0)	CS	MM	BIA	Percentile	-,100,-					19 (19.0)				
(Ottestad et al., 2018)	Norway/ Europe	74 (72–78)	CS	EWGSOP	BIA	Height	417-218-199				90 (21.6)	69 (31.7)	21 (10.6)			
(Öztürk et al., 2018)	Turkey/Asia	71.8 (6.01)	CS	EWGSOP	BIA	Height	423-240-183				106 (25.0)	51 (21.3)	55 (30.0)			
(Pagotto and Silveira, 2014)	Brazil / south America	70.2 (6.6)	CS	EWGSOP Other Other EWGSOP Other Other Other Other	DXA DXA DXA BIA BIA BIA BIA	Height Height Height Height Weight Weight Height	132-81-52	-	-	-	17 (13.0) 22 (16.8) 48 (36.6) 23 (17.6) 15 (11.3) 2 (1.3) 14 (10.7)	14 (15.2) 9 (11.4) 14 (17.7) 28 (34.2) 37 (45.6) 11 (13.6) 31 (38.7)	13 (10.6) 8 (15.4) 8 (15.4) 13 (25.0) 12 (23.1) 4 (7.7) 10 (19.6)	-	-	-

					BIA	Height					40 (30.5)	6 (7.6)	8 (15.4)			
(Papachristou et al., 2015)	UK /Europe	70.1 (4.4)	CS	EWGSOP FNIH	BIA	Height BMI	,-,-801	-	-	-	-	-	11 (1.4) 13 (1.6)	-	-	-
(Park et al., 2018)	South Korea/Asia	39.0 (8.9)	CS	MM	BIA	Weight	237,838-109,643-128,195				7207 (3.0)	3702 (3.4)	3505 (2.7)			
(Park et al., 2010)	Japan/Asia	72.5 (4.6)	CS	MM	DXA	Height	175-97-78				43 (24.6)	25 (25.8)	18 (23.0)			
(Park et al., 2017)	South Korea/Asia	55.0 (4.4)	CS	MM	BIA	Percentile	1270-496-774				139 (10.9)	26 (5.2)	113 (14.6)			
(Pedrero-Chamizo et al., 2015)	Spain/ Europe	72.2 (5.3)	CS	MM	BIA	Height	2747-2102-645				1098 (39.9)	847 (40.3)	251 (38.9)			
(Pereira et al., 2015)	Brazil / South America	68.3 (6.8)	CS	EWGSOP*	DXA	Height	-,-,198	-		-	-	-	20 (10.1)			
(Petta et al., 2017)	Italy/Europe	48.3 (13.4)	PP	MM	BIA	Weight	225-84-141				98 (43.6)	40 (47.6)	58 (41.1)			
(Poggiogalle et al., 2019a)	USA/America	92 (2)	CS	MM	DXA	Percentile	87-50-37				43 (49.4)	18 (36.0)	25 (67.6)			
(Poggiogalle et al., 2019b)	Italy/Europe	48 (14)	CS	MM	DXA	Weight	-,54,-					28 (52.6)				
(Rasaei et al., 2019)	Iran/Asia	36.52 (8.32)	CS	MM	BIA	Fat mass	-,301,-					27 (8.9)				
(Rathnayake et al., 2019)	Sri Lanka/South Asia	52.4 (5.6)	CS	Other	DXA	Height	-,270,-		8 (2.9)			6 (2.2)			2 (0.7)	
(Reid et al., 2018)	Australia/ Oceania	84.5 (8.2)	CS	EWGSOP	BIA	Height	102				41 (40.2)					
(Reijnierse et al., 2015)	UK, France, the Netherlands, Estonia, Finland / Europe	77.4 (5.1)	CS	EWGSOP IWGS FNIH MM MM MM MM MM	DXA DXA DXA DXA DXA DXA BIA BIA	Height Height BMI Height Height Height Body mass Height	431-,-,	- - 10 (2.3) - - - 24 (5.6) 47 (10.9)	-	-	40 (9.3) 26 (6.0) 7 (1.6) 62 (14.4) 74 (17.2) 4 (0.9) 23 (5.3) 42 (9.7)	-	-	- 3 (0.7) - - - - 1 (0.2) 5 (1.2)	-	-
(Ren et al., 2016)	China/Asia	49.4 (11.7)	CS	EWGSOP	BIA	Height	131-51-80	18 (13.7)	6 (11.8)	12 (15.0)						
(Rodondi et al., 2012)	Switzerland/ Europe	85.9 (0.5)	CS	MM	DXA	Height	151,-,-	64 (42.4)			42 (27.8)			22 (14.6)		

(Rodríguez-García et al., 2018)	Mexico/North America	≥50	CS	EWGSOP	BIA	Height	724-521-203	110 (15.2)	80 (15.4)	30 (14.8)						
(Rodríguez-Rejón et al., 2019)	Spain/Europe	84.9 (6.7)	CS	EWGSOP	BIA	Height	249-187-62				143 (57.4)	119 (63.6)	24 (38.7)			
(Rossi et al., 2017)	Italy/Europe	71.70 (2.28)	CS	EWGSOP	DXA	Height	274-177-97				92 (33.6)	64 (36.2)	28 (28.9)			
(Roth et al., 2004)	USA/America	72.8 (0.8)	CS	MM	DXA	Height	-,-,302						75 (24.8)			
(Ryan et al., 2017)	USA/North America	63.0 (1.0)	PP	EWGSOP IWGS MM MM	DXA	Height Height Height BMI	168-,-, 168-,- 190-74-116 190-74-116	-	-	-	24 (14.3) 28 (16.7) 32 (16.8) 34 (17.9)	- - 12 (16.2) 7 (9.5)	- - 20 (17.2) 25 (21.6)	-	-	-
(Sanada et al., 2010)	Japan/Asia	28.1 (7.2)	CS	MM	DXA	Height	959-263-266	246 (25.6)	178 (67.7)	68 (25.6)	219 (22.8)	156 (59.3)	63 (23.7)	27 (2.8)	22 (8.4)	5 (1.9)
(Sánchez-Rodríguez et al., 2019)	Spain/Europe	81.4 (5.9)	CS	EWGSOP2 EWGSOP	BIA	Height	90-68-22	-	-	-	23 (25.6) 16 (17.8)	20 (29.4) 13 (19.1)	3 (13.6) 3 (13.6)	-	-	-
(Santos et al., 2017)	Brazil / South America	83.3 (2.7)	CS	Other	DXA	Height	116-,-,	-	-	-	33 (28.5)	-	-	-	-	-
(Schaap et al., 2018)	Netherland/ Europe	75.2 (6.4)	PP	EWGSOP FNIH	DXA	Height BMI	496-,-,	-	-	-	158 (31.9) 496 (39)					
(Scott et al., 2016a)	Tasmania/ Australia / Oceania	62.0 (7.0)	CS	Other	DXA	Residual	1092-351-741	-	-	-	361 (33.0)	186 (52.9)	175 (23.6)			
(Scott et al., 2019)	Sweden / Europe	70.0 (0.1)	CS	EWGSOP2	DXA	Height	3334-1675-1659	-	-	-	34 (1.0)	19 (1.1)	15 (0.9)	-	-	-
(Senior et al., 2015)	Australia / Oceania	84.5 (8.2)	CS	EWGSOP	BIA	Height	102-71-31				41 (40.2)	26 (36.6)	15 (48.4)			
(Sheng et al., 2019)	China/Asia	77.2 (6.6)	CS	EWGSOP	DXA	Height	94,-,-				25 (26.6)					
(Sherk et al., 2009)	USA/America	63.6 (0.6)	CS	MM	DXA	Height	-,55,-					7 (12.7)				
(Silva et al., 2013)	Brazil / South America	66.8 (5.4)	CS	MM	DXA	Height	-,272,-					198 (72.8)				
(Silva Neto et al., 2016)	Brazil / South America	65.6 (6.7)	CS	EWGSOP MM	DXA	Height Height	70-39-31				7 (10.0) 11 (16.0)	2 (5.1) 3 (7.7)	5 (16.1) 8 (25.8)			
(Singh et al., 2014)	USA/America	63.6 (1.0)	CS	MM	DXA	Height	60,-,-				12 (20.0)					
(Singhal et al., 2019)	India/ Asia	72.5 (6.4)	CS	AWGS	DXA	Height	100-31-69				53 (53.0)	19 (61.3)	34 (49.3)			
(Sjöblom et al., 2013)	Finland/ Europe	67.9 (65-72)	CS	Other	DXA	Height	-,597,-					69 (11.6)				
(Souza et al., 2017)	Brazil/ South America	73.6 (9.2)	CS	EWGSOP FNIH	DXA	Height BMI	100-59-41				12 (12.0) 29 (29.0)	- 18 (30.5)	- 11 (26.8)			

(Soysal et al., 2019)	Turkey/Asia	74.5 (7.5)	CS	EWGSOP	BIA	Height	-,-,305						95 (31.1)			
(Spira et al., 2016)	Germany/ Europe	68.2(3.6)	CS	MM	DXA	Height	1405-783-622				341 (24.3)	181 (23.1)	160 (25.7)			
(Steffl et al., 2016)	Czech Republic/ Europe	83.0 (6.3)	CS	EWGSOP	BIA	Height	77,-,-				34 (44.2)					
(Stoever et al., 2017)	Germany/ Europe	72.5 (3.9)	CS	EWGSOP	BIA	Weight	-,-,71						33 (46.5)			
(Su et al., 2019)	Japan/Asia	76.0 (5.8)	CS	EWGSOP2	BIA	Height	310-221-89	-	-	-	25 (8.1)	16 (7.2)	9 (10.1)	-	-	-
(Sugie et al., 2017)	Japan/Asia	79 (65-97)	PP	MM	DXA	Height	63-43-20				24 (38.0)	11 (25.6)	13 (65.0)			
(Sugimoto et al., 2019)	Japan/Asia	71.7 (8.0)	CS	AWGS	BIA	Height	746-296-450				52 (6.9)	20 (6.8)	32 (7.1)			
(Suzuki et al., 2018)	Japan/Asia	81 (75-85)	CS	AWGS	BIA	Height	-,245,-					29 (11.8)				
(Tabibi et al., 2018)	Iran /Asia	53.5 (4.8)	CS	Other	BIA	Height	79-44-35				9 (8.8)	1 (2.3)	8 (22.8)			
(Tanaka et al., 2018)	Japan/Asia	72.8 (5.4)	CS & PP	AWGS	BIA	Height	1904-954-950				115 (6.0)	75 (7.9)	40 (4.2)			
(Tang et al., 2018)	Taiwan/Asia	74.8 (5.5)	PP	FNIH	DXA	BMI	728-343-385	-	-	-	69 (9.5)	23 (6.7)	46 (11.9)	-	-	-
(Tanimoto et al., 2012)	Japan/Asia	74.2 (6.4)	CS	EWGSOP	BIA	Height	1158-794-364				126 (10.9)	85 (10.7)	41 (11.3)			
(Tasar et al., 2015)	Turkey/Europe[¥]	77.3 (7.2)	CS	EWGSOP	BIA	Body Mass	211-124-77				71 (33.6)	23 (18.5)	48 (62.3)			
(Tay et al., 2015)	Asia	69.3 (7.7)	CS	AWGS	DXA	Height	200-137-63				50 (25.0)	34 (24.8)	16 (25.4)			
(Tessier et al., 2019)	Canada/ North America	72.6 (5.5)	CS	FNIH	DXA	BMI	9088-4363-4725	-	-	-	821 (9)	350 (8)	471 (10)	-	-	-
(Tichet et al., 2008)	France/Europe	56.6 (4.8)	CS	MM	BIA	Height Weight	1106-526-580				18 (1.6) 89 (8.0)	8 (1.5) 54 (10.3)	10 (1.7) 35 (6.0)			
(Trajanoska et al., 2018)	Netherlands/Europe	72.4 (8.7)	CS	EWGSOP	DXA	Height	5911-3361-2290				260 (4.4)	98 (2.9)	162 (7.1)			
(Tramontano et al., 2017)	Peru / South America	75.4 (6.9)	CS	IWGS	BIA	Height	222-120-100	-	-	-	39 (17.6)	38 (31.7)	1 (1)	-	-	-
(Tuzun et al., 2018)	Turkey/Europe and Asia[¥]	53.4 (10.4)	CS	MM	BIA	Height Body Mass BMI	295-176-119	1 (0.3) 101 (34.0)	61 (34.7)	40(33.6)	1 (0.3) 87 (29.0) 16 (5.0)	0 (0.0) 56(31.8) 1 (0.6)	1 (0.8) 31(26.0) 15 (12.6)	14 (13.9)	5 (2.8)	9 (7.6)
(Tüzün et al., 2019)	Turkey/Asia	40.9 (12.0)	RP	MM	BIA	Height BMI Muscle mass Weight	524-331-193	- - - 114(21.8)	- - - 60(18.1)	- - - 54(27.9)	1 (0.2) 17 (3.2) 1 (0.2) 111 (21.8)	- 0 (0.0) - 59 (17.8)	1 (0.5) 17 (8.8) 1 (0.5) 52 (26.9)	- - - 3 (0.6)	- - - 1 (0.3)	- - - 2 (1.0)

(Urzi et al., 2017)	Slovenia/ Europe	84.3 (7.9)	CS	EWGSOP	BIA	Height	80-56-24				31 (38.7)	23 (41.0)	8 (33.3)			
(van de Bool et al., 2015)	Netherlands/ Europe	63.0 (58.0-68.8)	RP	MM	DXA	Height	505-217-288				437 (86.5)	198 (91.2)	239 (82.9)			
(Velazquez-Alva et al., 2017)	Mexico/North America	73.8 (6.7)	CS	EWGSOP	DXA	Height	-,137,-					20 (14.6)				
(Vermeiren et al., 2019)	Belgium/ Europe	83.3 (3.0)	CS	MM	DXA BIA BIA BIA BIA DXA BIA BIA BIA BIA DXA BIA BIA BIA BIA	Baumgartne Kyle Sergi Scafoglieri Butierfly Delmonico Kyle Sergi Scafoglieri Butierfly Newman Kyle Sergi Scafoglieri Butierfly	174-83-91				59 (34.0) 14 (8.0) 28 (16.0) 23 (13.0) 50 (29.0) 76 (44.0) 17 (10.0) 31 (18.0) 26 (15.0) 57 (33.0) 75 (43.0) 17 (10.0) 29 (17.0) 25 (14.0) 56 (32.0)	21 (25.3) 5 (6.0) 6 (6.0) 6 (7.2) 18 (21.7) 38 (45.8) 8 (9.6) 9 (10.8) 9 (10.8) 26 (31.3) 38 (45.8) 8 (9.6) 9 (10.8) 9 (10.8) 26 (31.3)	38 (41.8) 9 (9.9) 23 (25.3) 17 (18.7) 32 (35.2) 38 (41.8) 9 (9.9) 22 (24.2) 17 (18.7) 31 (34.1) 37 (40.7) 9 (9.9) 20 (22.0) 16 (17.6) 30 (33.0)			
(Walsh et al., 2006)	USA/America	57.0 (11.0)	CS	MM	DXA	Height	-,82,-					16 (19.5)				
(Wang et al., 2019)	China/Asia	68.8 (6.5)	CS	MM	BIA	Height	945-480-465				333 (35.2)	176 (36.7)	157 (33.8)			
(Wang et al., 2018)	China/Asia	71.2(7.6)	CS	AWGS	DXA	Height	135,-,-	19 (14.0)			14 (10.4)			5 (3.7)		
(Wang et al., 2016)	China/Asia	69.0 (28.6)	RP	AWGS	BIA	Height	1090-570-520				131 (12.0)	58 (10.2)	73 (14.0)			
(Wen et al., 2015)	China/Asia	65.7 (4.6)	CS	EWGSOP IWGS AWGS MM MM	DXA	Height Height Height Height Body Mass	286-150-136	- - - 18 (6.3) 122 (42.6)	- - - 1 (0.7) 89 (59.2)	- - - 17 (12.2) 33 (24.4)	1 (0.4) 17 (5.9) 9 (3.2) 17 (5.9) 108 (37.8)	0 7 (4.7) 1 (0.7) 1 (0.7) 78 (51.7)	1 (0.4) 10 (7.4) 8 (5.9) 16 (11.4) 30 (22.2)	- - - 1 (0.4) 14 (4.9)	- - - 0 11 (7.5)	- - - 1 (0.8) 3 (2.2)
(Westbury et al., 2018)	UK/Europe	78.8 (2.5)	CS	EWGSOP	DXA	Height	131-99-32				26 (19.9)	21 (21.2)	5 (15.6)			
(Wiriya et al., 2019)	Thailand/Asia	68.6 (6.8)	CS	AWGS	BIA	Height	396-299-97	5(1.3)	5(1.7)	0(0.0)	1(0.3)	1(0.3)	0	4(1.0)	4(1.3)	0(0.0)
(Woo et al., 2015)	Hong Kong/Asia	74.1 (5.6)	PP	EWGSOP IWGS FNIH AWGS	DXA	Height Height BMI Height	4000-2000-2000	-	-	-	361 (9.0) 807 (20.2) 222 (5.6) 293 (7.3)	171 (8.6) 365 (18.2) 68 (3.4) 106 (5.3)	190 (9.5) 442 (22.1) 154 (7.7) 187 (9.4)	-	-	-

(Wu et al., 2013)	Taiwan/Asia	63.6 (10.1)	CS	MM	BIA	Height	600-456-144				245 (40.8)	198 (43.4)	47 (32.6)			
(Wu et al., 2014)	Taiwan/Asia	74 (6.0)	CS & PP	Other*	BIA	Height Height	2155-1100-1085	85(3.9) 157(7.3)	28(2.5) 71(6.5)	57(5.2) 86(8.1)	50(2.3) 105(4.9)	11(1.0) 50(4.6)	33(3.0) 55(5.2)	35(1.6) 52(1.5)	17(1.5) 21(1.9)	24(2.2) 31(2.9)
(Xiao et al., 2018)	USA/America	55.6 (11.5)	RP	MM	BIA	Percentile	144,-,-				73 (50.7)					
(Xu et al., 2018)	China/Asia	60.2 (11.3)	CS	AWGS	BIA	Percentile	4824-280-2024				312 (6.5)	196 (7.0)	116 (5.7)			
(Yadigar et al., 2016)	Turkey/ Asia	71.9 (7)	CS	EWGSOP	BIA	Body Mass	214-148-66				105 (49.1)	64 (43.2)	41 (62.1)			
(Yalcin et al., 2016)	Turkey/ Asia	79.1 (7.9)	CS	EWGSOP	BIA	Height	141-62-79				41 (29.1)	24 (38.7)	17 (21.5)			
(Yamada et al., 2019)	Japan/Asia	81.0 (7.0)	CS	AWGS	BIA	Height	1009-724-285				166 (6.5)	105 (14.5)	61 (21.4)			
(Yamada et al., 2013)	Japan/Asia	74.9 (5.5)	CS	EWGSOP	BIA	Height	1882-1314-568				414 (22.0)	290 (22.1)	124 (21.8)			
(Yang et al., 2015)	Taiwan/Asia	75.0 (6.4)	CS	MM	DXA	Height	844-396-448				161 (19.0)	69 (17.4)	92 (20.5)			
(Yang et al., 2018)	China/Asia	71.5 (5.8)	CS	AWGS	BIA	Height	384-224-160				61 (15.9)	42 (11.9)	19 (18.8)			
(Yang et al., 2016)	China/Asia	52.3 (9.7)	RP	MM	DXA	Height	1555-504-1051				550 (35.4)	181 (35.9)	369 (35.1)			
(Yasemin et al., 2019)	Turkey /Asia	60.2 (10.6)	CS	EWGSOP	BIA	Body mass	602-358-244				135 (22.4)	100 (27.9)	35 (14.3)			
(Yazar and Olgun Yazar, 2019)	Turkey/ Asia	≥18	CS	EWGSOP	BIA	Width of neck	515-258-257	62 (12.0)	26 (10.1)	36(14.0)	27 (5.2)	6 (2.0)	21(8.2)	35 (6.8)	20 (7.8)	15 (5.8)
(Yoowannakul et al., 2018)	UK /Europe	66.3 (14.7)	CS	EWGSOP AWGS FNIH1 FNIH2	BIA	Height Height ALM BMI	600-227-373				228 (38.0) 198 (33.0) 215 (35.8) 170 (28.3)	74 (12.3) 75 (33.0) 92 (40.5) 51 (22.5)	154 (31.9) 123 (32.9) 123 (33.0) 119 (31.9)			
Yoshida 2014(Yoshida et al., 2014)	Japan/Asia	73.6 (6.2)	CS	EWGSOP	BIA	Height	4811-2468-2343				360 (7.5)	169 (6.8)	191 (8.2)			
(Yu et al., 2014b)	Australia/ Oceania	73.0 (5.8)	PP	Other	DXA	Height Gender Regression	986-375-611				16 (1.6) 73 (7.4) 71 (7.2)	1 (0.3) 35 (9.3) 32 (8.5)	15 (2.5) 38 (6.2) 39 (6.4)			
(Yuki et al., 2017)	Japan/Asia	72.2 (0.6)	PP	AWGS	DXA	Height	720-355-365				34 (4.7)	16 (4.5)	18 (4.9)			
(Zambrano et al., 2020)	Brazil/South America	57 (8.5)	CS	Other	CT scan	Height	118,-,-				20 (17.0)					
(Zeng et al., 2018)	China/ Asia	81.6 (3.3)	CS	EWGSOP IWGS FNIH	BIA	Height Height BMI	277-194-83	-	-	-	90 (32.5) 106 (38.3) 87 (31.4)	69 (35.6) 84 (42.3) 68 (35.1)	21 (25.3) 24 (28.9) 19 (22.9)	-	-	-

				AWGS		Height					95 (34.3)	82 (42.3)	13 (15.7)			
(Zengin et al., 2018)	Gambia / Africa	61.0 (12.4)	PP	EWGSOP FNIH	DXA	Height BMI	488-249-239				71 (14.5) 160 (32.8)	26 (10.4) 112 (45)	45 (18.8) 48 (20.1)			
(Zhang et al., 2019)	China/ Asia	72.3 (5.2)	CS	AWGS	BIA	Height	1002-,-,-				107 (10.7)					
(Zoico et al., 2004)	Italy/Europe	71.7 (2.4)	CS	MM	DXA	Height Weight	-,167,-		40(23.9) 69(41.3)			30 (17.9) 22(13.2)			10 (5.9) 47 (28.1)	

CS: cross-sectional; PP: prospective; RP: retrospective.

*Modified version of the classification

¥European portion of Turkey

2.1.5 Supplementary Table 3. Cut-off points used for the different studies and classifications included in the systematic review and meta-analyses

Study	Classification used	Assessment method for muscle mass	Correction method for muscle mass	Cut-off points muscle mass		Cut-off points grip strength		Cut-off points gait speed	
				Women	Men	Women	Men	Women	Men
(Adebusoye et al., 2018)	EWGSOP	BIA	Height	34.7 kg	42.8kg	-	-	≤0.8 m/s	≤0.8 m/s
(Aibar-Almazán et al., 2018)	EWGSOP	BIA	Height	6.42 kg/m^2	-	<20 kg	-	≤0.8 m/s	-
(Akune et al., 2014)	EWGSOP	BIA	Height	5.8 kg/m^2	7.0 kg/m^2	20 kg	30 kg	0.8 m/s	0.8 m/s
(Alkahtani, 2017)	MM	BIA (inbody) BIA (tanita) DXA	Height	- - -	6.42 kg/m^2 7.45 kg/m^2 6.51 kg/m^2	- - -	- - -	- - -	- - -
(Anastácio et al., 2019)	MM	BIA	FFMI	<15 kg/m^2	<17.4 kg/m^2	-	-	-	-
(Androga et al., 2017)	MM	DXA	Height	<5.45 kg/m^2	7.26 kg/m^2	-	-	-	-
(As'habi et al., 2018)	Other	BIA	Height	10.76 kg/m^2	10.76 kg/m^2	<18 kg	<26 kg	<0.8 m/s	<0.8 m/s
(Ates Bulut et al., 2018)	EWGSOP	BIA	Height	6.42 kg/m^2	8.87 kg/m^2	<20 kg	<30 kg	<0.8 m/s	<0.8 m/s
(Bahat et al., 2018)	EWGSOP IWGS FNIH	BIA	Height Height Height	<6.42 kg/m^2 ≤ 5.67 kg/m^2 <0.512	<8.87 kg/m^2 ≤7.23 kg/m^2 <0.789	<20 kg - <16	<30 kg - <26	<0.8 m/s <1.0 m/s < 0.8 m/s	<0.8 m/s <1.0 m/s < 0.8 m/s
(Barbosa-Silva et al., 2016)	EWGSOP	DXA	Height	5.62 kg/m^2	7.76 kg/ m^2	<20 kg	<30 kg	<0.8 m/s	<0.8 m/s
Bataille 2017 (Bataille et al., 2017)	EWGSOP	BIA	Height	<6.42 kg/m^2	<8.87 kg/ m^2	<20 kg	<30 kg	-	-
(Beaudart et al., 2015)	EWGSOP	DXA	Height	<5.5 kg/ m^2	<7.26 kg/ m^2	<20 kg	<30 kg	<0.8 m/s.	<0.8 m/s.

(Bellanti et al., 2018)	MM	DXA	Height	<5.67 kg/ m^2	<7.25 kg/ m^2	-	-	-	-
(Benavides-Rodríguez et al., 2017)	EWGSOP	BIA	Height	<6.42 kg/ m^2	-	<20 kg	-	≤0.8 m/s	-
(Bering et al., 2018)	EWGSOP	DXA	Height	<5.45kg/ m^2	<7.26 kg/ m^2	<20 kg	<30 kg	-	-
(Bijlsma et al., 2013)	MM	BIA DXA	Height Height	<5.45 kg/ m^2 <5.67 kg/ m^2	<7.26 kg/ m^2 <7.25 kg/ m^2	- -	- -	- -	- -
(Boetto et al., 2019)	EWGSOP FNIH	BIA	Height BMI	<5.67 kg/ m^2 <0.512	<7.23 kg/ m^2 <0.789	<17-21Kg [adjusted for BMI] <16	<29-32kg [adjusted for BMI] <26	<0.8 m/s <0.8 m/s	<0.8 m/s <0.8 m/s
(Bouchard et al., 2009)	MM	DXA	Height	<6.29 kg/ m^2	<8.51 kg/m2	-	-	-	-
(Bravo-José et al., 2018)	EWGSOP	BIA	Height	<6.68 kg/m^2	<8.31 kg/m^2	<20kg	<30 kg	<0.8 m/s	<0.8 m/s
(Buckinx et al., 2017)	EWGSOP	BIA	Height	<6.42 kg/m^2	<8.87 kg/m^2	<20kg	<30 kg	<0.8 m/s	<0.8 m/s
(Buehring et al., 2013a)	MM	DXA	Height	<5.45 kg/m^2	<7.26 kg/m^2	-	-	-	-
(Buehring et al., 2013b)	MM	DXA	Height	<5.45 kg/m^2	<7.26 kg/m^2	-	-	-	-
(Bunout et al., 2018)	Other	DXA	Height	<5.6 kg/m^2	<7.5 kg/m^2	<1 sex-age zscore	<1 sex-age zscore	-	-
(Byun et al., 2017)	EWGSOP	BIA	Height	<2SD reference group	<2SD reference group	≤20kg	≤30kg	-	-
(Caan et al., 2018)	MM	CT scan	Height	<40 cm^2/m^2	-	-	-	-	-
(Caan et al., 2017)	MM	CT scan	Height	<46.6cm^2/ m^2 38.5 cm^2/m^2	<52.3 cm^2/h^2 <54.3 cm^2/h^2	- -	- -	-	-
(Castillo et al., 2003)	MM	BIA	Height	<2SD	<2SD	-	-	-	-
(Chalhoub et al., 2015)	EWGSOP*	DXA	Residual	-	-	<20kg	<30 kg	<0.8 m/s	<0.8 m/s

(Chang et al., 2015)	MM	BIA	Height Weight	<4.93 kg/m^2 24.5%	<6.74 kg/m^2 <29.4%	- -	- -	- -	- -
(Chang et al., 2017)	AWGS	BIA	Height	<5.7 kg/m^2	<7.0 kg/m^2	<18 kg	<26 kg	-	-
(Chaput et al., 2007)	MM	DXA	Height	<2DS Reference	<2DS Reference	-	-	-	-
(Chen et al., 2017)	MM	DXA	Regression Height	<3.4 residual <2 SD	- -	- -	- -	- -	- -
(Cheng et al., 2014)	MM	DXA	Height	<5.42 kg/m^2	<7.01 kg/m^2	-	-	-	-
(Cherin et al., 2014)	EWGSOP	DXA	Height	5.45kg/m^2	7.26 kg/m^2	20 kg	30kg		
(Chien et al., 2008)	MM	BIA	Height	<6.42 kg/m^2	<8.87kg/m^2	-	-	-	-
(Chien et al., 2015)	MM	BIA	Height	<6.42 kg/m^2	<8.87kg/m^2	-	-	-	-
(Choe et al., 2018)	MM	CT scan	BMI	7.47 cm^2(kg/m^2)	8.37 cm^2 (kg/m^2)	-	-	-	-
(Choe et al., 2017)	FNIH AWGS	BIA	BMI Height	<0.512 <5.4 kg/m^2	<0.789 <7.0 kg/m^2	<16 kg <18 kg	<26 kg <26 kg	<0.8 m/s <0.8 m/s	<0.8 m/s <0.8 m/s
(Christensen et al., 2018)	EWGSOP	DXA	Height	<5.67 kg/m^2	<7.23 kg/m^2	<20 kg	<30 kg	<0.8 m/s	<0.8 m/s
(Clynes et al., 2015)	EWGSOP IWGS FNIH	DXA	Height Height BMI	<5.5 kg/m^2 ≤ 5.67 kg/m^2 <0.512	<7.26 kg/m^2 ≤7.23 kg/m^2 <0.789	- <20Kg <16Kg	- <30Kg <26Kg	<1 m/s <1m/s	<1 m/s <1m/s
(Coin et al., 2008)	MM	DXA	Height	<5.45 kg/m^2	<7.26 kg/m^2	-	-	-	-
(Conzade et al., 2019)	EWGSOP	DXA	Height	<6.33 kg/m^2	<8.72 kg/m^2	<20 kg	<30 kg	<0.8 m/s	<0.8m/s
(Costa et al., 2015)	MM	DXA	Height Newman	<5.45 kg/m^2 <-1.082	<7.26 kg/m^2 <-2.021	- -	- -	- -	- -
(Coto Montes et al., 2017)	EWGSOP	BIA	Height	<6.68 kg/m^2	<8.31 kg/m^2	<20 kg	<30 kg	<0.8 m/s	<0.8m/s
(Cravo et al., 2017)	MM	CT scan	Height	<41 cm/m^2	<43 cm/m^2	-	-	-	-

(Cuesta et al., 2015)	EWGSOP	BIA	Height	<6.68 kg/m^2	<8.31 kg/m^2	<20 kg	<30 kg	<0.8 m/s	<0.8 m/s
(Davies et al., 2018)	EWGSOP* FNIH	DXA	Height BMI	<5.67k/m^2 <0.512	<7.23 kg/m^2 <0.789	Fried et al. <16Kg	Fried et al. <26Kg	<0.8 m/s <0.8 m/s	<0.8 m/s <0.8 m/s
(De Rosa et al., 2015)	MM	BIA	Height Weight	<6.75kg/m^2 <27.6%	<10.75kg/m^2 <37%	- -	- -	- -	- -
(de Souza Genaro et al., 2015)	EWGSOP	DXA	Height	<5.45 kg/m^2 <0.512	<7.26 kg/m^2 <0.789	<20 kg <16 kg	<30 kg <26 kg	<0.8 m/s <0.8 m/s	<0.8 m/s <0.8 m/s
(Delmonico et al., 2007)	MM	DXA	Height Regression	<5.67 kg/m^2 <20 lower percentile	<7.25 kg/m^2 <20 lower percentile	- -	- -	- -	- -
(Dodds et al., 2017)	EWGSOP*	BIA	Height	<8.87 kg/m^2	<6.67 kg/m^2	<16 kg	<26 kg	<0.8 m/s	<0.8 m/s
(Domiciano et al., 2013)	MM	DXA	Height Newman	<5.45 kg/m^2 <-1.45 residual	- -	- -	- -	- -	- -
(Dorosty et al., 2016)	EWGSOP	BIA	Height	<6.42 kg/m^2	<8.87 kg/m^2	<20 kg	<30 kg	<0.8 m/s	<0.8 m/s
(dos Santos et al., 2014)	MM	DXA	Height Newman	<5.45 kg/m^2 <3.44	- -	- -	- -	- -	- -
(Dufour et al., 2013)	MM	DXA	Height Newman	<5.45 kg/m^2 Lowest quartile	<7.26 kg/m^2 Lowest quartile	- -	- -	- -	- -
(Dupuy et al., 2015)	EWGSOP IWGS MM MM MM Other	DXA	Height Height Height Newman Delmonico Height	5.45kg/m^2 <5.67 kg/m^2 <5.45 kg/m^2 20th percentile <5.67 kg/m^2 5.45kg/m3	- - - - - -	<20 kg - - - - -	- - - - - -	<0.8 m/s <1m/s - - - - <0.8 m/s	- - - - - -
(Dutra et al., 2019)	MM	BIA	Fat mass	<24.7%	-	-	-	-	-
(Eguchi et al., 2017)	MM	DXA	Height	<5.46 kg/m^2	-	-	-	-	-

(Emami et al., 2018)	MM	DXA	Height	-	<7.26 kg/m^2	-	-	-	-
(Fanelli Kuczmarski et al., 2013)	EWGSOP	DXA	Percentile	below 20th percenile	below 20th percenile	<20kg	<30kg	≤ 6 points	≤ 6 points
(Fonseca et al., 2019)	EWGSOP	DXA	Height	-	<7.26 kg/m^2	-	<30 kg	-	-
(Franzon et al., 2019)	EWGSOP2 EWGSOP	DXA	Height	-	<7.0 kg/m^2 <7.26 kg/m^2	-	< 27 kg <30 kg	-	≤0.8 m/s ≤0.8 m/s
(Frisoli et al., 2018)	EWGSOP	DXA	Height	<5.45 kg/m^2	<7.26 kg/m^2	<20kg	<30kg	<0.8 m/s	<0.8 m/s
(Fukuoka et al., 2019)	AWGS	BIA	Height	<5.7 kg/m^2	<7.0 kg/m^2	<18 kg	<26 kg	≤0.8 m/s	≤0.8 m/s
(Fung et al., 2019)	AWGS	BIA	Height	< 5.7 kg/m^2	< 7 kg/m^2	< 18 kg	< 26 kg	≤0.8 m/s	≤0.8 m/s
(Gan et al., 2020)	Other*	DXA	Weight	24.12%	28.64%	35.38%	51.26%		
(Gielen et al., 2015)	EWGSOP IWGS MM	DXA	Height	- - -	<7.26 kg/m^2 ≤7.23 kg/m^2 <7.26 kg/m^2	- - -	<30 kg - -	- - -	<0.8 m/s <1.0 m/s -
(Giglio et al., 2018)	EWGSOP	DXA	Height	<5.45 kg/m^2	<7.26 kg/m^2	< 20 kg	< 30 kg		
(Giusto et al., 2015)	Other*	DXA	Height	<5.9 kg/m^2	<7.7 kg/m^2	below 10th percentile	below 10th percentile		
(Glenn et al., 2017)	MM	DXA	BMI	<5.45 kg/m^2	<7.26 kg/m^2	-	-	-	-
(Gray et al., 2016)	MM	DXA	BMI	<0.512	<0.789	-	-	-	-
(Greenhall and Davenport, 2017)	MM	BIA	Height	<6.75 kg/m^2	<10.75 kg/m^2	-	-	-	-
(Gu et al., 2018)	MM	CT scan	Height	≤38.5 cm^2/m^2	≤52.4 cm^2/m^2	-	-	-	-
(Hai et al., 2017)	AWGS	BIA	Height	<5.7 kg/m^2	<7.0 kg/m^2	<18 kg	<26 kg	<0.8m/s	<0.8m/s
(Han and Chung, 2018)	AWGS	BIA	Height	<5.7 kg/m^2	<7.0 kg/m^2	< 18 kg	< 26 kg	< 0.8 m/s	< 0.8 m/s
(Han et al., 2016a)	AWGS	BIA	Height	<5.7 kg/m^2	<7.0 kg/ m^2	< 18 kg	<26kg	<0.8m/s	<0.8m/s
(Han et al., 2017)	MM	DXA	Height	<5.4 kg/m^2	<7.0 kg/m^2				

(Han et al., 2016b)	EWGSOP	BIA	Height Weight	<6.57kg/m^2 <30.7 %	<8.83 kg/m^2 <35.7%	<20 kg <20 kg	<30 kg <30 kg	<0.8m/s <0.8m/s	<0.8 m/s <0.8m/s
(Harita et al., 2019)	AWGS	BIA	Height	<5.7 kg/m^2	<7.0 kg/m^2	<18 kg	<26 kg		
(Hars et al., 2016)	MM Delmonico Delmonico EWGSOP2 FNIH	DXA	Height Height Percentile Height BMI	<5.45 kg/m^2 <5.67 kg/m^2 <5.67 kg/m^2 <5.67 <0.512	<7.26 kg/m^2 <7.25 kg/m^2 <7.25 kg/m^2 <7.23 <0.789	- - - - - -	- - - - - -	- - - - - -	- - - - - -
(Hashemi et al., 2016)	EWGSOP	DXA	Height	<5.45 (kg/m^2)	<7.26 (kg/m^2)	<20 kg	<30 kg	<0.8m/s	<0.8m/s
(Hayashi et al., 2013)	Other*	BIA	Height	<5.46 kg/m^2	<6.87 kg/m^2	<14 kg	<24 kg	-	-
(Hayashi et al., 2018)	Other*	BIA	Height	<5.7 kg/m^2	<7.0 kg/m^2	<18kg	<26 kg	-	-
He 2016 (He et al., 2016b)	EWGSOP* MM	DXA	Height	<5.45 kg/m^2 <4.79 kg/m^2	<7.26 kg/m^2 <6.08 kg/m^2	Fried et al. -	Fried et al. -	-	-
(He et al., 2018)	EWGSOP IWGS FNIH AWGS	BIA	Height Height BMI Height	<5.08 kg/m^2 ≤ 5.67 kg/m^2 <0.512 <5.7	<6.28 kg/m^2 ≤7.23 kg/m^2 <0.789 <7.0	<20 kg - <16 kg <18	<30 kg - <26 kg <26	<0.8 m/s <1m/s <0.8 m/s <0.8 m/s	<0.8 m/s <1 m/s <0.8 m/s <0.8 m/s
(Hedayati and Dittmar, 2010)	MM	BIA	Weight	<1SD from the reference group	<1SD from the reference group	-	-	-	-
(Hida et al., 2018)	MM	BIA	Height	<5.8kg/ m^2	<7.0 kg/ m^2	-	-	-	-
(Hirai et al., 2019)	AWGS	BIA	Height	<5.7 kg/ m^2	<7.0 kg/m^2	18 kg	26 kg	<0.8 m/s	<0.8 m/s

(Hirani et al., 2015)	FNIH	DXA	ALM	-	<19.75	-	<26 kg		<0.8 m/s
(Hiraoka et al., 2016)	EWGSOP* AWGS*	CT scan	Height	2.50 cm^2/ m^2 2.50 cm^2/ m^2	4.24 cm^2/ m^2 4.24 cm^2/ m^2	<20 kg <18 kg	<30 kg <26 kg	- -	- -
(Hoffmann et al., 2016)	MM	DXA	Height	<5.45 kg/ m^2	<7.26 kg/m^2	-	-	-	-
(Hong et al., 2019)	MM	BIA	Weight	<23 %	<29.1%	-	-	-	-
(Hsu et al., 2014)	EWGSOP	BIA	Height	-	<8.87 kg/m^2	-	<22.5 kg	-	<0.8 m/s
(Hu et al., 2017)	AWGS	DXA	Height	<4.91 kg/m^2	<6.89 kg/m^2	<18 kg	<26 kg	<0.8 m/s	<0.8 m/s
(İlhan et al., 2019)	EWGSOP	BIA	Height	<7.4 kg/m^2	<9.2 kg/m^2	<22 kg	<32 kg	<0.8 m/s	<0.8 m/s
(Ishii et al., 2014)	EWGSOP	BIA	Height	<5.8 kg/m^2	<7.0 kg/ m^2	<20 kg	<30 kg	<1.26m/s	<1.26m/s
(Isoyama et al., 2014)	EWGSOP	DXA	Height	<5.5 kg/m^2	<7.3 kg/m^2	<20 kg	<30 kg	-	-
(Ishikawa et al., 2018)	AWGS	DXA	Height	<5.4 kg/m^2	<7.0 kg/m^2	<18 kg	<26 kg	<0.8 m/s	<0.8 m/s
(Iwasaki et al., 2017)	AWGS	BIA	Height	<5.7 kg/m^2	<7 kg/m^2	<18 kg	<26 kg	<0.8 m/s	<0.8 m/s
(Jang et al., 2018)	AWGS Kim 2016 FNIH	BIA	Height Weight BMI	Lower quintile Lower quintile Lower quintile	Lower quintile Lower quintile Lower quintile	18 kg 18 kg 18 kg	26 kg 26 kg 26 kg	0.8 m/s 0.8 m/s 0.8 m/s	0.8 m/s 0.8 m/s 0.8 m/s
(Janssen, 2006)	MM	BIA	Height	<6.76 kg/m^2	<10.76 kg/m^2	-	-	-	-
(Jones et al., 2020)	EWGSOP	BIA	Height	<6.42	<8.87	<20 kg	<30 kg	-	-
(Kamijo et al., 2018)	AWGS	BIA	Height	<5.7 kg/m^2	<7 kg/m^2	<18 kg	<26 kg	<0.8 m/s	<0.8 m/s
(Kera et al., 2017)	AWGS	BIA	Height	<5.91 kg/m^2	<7.09 kg/m^2	<20 kg	<25 kg	<1 m/s	<1 m/S
(Kim et al., 2018a)	MM	CT scan	Height	<39 cm/m^2	<55 cm/m^2	-	-	-	-
(Kim et al., 2016a)	MM	BIA	Weight	<8.22	<10.74	-	-	-	-

(Kim et al., 2018b)	FNIH AWGS Other	DXA	BMI Height	<0.512 <5.4 kg/m^2 <5.7 kg/m^2	<0.789 <7.0 kg/m^2 <7.69 kg/m^2	<16 kg <18 kg <19 kg	<26 kg <26 kg <31 kg	- - -	- - -
(Kim et al., 2016b)	Other	DXA	Weight	<20.37%	<25.03%	<18 kg	<26 kg		
(Hyun Kim et al., 2020)	EWGSOP EWGSOP2 AWGS IWGS FNIH	DXA	Height Height Height BMI	<5.5 kg/m^2 <6 kg/m^2 <5.4 kg/m^2 <5.67 kg/m^2 <0.512	<7.26 kg/m^2 <7.0 kg/m^2 <7.0 kg/m^2 <7.23 kg/m^2 <0.798	<20 kg <16 kg <18 kg - <16 kg	<30 kg <27 kg <26 kg - <26 kg	<0.8 m/s ≤0.8 m/s <0.8 m/s <1 m/s <0.8 m/s	<0.8 m/s ≤0.8 m/s <0.8 m/s <1 m/s <0.8 m/s
(Kim and Won, 2019)	MM	BIA	BMI	<0.512	<0.789	-	-	-	-
(Kim et al., 2018c)	AWGS	BIA	Weight	<23%	-	<18Kg	-	<0.8m/s	-
(Kim et al., 2009)	MM	DXA	Height Weight	<5.14 kg/m^2 <20th percentile	<7.40 kg/m^2 <20th percentile	-	-	-	-
(Kirchengast and Huber, 2009)	MM	DXA	Height	<5.45	<7.26	-	-	-	-
(Kobayashi et al., 2020)	MM	BIA	Height	<5.8 kg/m^2	<7.0 kg/m^2	-	-	-	-
(Koo et al., 2017)	MM	BIA	Weight BMI	<22.9% <0.512	<29.0% <0.789	-	-	-	-
(Kruger et al., 2016)	MM	DXA	Height	<4.94 kg/m^2	-	-	-	-	-
(Kruger et al., 2015)	EWGSOP FNIH	DXA	Height BMI	<5.5 kg/m^2 <0.512	- -	<16kg <16	- -	<0.8 m/s <0.8 m/s	- -
(Krzymińska-Siemaszko et al., 2019)	EWGSOP	BIA	Height	<5.51	<7.35	< 20 kg	< 30 kg	-	-
(Kusaka et al., 2017)	AWGS	BIA	Height	<5.7 g/m^2	-	<18 kg	-	<0.8 m/s	-
(Kuyumcu et al., 2016)	Other	BIA	Height	<2SD	<17.51 kg/m^2	Fried et al.	Fried et al.		

(Kyle et al., 2001)	MM	DXA	Height	<5.36 kg/m^2 <6.96 kg/m^2	<7.06 kg/m^2 <8.83 kg/m^2	- -	- -	- -	- -
(Lamarca et al., 2014)	MM MM Other Other	DXA BIA DXA BIA	Height	<6.08 kg/m^2 <14.6 <2SD <5.16 <12.8	<8.12 kg/m^2 <18.1 <2SD <6.95 <15.9	- - - 10th per. 10th per.	- - - 10th per. 10th per.	- - - -	- - - -
(Landi et al., 2012)	EWGSOP	BIA	Height	<6.42 kg/m^2	<8.87 kg/m^2	<20Kg	<30Kg	<0.8 m/s	<0.8 m/s
(Lardiés-Sánchez et al., 2017)	EWGSOP	BIA	Height	<6.42 kg/m^2	<8.87 kg/m^2	<20Kg	<30 kg	<0.8 m/s	<0.8 m/s
(Lau et al., 2005)	MM	DXA	Height	<2SD	<2SD	-	-	-	-
(Lee and Park, 2015)	AWGS	DXA	Height	<5.4 kg/m^2	-	<18 kg		≤0.8 m/s	
(Legrand et al., 2013)	EWGSOP	BIA	Height	<6.42 kg/m^2	<8.87 kg/m^2	<20 kg	<30 kg	<0.8 m/s	<0.8 m/s
(Lera et al., 2017)	EWGSOP	DXA	Height	<5.77 kg/m^2	<7.19 kg/m^2	<15 Kg	<27 Kg	<0.8 m/s	<0.8 m/s
(Liguori et al., 2018)	EWGSOP*	BIA	Height	<6.42 kg/m^2	<8.87	Fried et al.	Fried et al.	-	-
(Lim et al., 2010)	MM MM	DXA	Height Weight	<5.27 kg/m^2 <25.1 %	<7.09 kg/m^2 <29.9%	- -	- -	- -	- -
(Lima et al., 2009)	MM	DXA	Height	<5.45 kg/m^2	-	-	-	-	-
(Lima et al., 2019)	EWGSOP*	DXA	FFM	<5.50 kg/m^2	-	<76.5 Nm	-	>7.4 s	-
(Lin et al., 2018)	EWGSOP	BIA	Height	<6.76 kg/m^2	<10.76	<20 kg	< 30 kg	<1.0 m/s	<1.0 m/s
(Lu et al., 2013)	MM	BIA	Weight	≤27.6%	≤37%	-	-	-	-
(Lu et al., 2020)	AWGS	DXA	Height	<5.4 kg/m^2	<7 kg/m^2	≤16 kg	≤18 kg	≤0.8	≤0.8
(Lucassen et al., 2017)	MM	DXA	Weight	<25.1%	<29.9%	-	-	-	-

(Marini et al., 2012)	MM	DXA	Height	<5.45 kg/m^2	<7.26 kg/m^2	-	-	-	-
(Maruya et al., 2019)	AWGS	BIA	Height	<5.7 kg/m^2	<7 kg/m^2	<18 kg	<26 kg	<1.0m/s	<1.0m/s
(Marzetti et al., 2014)	MM	BIA	Height	<6.42 kg/m^2	<8.87 kg/m^2	-	-	-	-
(Masanes et al., 2012)	MM	BIA	Height	<6.68 Kg/m^2	<8.25 Kg/m^2	-	-	-	-
(Matsumoto et al., 2019)	AWGS	BIA	Height	<5.7 kg/m^2	<7.0 kg/m^2	<18 kg	<26 kg	≤0.8m/s	≤0.8m/s
(Mazocco et al., 2019)	EWGSOP	DXA	Height	<5.62 kg/m^2	-	<20 kg	-	≤0.8m/s	-
(Melton et al., 2000)	MM	DXA	Height	<2DS	<2SD				
(Menant et al., 2017)	EWGSOP Baumgartner Bouchard	DXA	Height Height Height	<5.5 kg/m^2 <5.45 kg/m^2 <6.29 kg/m^2	<7.2 kg/m^2 <7.26 kg/m^2 <8.51 kg/m^2	<20 kg - -	<30 kg - -	<0.8 m/s - -	<0.8 m/s - -
(Mesinovic et al., 2019)	EWGSOP2	DXA	Height	<6 kg/m^2	<7 kg/m^2	<16 kg	<27 kg	≤0.8m/s	≤0.8m/s
(Mesquita et al., 2017)	MM	BIA	Height	<6.75 kg/m^2	<10.75 kg/m^2	-	-	-	-
(Mienche et al., 2019)	AWGS	DXA	Height	<5.4 kg/m^2	<7.0 kg/m^2	<18 kg	<26 kg	≤0.8m/s	≤0.8m/s
(Mijnarends et al., 2016a)	EWGSOP	CT scan	Percentile	<83.2 cm	<116.5 cm	20 kg	<30 kg	≤0.8m/s	≤0.8m/s
(Mijnarends et al., 2016b)	EWGSOP	BIA	Height	<6.75 kg/m^2	<10.75 kg/m^2	<20 kg	<30 kg	≤0.8m/s	≤0.8m/s
(Misra et al., 2019)	MM	DXA	Quartiles	Lowest quartile	Lowest quartile	-	-	-	-
(Miyakoshi et al., 2013)	MM	DXA	Height	<5.46 kg/m^2	-	-	-	-	-
(Mohseni et al., 2017)	EWGSOP	BIA	Height	<6.75 kg/m^2	-	Merkies et al.	-	≤0.8m/s	-
(Momoki et al., 2017)	AWGS	DXA	Height	<5.7 kg/m^2	-	<18 kg	-	-	-
(Montano-Loza et al., 2016)	MM	CT scan	Height	≤41 cm/m^2 ≤43 cm/m^2	-	-	-	-	-

(Moreira et al., 2016)	MM	BIA	Height	<6.08 kg/m^2	-	-	-	-	-
(Mori et al., 2017)	AWGS	BIA	Height	<5.7 kg/m^2	<7 kg/m^2	<18 kg	<26 kg	≤0.8m/s	<0.8 m/s
(Mori et al., 2019a)	AWGS	BIA	Height	<5.7 kg/m^2	<7.0 kg/m^2	<18 kg	<26 kg	<0.8 m/s	<0.8 m/s
(Mori and Tokuda, 2019)	AWGS	BIA	Height	<5.7 kg/m^2	<7 kg/m^2	<18 kg	<26 kg	<0.8 m/s	<0.8 m/s
(Mori et al., 2019b)	AWGS	DXA	Height	<5.4 kg/m^2	<7.0 kg/m^2	<18 kg	<26 kg	-	-
(Murakami et al., 2015)	AWGS	BIA	Height	<5.7 kg/m^2	<7 kg/m^2	<18 kg	<26 kg	<1 m/s	<1 m/s
(Murata et al., 2018)	AWGS	BIA	Height	<5.7 kg/m^2	<7 kg/m^2	<18 kg	<26 kg	<0.8 m/s	<0.8 m/s
(Nascimento et al., 2018)	MM	DXA	BMI	<0.512	-				
(Nasimi et al., 2019)	AWGS	BIA	Height	<5.7 kg/m^2	<7.0 kg/m^2	<18 kg	< 26 kg	< 0.8 m/s	<0.8 m/s
(Nishiguchi et al., 2015)	AWGS	BIA	Height	<5.7 kg/m^2	-	<18 kg	-	< 0.8 m/s	-
N(Nishimura et al., 2019)	AWGS	BIA	Height	<5.4 kg/m^2	<7.0 kg/m^2	<18 kg	<26 kg	<0.8 m/s	<0.8 m/s
(Norshafarina et al., 2013)	MM	BIA	Height	<6.75 kg/m^2	<10.75 kg/m^2	-	-	-	-
(Ohashi et al., 2018)	Other	CT scan	Height	<38 cm/m^2	<42 cm/m^2	<18 kg	<26 kg		
(Ohyama et al., 2019)	AWGS	BIA	Height	<5.7 kg/m^2	<7 kg/m2	<18 kg	<26 kg	<0.8 m/s	<0.8 m/s
(Okamura et al., 2019)	AWGS	BIA	Height	<5.7 kg/m^2	<7 kg/m^2	<18 kg	<26 kg	-	-
(Olesen et al., 2019)	EWGSOP	BIA	Height	<6.76 kg/m^2	<10.76 kg/m^2	<20 kg	<30 kg	by age	by age
(Oliveira Neta et al., 2018)	MM	BIA	Percentile	<6.22 kg/m^2	-	-	-	-	-
(Ottestad et al., 2018)	EWGSOP	BIA	Height	<6·42 kg/m^2	<8·87 kg/m^2	<20 kg	<30 kg	<0·8 m/s	<0·8 m/s
(Öztürk et al., 2018)	EWGSOP	BIA	Height	<7.4kg/ m^2	<9.2 kg/ m^2	<22 kg	<32 kg	<0.8 m/s	<0.8 m/s
(Pagotto and Silveira, 2014)	EWGSOP Other Other EWGSOP Other Other	DXA DXA DXA BIA	Height Height Height Height Weight	5.45 kg/m^2 5.67 kg/m^2	<7.26 kg/m^2 <7.23 kg/m^2 <7.40 kg/m^2 <31% <34.4%	- - - - -	- - - - -	- - - - -	- - - - -

	Other Other	BIA BIA BIA BIA	Weight Height Height	6.40 kg/m^2 <22% <26.6% ≤ 5.75 kg/m^2 <7 kg/m^2 <6.42 kg/m^2	≤ 8.50 kg/^{2} <9.5 kg/m^2 <8.87 g/m^2	- - -	- - -	- - -	- - -
(Papachristou et al., 2015)	EWGSOP FNIH	BIA	Height BMI	- -	<7.23 kg/ m^2 <0.789	- -	<30 kg <26 kg	- -	≤0.8 m/s ≤0.8 m/s
(Park et al., 2018)	MM	BIA	Weight	<32.2%	<36.7%	-	-	-	-
(Park et al., 2010)	MM	DXA	Height	<5.21 kg/m^2	<6.53 kg/m^2	-	-	-	-
(Park et al., 2017)	MM	BIA	Percentile	<90%	<90%	-	-	-	-
(Pedrero-Chamizo et al., 2015)	MM	BIA	Height	<5.80 kg/m^2	<8.11 kg/m^2	-	-	-	-
(Pereira et al., 2015)	EWGSOP*	DXA	Height	-	<7.26 kg/m^2	-	Fried et al.	-	-
(Petta et al., 2017)	MM	BIA	Weight	≤28%	≤37%	-	-	-	-
(Poggiogalle et al., 2019a)	MM	DXA	Percentile	<6.398 kg/m^2	<7.367kg/m^2	-	-	-	-
(Poggiogalle et al., 2019b)	MM	DXA	Weight	<23.47%	<28.27%	-	-	-	-
(Rasaei et al., 2019)	MM	BIA	Fat mass	2 highest quartiles	-	-	-	-	-
(Rathnayake et al., 2019)	Other	DXA	Height	<5.03 kg/m^2	-	9.66kg	-	0.96m/s	-
(Reid et al., 2018)	EWGSOP	BIA	Height	<6.42kg/m^2	<8.87 kg/m^2	< 20kg	< 30 kg	< 0.8 m/s	< 0.8 m/s
(Reijnierse et al., 2015)	EWGSOP IWGS FNIH MM MM MM MM MM	DXA DXA DXA DXA DXA DXA BIA BIA	Height Height BMI Height Height Height Body mass Height	≤6.75kg/m^2 ≤5.67 kg/m^2 <0.512 ≤ 5.42 kg/m^2 ≤5.67 kg/m^2 ≤4.73 kg/m^2	≤10.75 kg/m^2 ≤7.23 kg/m^2 <0.789 ≤7.26 kg/m^2 7.25 kg/m^2 6.19 kg/m^2 <37% ≤10.75 kg/m^2	<20 kg - <16Kg - - - - -	<30 kg - <26Kg - - - - -	≤0.8 m/s <1.0 m/s < 0.8 m/s - - - - -	≤0.8 m/s <1.0 m/s < 0.8 m/s - - - - -

				<28% ≤6.75kg/m^2					
(Ren et al., 2016)	EWGSOP	BIA	Height	< 5.75	<5.76	< 20kg	< 30 kg	-	-
(Rodondi et al., 2012)	MM	DXA	Height	<6.44 kg/m^2	<8.51 kg/m^2	-	-	-	-
(Rodríguez-García et al., 2018)	EWGSOP	BIA	Height	≤ 8.69 kg/m^2	≤ 6.38 kg/m^2	< 18.4 kg	< 29.1 kg	-	-
(Rodríguez-Rejón et al., 2019)	EWGSOP	BIA	Height	<6.68 kg/m^2	<8.31 kg/m^2	<20 kg	<30 kg	<0.8point	<0.8point
(Rossi et al., 2017)	EWGSOP	DXA	Height	<5.5 kg/m^2	<7.26 kg/m^2	<5.33 kg	<9.66 kg	0.8 m/s	0.8 m/s
(Roth et al., 2004)	MM	DXA	Height	-	<7.26 kg/m^2	-	-	-	-
(Ryan et al., 2017)	EWGSOP IWGS MM MM	DXA	Height Height Height BMI	<5.67 kg/m^2 ≤5.67 kg/m^2 <5.45 kg/m^2 <0.512	<7.23 kg/m^2 ≤ 7.23 kg/m^2 <7.26 kg/m^2 <0.789	-	-	<0.8 m/s <1.0 m/s	<0.8 m/s <1.0 m/s
(Sanada et al., 2010)	MM	DXA	Height	<6.12 kg/m^2	<6.87 kg/m^2	-	-	-	-
(Sánchez-Rodríguez et al., 2019)	EWGSOP2 EWGSOP	BIA	Height	<5.5 kg/m^2 <6.68 kg/m^2	<7.0 kg/m^2 <8.31 kg/m^2	<15Kg <20 Kg	<20Kg <30 Kg	≤0.8m/s <0.8 m/s	≤0.8m/s <0.8 m/s
(Santos et al., 2017)	Other	DXA	Height	<5.57kg/m^2	<7.59kg/m^2				
(Schaap et al., 2018)	EWGSOP FNIH	DXA	Height BMI	<5.45 kg/m^2 <15.02 kg	<7.26 kg/m^2 <19.75 kg	<20 kg <16 kg	<30 kg <26 kg	0.8 m/s ≤0.8 m/s	0.8 m/s ≤0.8 m/s
(Scott et al., 2016a)	Other	DXA	Residual	≤ 0.92	≤1.09	<47.5	≤112 kg		
(Scott et al., 2019)	EWGSOP2	DXA	Height	<6kg/m^2	<7.0 kg/m^2	<16 kg	<27 kg		
(Senior et al., 2015)	EWGSOP	BIA	Height	<6.42 kg/m^2	< 8.87 kg/m^2	<20 kg	<30 kg	≤0.8 m/s	≤0.8 m/s

(Sheng et al., 2019)	EWGSOP	DXA	Height	5.5 kg/m^2	7.26 kg/m^2	<20 kg	<30 kg	<8 m/s	<8 m/s
(Sherk et al., 2009)	MM	DXA	Height	<5.45 kg/m^2	-	-	-	-	-
(Silva et al., 2013)	MM	DXA	Height	<5.45 kg/m^2	-	-	-	-	-
(Silva Neto et al., 2016)	EWGSOP MM	DXA	Height Height	<5.45 kg/m^2 <5.45 kg/m^2	<7.26 kg/m^2 <7.26 kg/m^2	<20 kg -	<30 kg -	<0.8 m/s -	<0.8 m/s -
(Singh et al., 2014)	MM	DXA	Height	<5.45 kg/m^2	<7.26 kg/m^2	-	-	-	-
(Singhal et al., 2019)	AWGS	DXA	Height	<5.4 kg/m^2	<7.0 kg/m^2	<18. kg	<26 kg	<0.8 m/s	<0.8 m/s
(Sjöblom et al., 2013)	Other	DXA	Height	<6.3kg/m^2	-	Lowest quartile		Lowest quartile	
(Souza et al., 2017)	EWGSOP FNIH	DXA	Height BMI	<0.512	<0.789	<16 kg	<26 kg	<0.8 m/s	<0.8 m/s
(Soysal et al., 2019)	EWGSOP	BIA	Height	-	<8.87 kg/m^2	-	<30 kg	-	<0.8m/s
(Spira et al., 2016)	MM	DXA	Height	<5.5 kg/m^2	<7.26 kg/m^2	-	-	-	-
(Steffl et al., 2016)	EWGSOP	BIA	Height	<6.75 kg/m^2	<10.75 kg/m^2	<20 kg	<30kg	<0.8 m/s	0.8 m/s
(Stoever et al., 2017)	EWGSOP	BIA	Weight	-	<37%	-	32 -30 kg	<1 m/s	<1 m/s
(Su et al., 2019)	EWGSOP2	BIA	Height	<6kg/m^2	<7 kg/m^2	<16 kg	<27 kg	-	-
(Sugie et al., 2017)	MM	DXA	Height	<5.4 kg/m^2	<7 kg/m^2	-	-	-	-
(Sugimoto et al., 2019)	AWGS	BIA	Height	<5.7 kg/m^2	<7 kg/m^2	<18 kg	<26 kg	<0.8 m/s	<0.8 m/s
(Suzuki et al., 2018)	AWGS	BIA	Height	<5.7 kg/m^2	-	<18 kg	-	<0.8m/s	-
(Tabibi et al., 2018)	Other	BIA	Height	<6.76 kg/m^2	<10.76 kg/m^2	<18 kg	<26 kg	<0.8 m/s	<0.8 m/s
(Tanaka et al., 2018)	AWGS	BIA	Height	<5.7 kg/m^2	<7.0 kg/m^2	<18 kg	<26 kg	<0.8 m/s	<0.8 m/s
(Tang et al., 2018)	FNIH	DXA	BMI	<0.512	<0.789	<16 kg	<26 kg	<1 m/s	<1 m/s
(Tanimoto et al., 2012)	EWGSOP	BIA	Height	<5.8 kg/m^2	<7.0 kg/m^2	19.3 kg	30.0 kg	<1.19m/s	<1.27 m/s

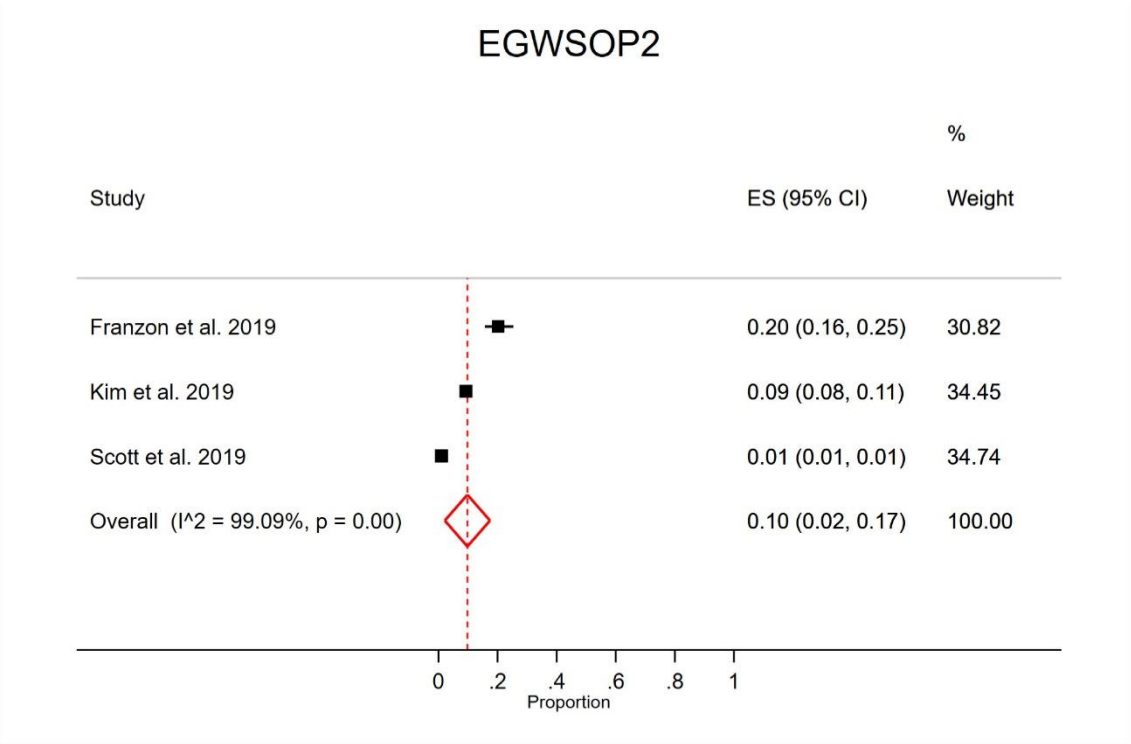
(Tasar et al., 2015)	EWGSOP	BIA	Body Mass	<20th percentile	<20th percentile	<20 kg	<30 kg	<0.8 m/s	<0.8 m/s
(Tay et al., 2015)	AWGS	DXA	Height	<5.7 kg/m^2	<7.0 kg/m^2	<18 kg	<26 kg	<0.8 m/s	<0.8 m/s
(Tessier et al., 2019)	FNIH	DXA	BMI	<0.512	<0.789	<16 kg	<26 kg	-	-
(Tichet et al., 2008)	MM	BIA	Height Weight	<6.2 kg/m^2 <26.6%	<8.6 kg/m^2 <34.4%	-	-	-	-
(Trajanoska et al., 2018)	EWGSOP	DXA	Height	<5.67 kg/m^2	<7.25 kg/m^2	by bmi	by bmi	By height	By height
(Tramontano et al., 2017)	IWGS	BIA	Height	<5.67 kg/m^2	<7.23 kg/m^2	-	-	<1 m/s	<1 m/s
(Tuzun et al., 2018)	MM	BIA	Height Body Mass BMI	<5.76 kg/m^2 <27.6% <0.512	<8.51 kg/m^2 <37% <0.789	-	-	-	-
(Tüzün et al., 2019)	MM	BIA	Height BMI Muscle mass Weight	<5.45 kg/m^2 <0.512 <6.75 <27.6% ≤ 5.67 kg/m^2	<7.26 kg/m^2 <0.789 <10.75 <37.0% ≤7.23 kg/m^2	- - - - -	- - - - -	- - - - -	- - - - -
(Urzi et al., 2017)	EWGSOP	BIA	Height	6.42 kg/m^2	<8.87 kg/m^2	<20 kg	<30 kg	<0.8 m/s	<0.8 m/s
(van de Bool et al., 2015)	MM	DXA	Height	≤ 5.67 kg/m^2	≤7.23 kg/m^2	-	-	-	-
(Velazquez-Alva et al., 2017)	EWGSOP	DXA	Height	<5.5 kg/m^2	-	<20 kg	-	<0.8 m/s	-
(Vermeiren et al., 2019)	MM	DXA BIA BIA BIA BIA DXA BIA BIA BIA BIA DXA BIA BIA BIA	Baumgartne Kyle Sergi Scafoglieri Butierfly Delmonico Kyle Sergi Scafoglieri Butierfly Newman Kyle Sergi Scafoglieri	<5.5 kg/m^2 <5.5 kg/m^2 <5.5 kg/m^2 <5.5 kg/m^2 <5.5 kg/m^2 <5.5 kg/m^2 <5.67 kg/m^2 <5.67 kg/m^2	≤7.26 kg/m^2 ≤7.23 kg/m^2 ≤7.23 kg/m^2 ≤7.23 kg/m^2 ≤7.23 kg/m^2 <7.25 kg/m^2 <7.25 kg/m^2 <7.25 kg/m^2 <7.25 kg/m^2 <7.25 kg/m^2 <7.23 kg/m^2 <7.23 kg/m^2 <7.23 kg/m^2 <7.23 kg/m^2	- - - - - - - - - - - - - -	- - - - - - - - - - - - - -	- - - - - - - - - - - - - -	- - - - - - - - - - - - - -

		BIA	Butierfly	<5.67 kg/m^2 <5.67 kg/m^2 <5.67 kg/m^2 <5.67 kg/m^2 <5.67 kg/m^2 <5.67 kg/m^2 <5.67 kg/m^2 <5.67 kg/m^2	<7.23 kg/m^2	- -	- -	- -	- -
(Walsh et al., 2006)	MM	DXA	Height	<5.45 kg/m^2	-	-	-	-	-
(Wang et al., 2019)	MM	BIA	Height	<5.7 kg/m^2	<7.0 kg/m^2	-	-	-	-
(Wang et al., 2018)	AWGS	DXA	Height	5.4 kg/m^2	7.0 kg/m^2	18 kg	26 kg	0.8 m/s.	0.8 m/s.
(Wang et al., 2016)	AWGS	BIA	Height	5.7 kg/m^2	7.0 kg/m^2	< 18 kg	< 26 kg	< 0.8 m/s	< 0.8 m/s
(Wen et al., 2015)	EWGSOP IWGS AWGS MM MM	DXA	Height Height Height Height Body Mass	<4.23 kg ≤ 5.67 kg/m^2 <5.4 kg/m^2 <5.18 kg/m^2 <60.4	<5.85 kg/m^2 ≤7.23 kg/m^2 <7.0 kg/m^2 <6.91 kg/m^2 <69	<20 kg - <18 kg - -	<30 kg - <26 kg - -	≤0.8 m/s <1.0 m/s <0.8 m/s - -	≤0.8 m/s <1.0 m/s <0.8 m/s - -
(Westbury et al., 2018)	EWGSOP	DXA	Height	≤ 5.67 kg/m^2	≤ 7.23 kg/m^2	< 20 kg	< 30 kg	≤ 0.8 m/s	≤ 0.8 m/s
(Wiriya et al., 2019)	AWGS	BIA	Height	< 5.7 kg/m^2	< 7.0 kg/m^2	<18 kg	<26 kg	≤0.8	≤0.8
(Woo et al., 2015)	EWGSOP IWGS FNIH AWGS	DXA	Height Height BMI Height	<5.44 kg/m^2 ≤ 5.67 kg/m^2 <0.512 <5.4 kg/m^2	<6.52 kg/m^2 ≤7.23 kg/m^2 <0.789 <7.0 kg/m^2	<18 kg <16 kg <18 kg <18 kg	<26 kg <26 kg <26 kg <26 kg	≤0.8 <1.0 m/s <0.8 m/s ≤0.8 m/s	≤0.8 <1.0 m/s <0.8 m/s ≤0.8 m/s

(Wu et al., 2013)	MM	BIA	Height	<6.42 kg/m^2	<8.87 kg/m^2				
(Wu et al., 2014)	Other*	BIA	Height Height	5.28 kg/m^2 <5.70 kg/m^2	6.76 kg/m^2 <7.09 kg/m^2	<20 perc. <20 perc.	<20 perc. <20 perc.	<20 perc. <20 perc.	<20 perc. <20 perc.
(Xiao et al., 2018)	MM	BIA	Percentile	95% perc.	95% perc.	-	-	-	-
(Xu et al., 2018)	AWGS	BIA	Percentile	Lower than 20th perc.	Lower than 20th perc.	<18 kg	<26 kg	≤0.8	≤0.8
(Yadigar et al., 2016)	EWGSOP	BIA	Body Mass	<6.42 kg/m^2	<8.87 kg/m^2	<20 kg	<30 kg	>15 s	>15 s
(Yalcin et al., 2016)	EWGSOP	BIA	Height	<6.42 kg/m^2	<8.87 kg/m^2	<20 kg	<30 kg	<0.8 m/s	<0.8 m/s
(Yamada et al., 2019)	AWGS	BIA	Height	<5.7 kg/m^2	<7.0 kg/m^2	<18 kg	<26 kg	<0.8 m/s	<0.8 m/s
(Yamada et al., 2013)	EWGSOP	BIA	Height	<5.07 kg/m^2	<6.75 kg/m^2	<20 kg	<30 kg	<0.8 m/s	<0.8 m/s
(Yang et al., 2015)	MM	DXA	Height	<5.46 kg/m^2	<6.87 kg/m^2	-	-	-	-
(Yang et al., 2018)	AWGS	BIA	Height	<5.7 kg/m^2	<7.0 kg/m^2	<18 kg	<26 kg	<0.8 m/s	<0.8 m/s
(Yang et al., 2016)	MM	DXA	Height	<5.45 kg/m^2	<7.26 kg/m^2	-	-	-	-
(Yasemin et al., 2019)	EWGSOP	BIA	Body mass	<28%	<37%	<20 kg	<30 kg	-	-
(Yazar and Olgun Yazar, 2019)	EWGSOP	BIA	Width of neck	<8.89 kg/m^2	<10.5 kg/m^2	<20 kg	<30 kg	<0.8 m/s	<0.8 m/s
(Yoowannakul et al., 2018)	EWGSOP AWGS FNIH1 FNIH2	BIA	Height Height ALM BMI	<5.67 kg/m^2 <5.7 kg/m^2 <15.02 <0.512	<7.23 kg/m^2 <7.0 kg/m^2 <19.75 <0.789	<20 <18 kg <16 kg <16Kg	<30 kg <26 kg <26 kg <26Kg	- - - -	- - - -
Yoshida 2014(Yoshida et al., 2014)	EWGSOP	BIA	Height	<5.91 kg/m^2	<7.09 kg/m^2	18.2 kg	28.8 kg	<0.8 m/s	<0.8 m/s
(Yu et al., 2014b)	Other	DXA	Height Gender Regression	<2SD <20%gender spec <20% residual	<2SD <20%gender spec <20% residual	<20 kg <20 kg <20 kg	<30 kg <30 kg <30 kg		

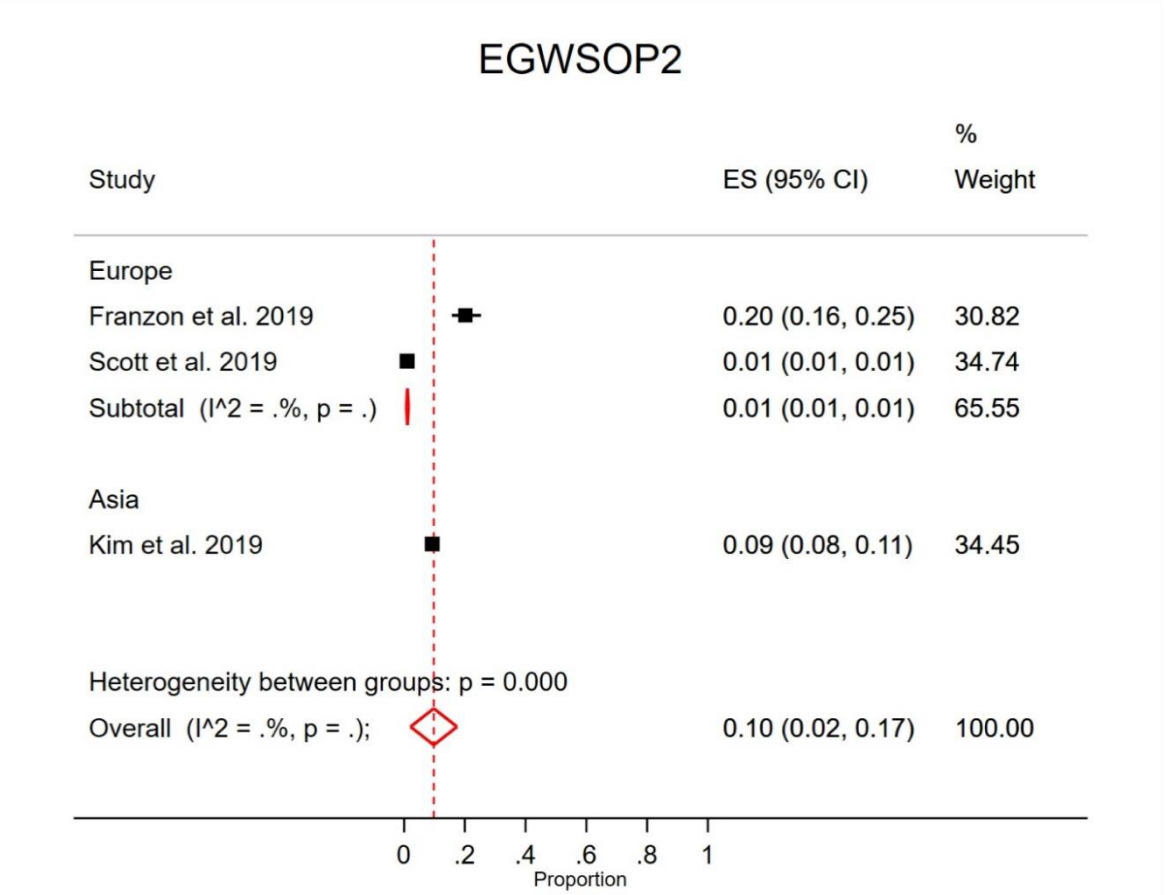
(Yuki et al., 2017)	AWGS	DXA	Height	<5.4 kg/m^2	<7.0 kg/m^2	<18 kg	<26 kg	<0.8 m/s	<0.8 m/s
(Zambrano et al., 2020)	Other	CT scan	Height	<39 cm/m^2	<50 cm/m^2	<20 kg	<30 kg		
(Zeng et al., 2018)	EWGSOP IWGS FNIH AWGS	BIA	Height Height BMI Height	<4.97 kg/m^2 ≤ 5.67 kg/m^2 <0.512 <5.7 kg/m^2	<6.12 kg/m^2 ≤7.23 kg/m^2 <0.789 <7.0 kg/m^2	<20 kg - <16Kg <18 kg	<30 kg - <26Kg <26 kg	<0.8 m/s 1 m/s <0.8 m/s <0.8 m/s	0.8 m/s 1m/s <0.8 m/s <0.8 m/s
(Zengin et al., 2018)	EWGSOP FNIH	DXA	Height BMI	<5.45 kg/m^2 <15.02 kg	<7.25 kg/m^2 <19.75kg	<20 kg <16 kg	<30 kg <26 kg	-	-
(Zhang et al., 2019)	AWGS	BIA	Height	<5.7 kg/m^2	<7.0 kg/m^2	<18 kg	<26 kg	<0.8 m/s	<0.8 m/2
(Zoico et al., 2004)	MM	DXA	Height Weight	<5.6 kg/m^2 <26.7%	- -	- -	- -	- -	- -

*Modified version of the classification.



2.1.6 Supplementary Figure 1a. Prevalence of sarcopenia using the EWGSOP2.

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence. EWGSOP2: European Working Group on Sarcopenia in Older People 2.

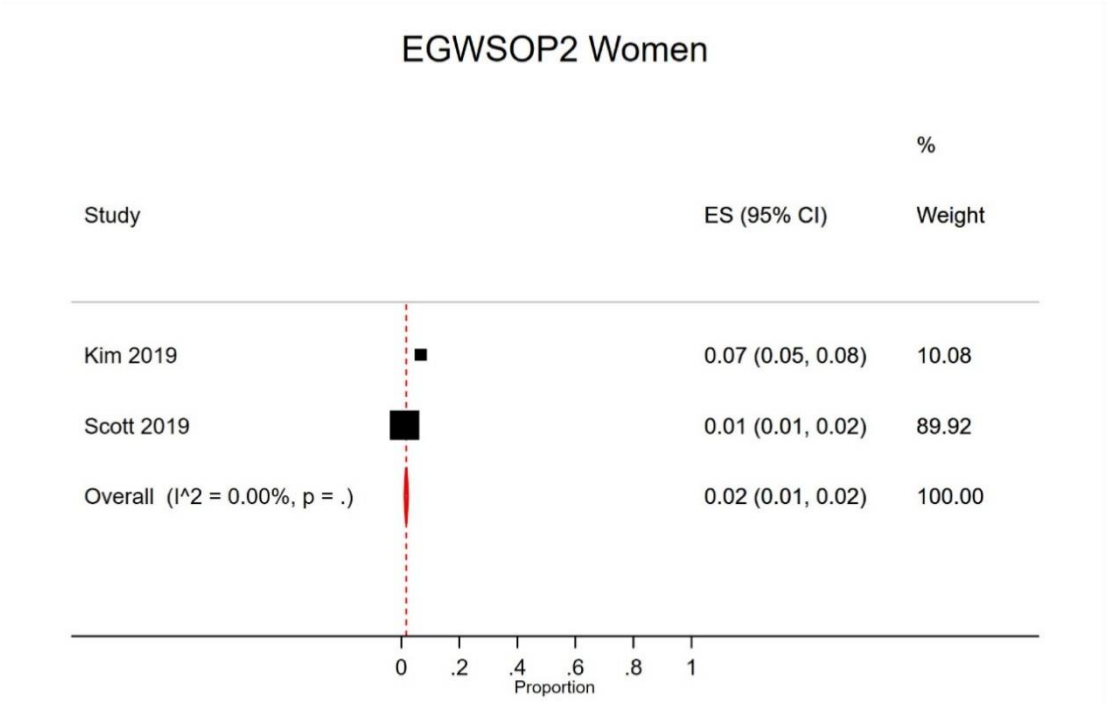


2.1.7 Supplementary Figure 1b. Prevalence of sarcopenia using the EWGSOP2 by region of origin.

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence. EWGSOP2: European Working Group on Sarcopenia in Older People 2.

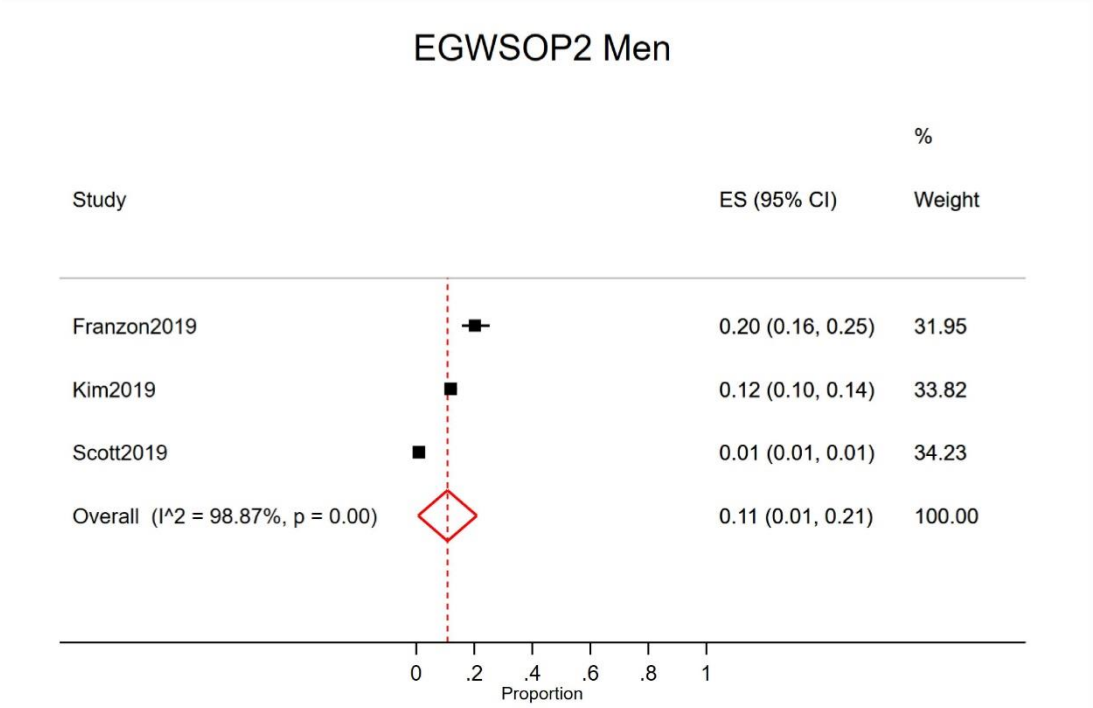
2.1.8 *Supplementary Figure 1c. Prevalence of sarcopenia using the EWGSOP2 by age categories.

*There was no data available for individuals younger than 60 years.



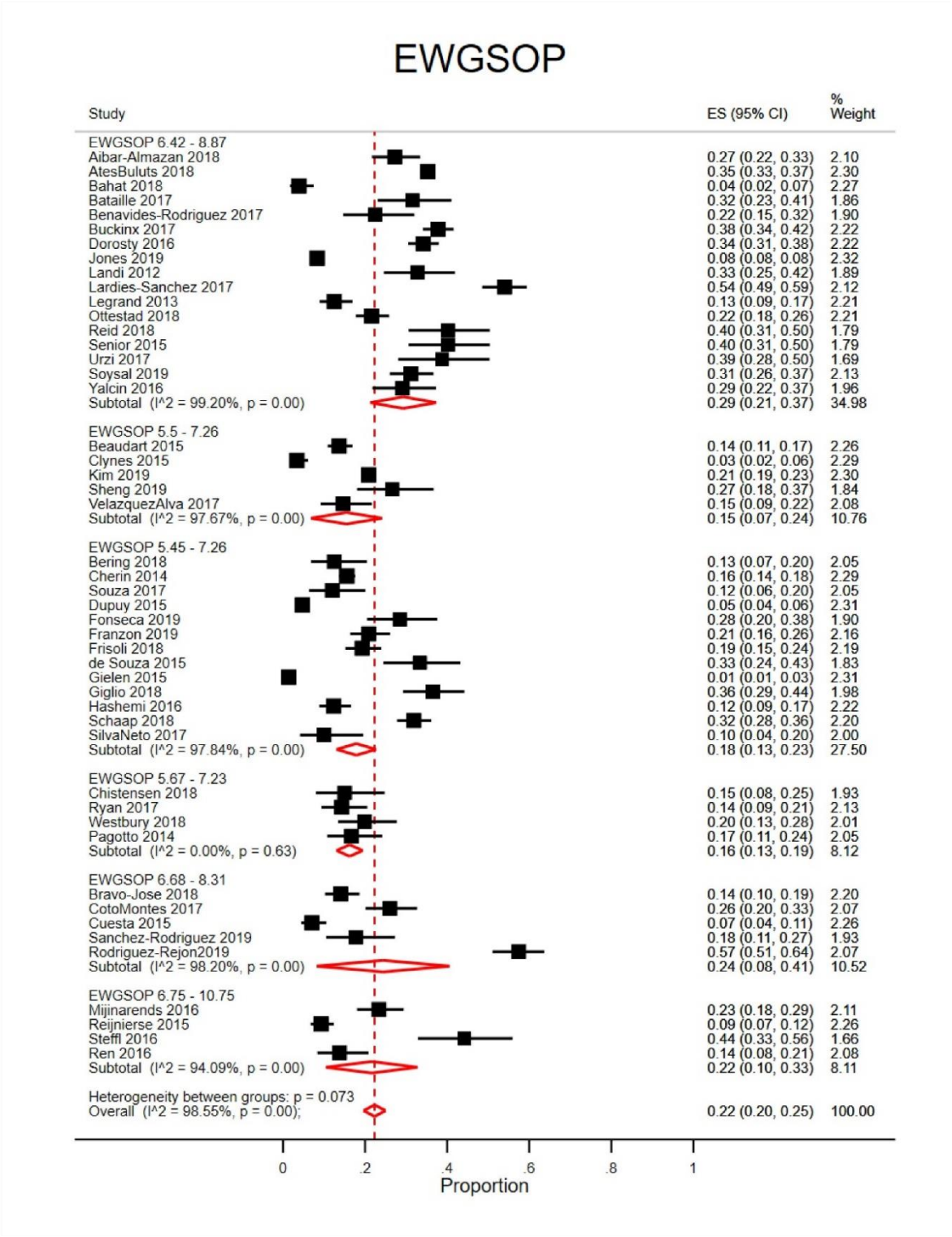
2.1.9 Supplementary Figure 1d. Prevalence of sarcopenia using the EWGSOP2 in women.

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence. EWGSOP2: European Working Group on Sarcopenia in Older People 2.



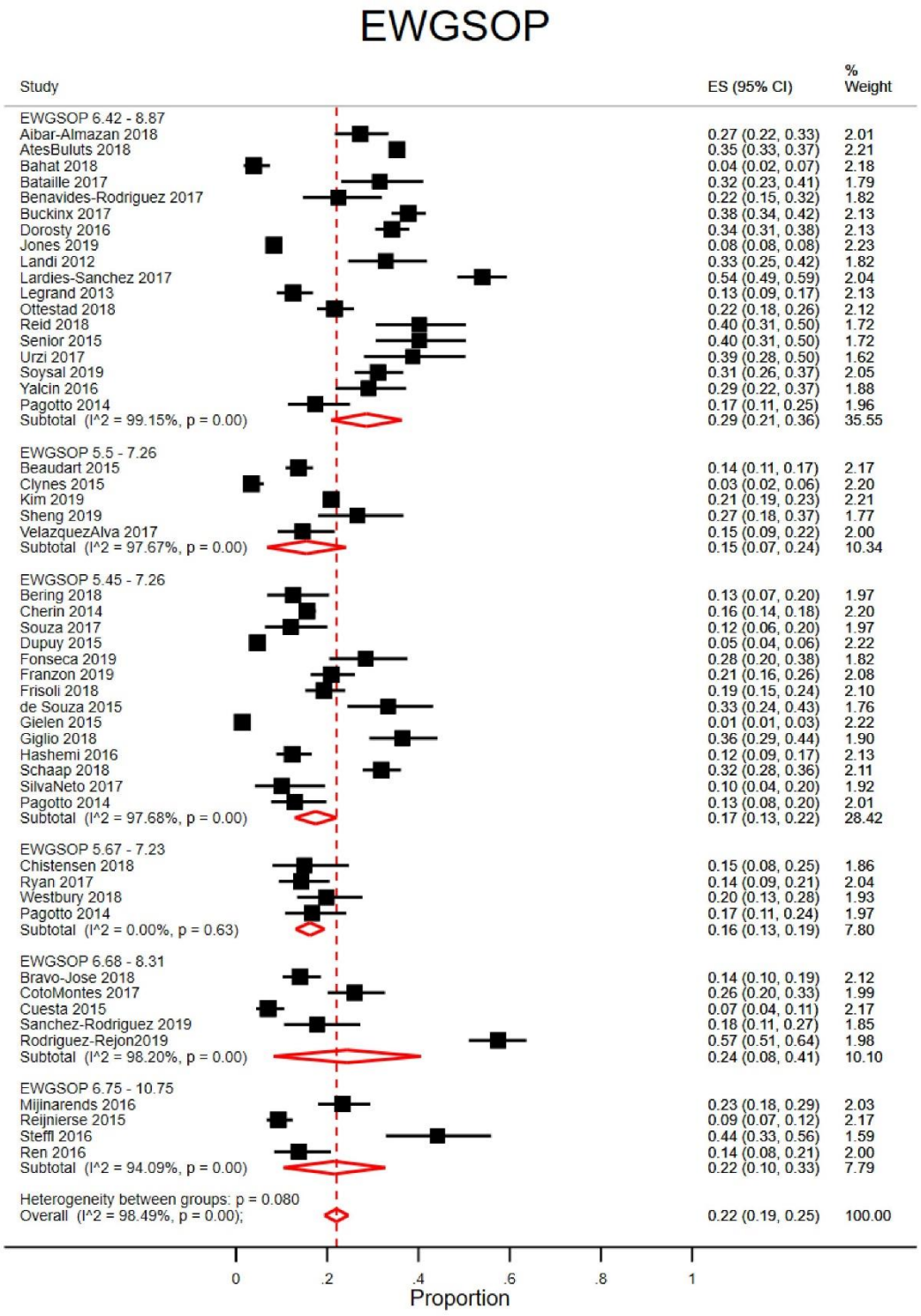
2.1.10 Supplementary Figure 1e. Prevalence of sarcopenia using the EWGSOP2 in men.

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence. EWGSOP2: European Working Group on Sarcopenia in Older People 2.



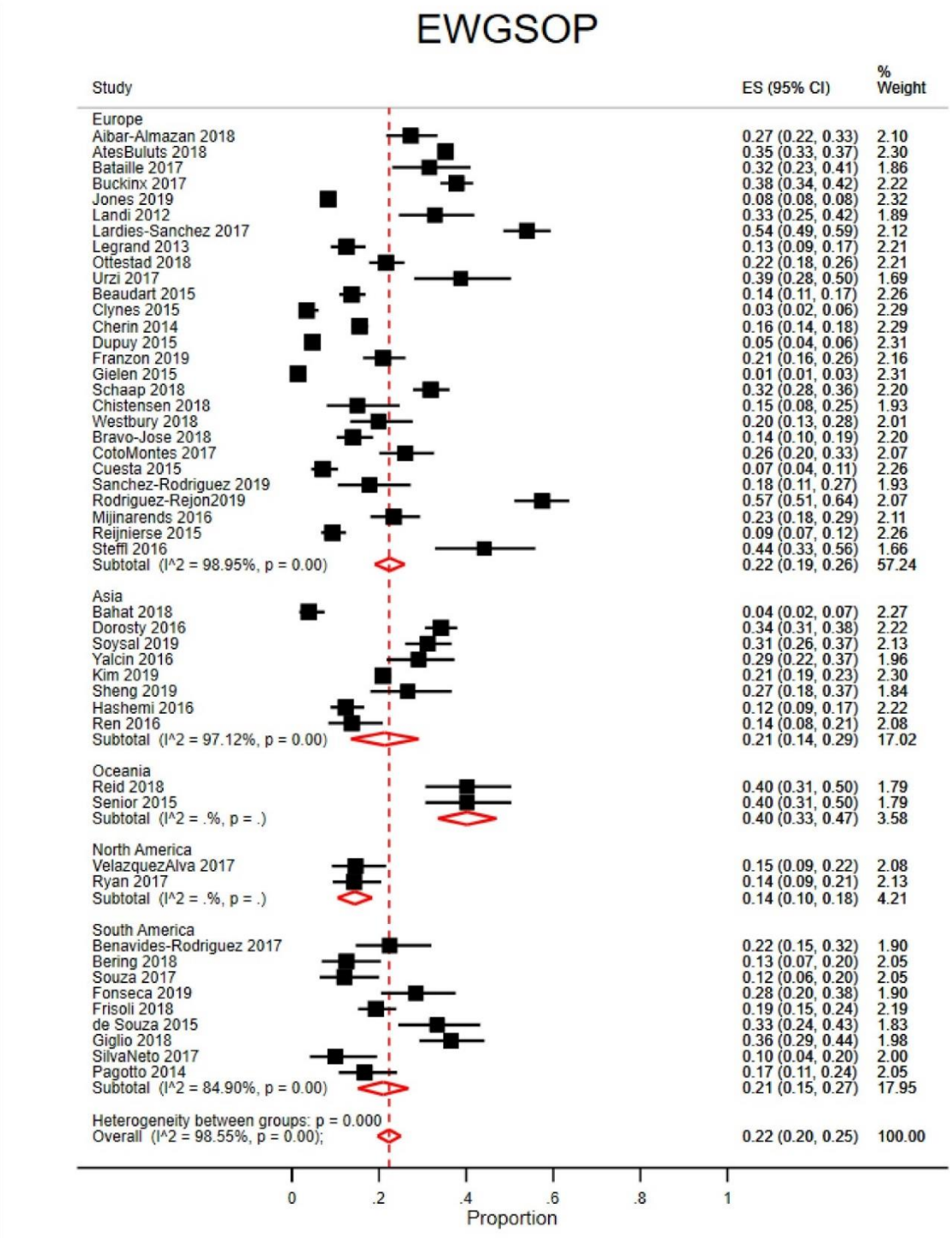
2.1.11 Supplementary Figure 2a.1. Prevalence of sarcopenia using the EWGSOP (excluding those who reported the prevalence more than once using different cut-off points).

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence. EWGSOP: European Working Group on Sarcopenia in Older People.



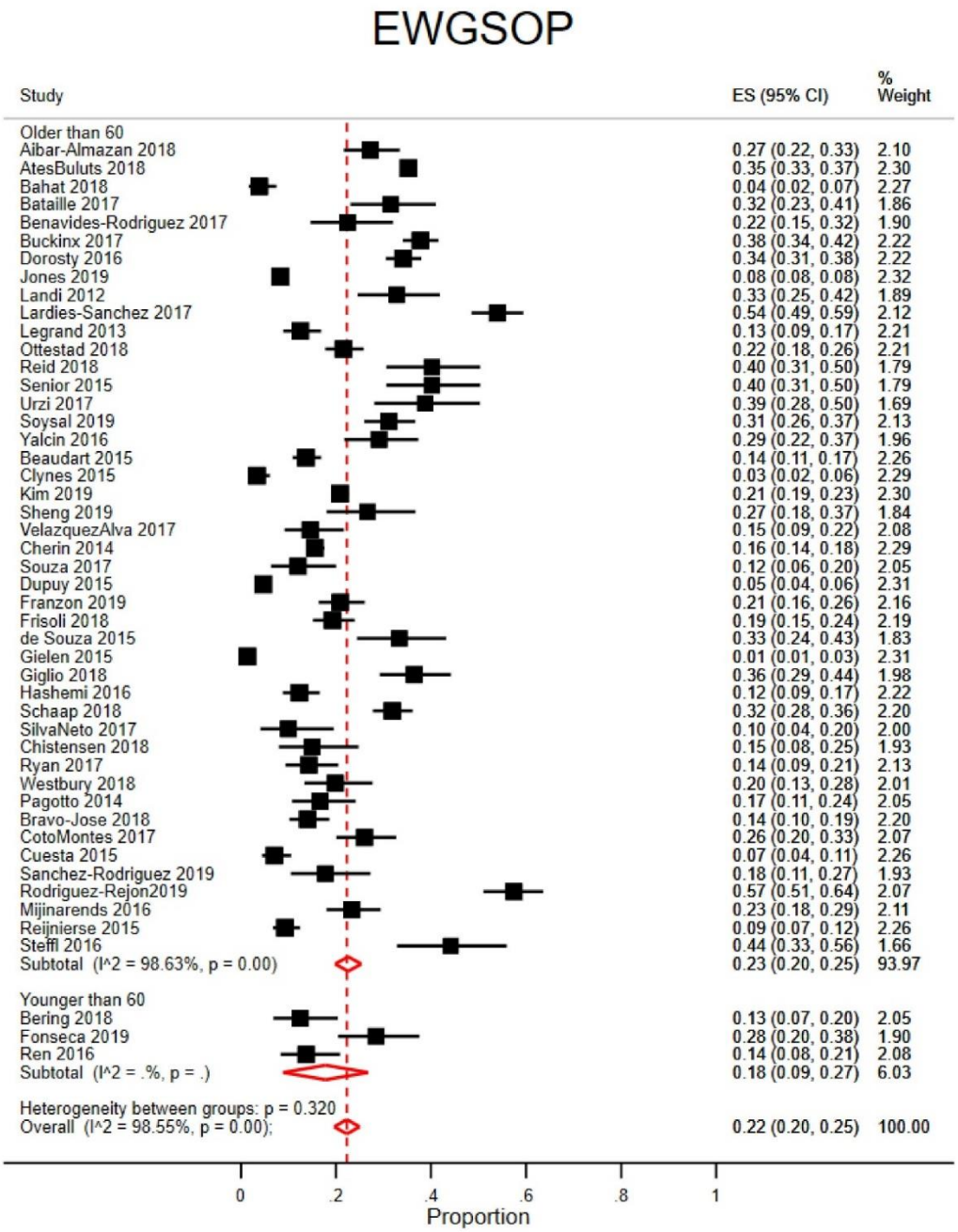
2.1.12 Supplementary Figure 2a.2. Prevalence of sarcopenia using the EWGSOP (all cut-off points).

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence. EWGSOP: European Working Group on Sarcopenia in Older People.



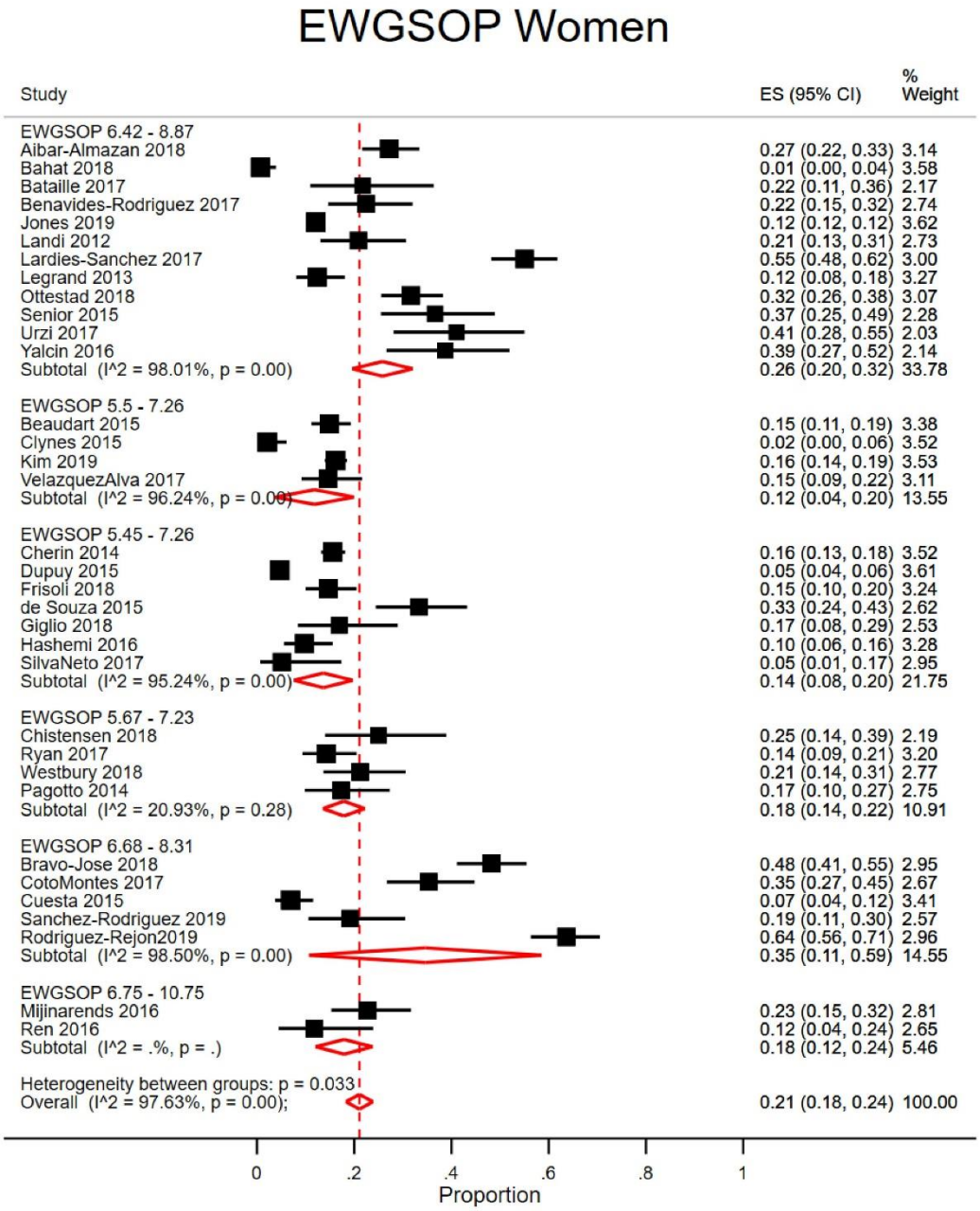
2.1.13 Supplementary Figure 2b. Prevalence of sarcopenia using the EWGSOP by region of origin (excluding those who reported the prevalence more than once using different cut-off points).

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence. EWGSOP: European Working Group on Sarcopenia in Older People.



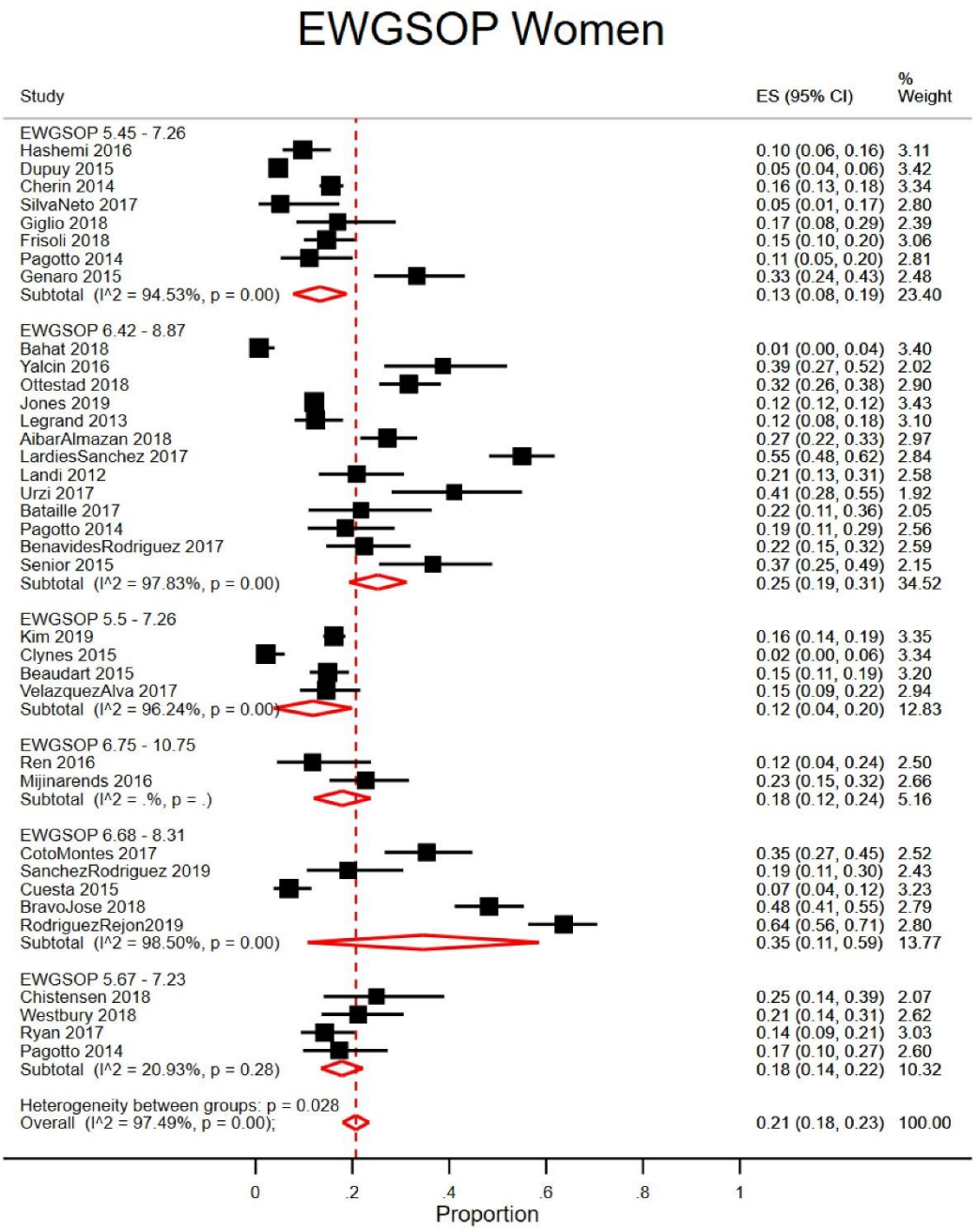
2.1.14 Supplementary Figure 2c. Prevalence of sarcopenia using the EWGSOP by age categories (excluding those who reported the prevalence more than once using different cut-off points).

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence. EWGSOP: European Working Group on Sarcopenia in Older People.



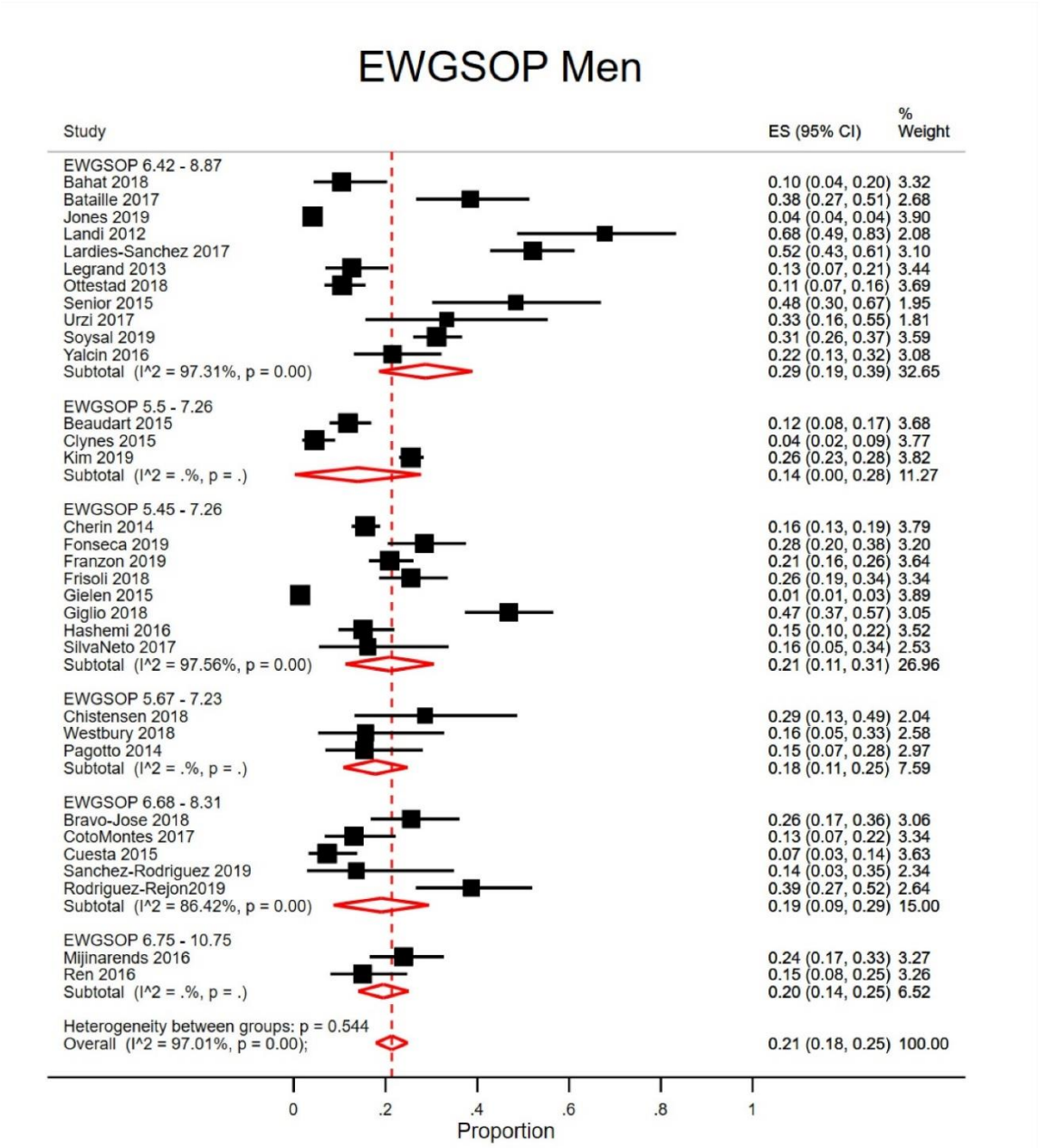
2.1.15 Supplementary Figure 2d.1. Prevalence of sarcopenia using the EWGSOP in women (excluding those who reported the prevalence more than once using different cut-off points).

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence. EWGSOP: European Working Group on Sarcopenia in Older People.



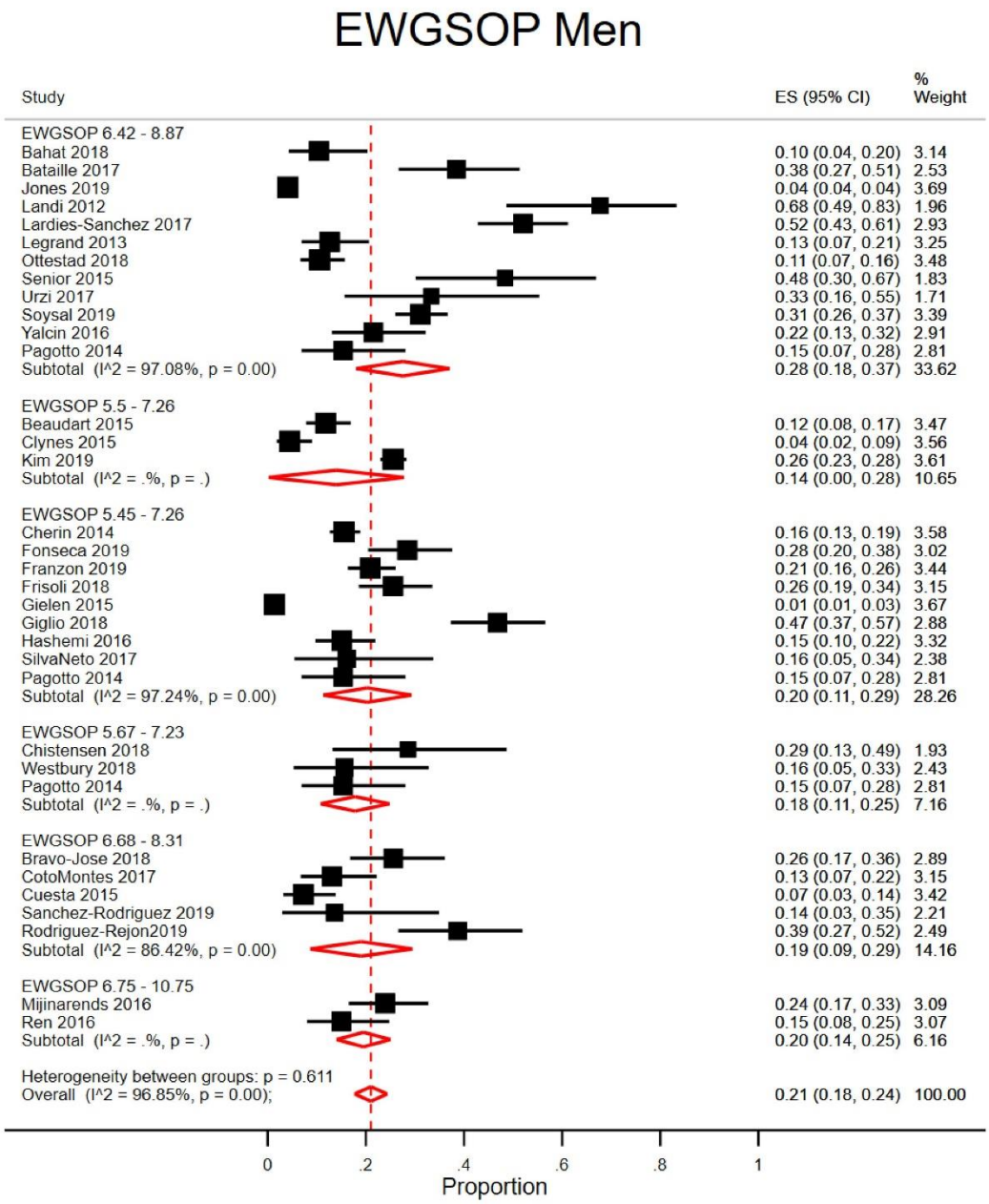
2.1.16 Supplementary Figure 2d.2. Prevalence of sarcopenia using the EWGSOP in women (all cut-off points).

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence. EWGSOP: European Working Group on Sarcopenia in Older People.



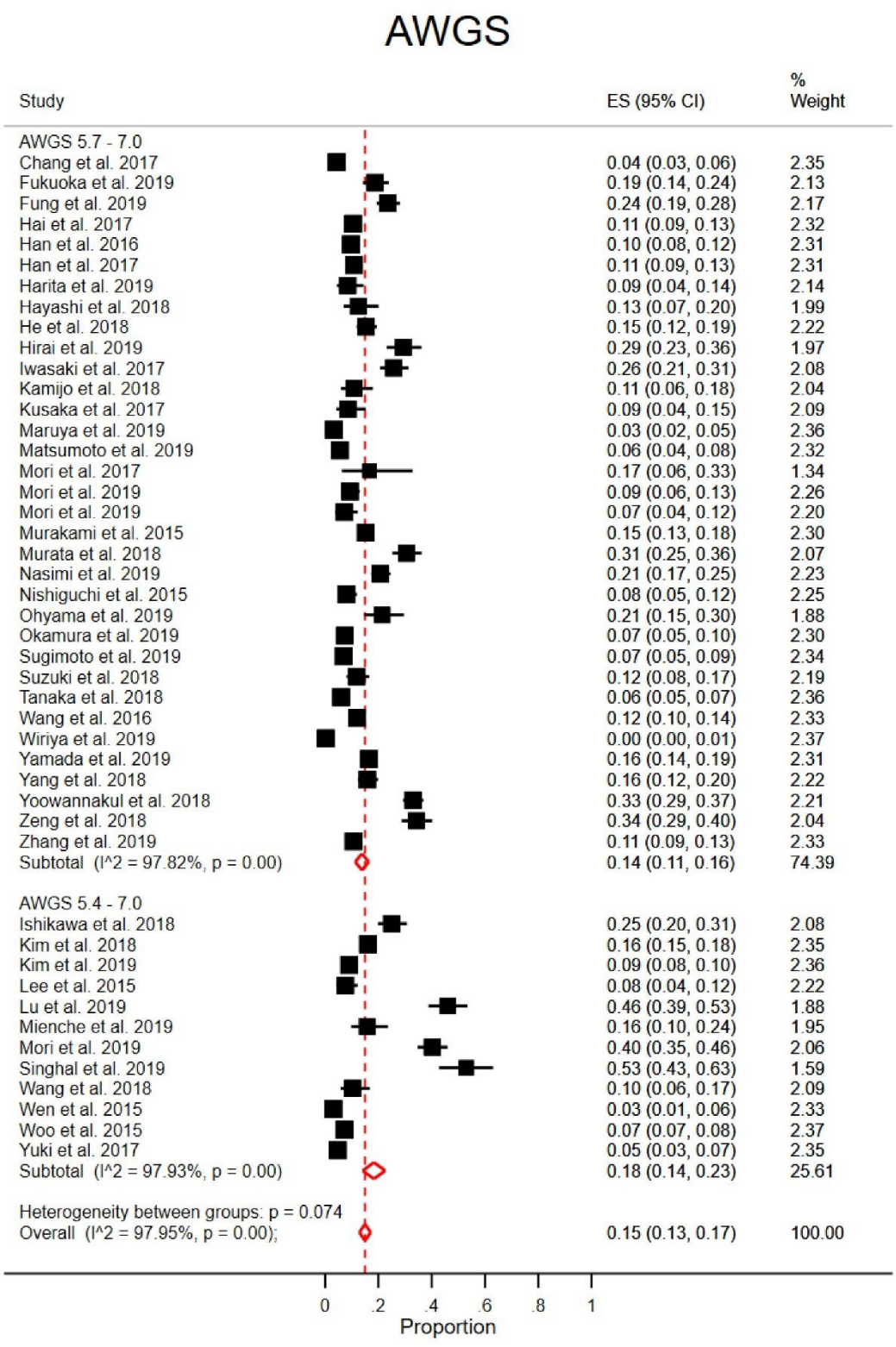
2.1.17 Supplementary Figure 2e.1. Prevalence of sarcopenia using the EWGSOP in men (excluding those who reported the prevalence more than once using different cut-off points).

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence. EWGSOP2: European Working Group on Sarcopenia in Older People.



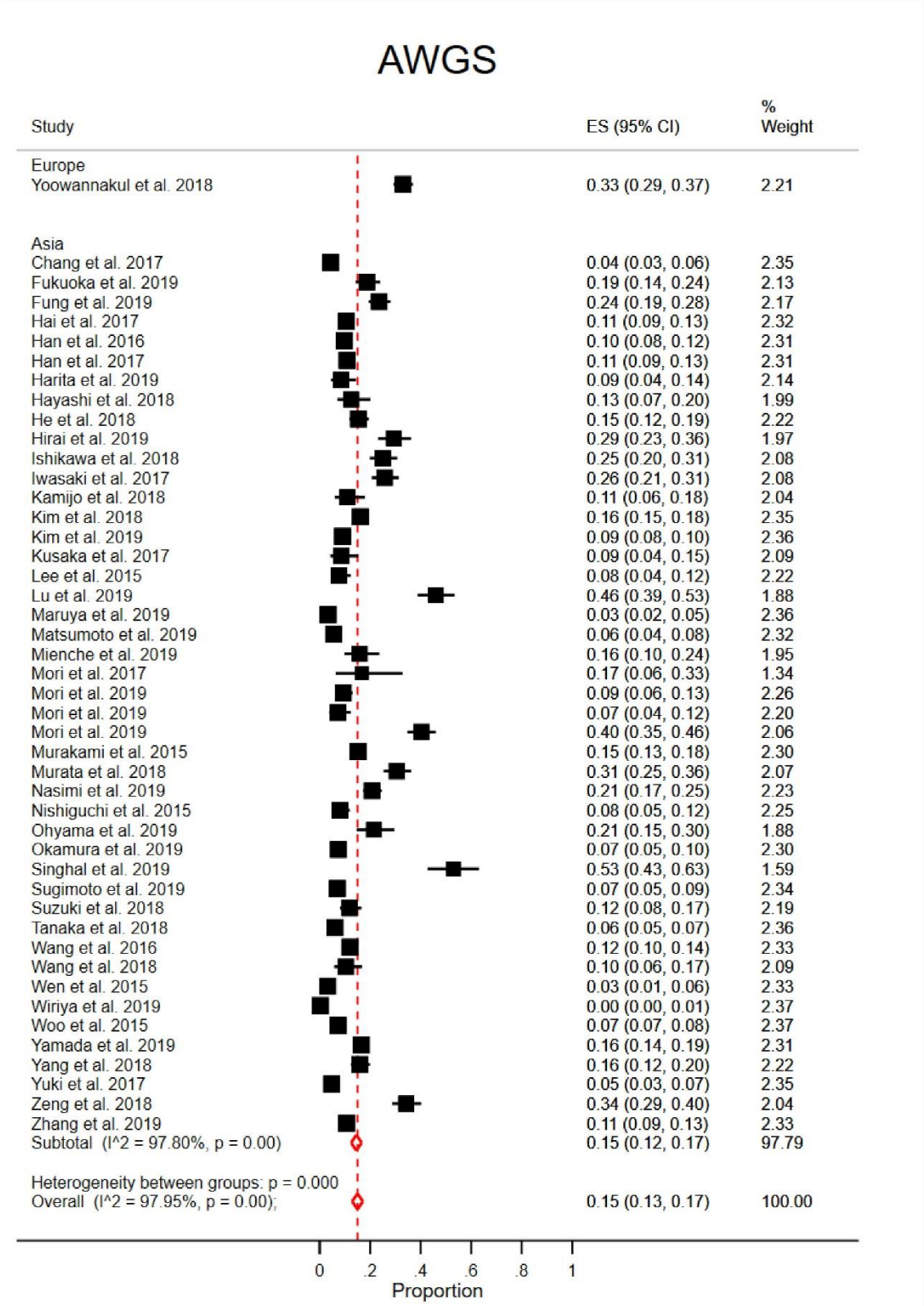
2.1.18 Supplementary Figure 2e.2. Prevalence of sarcopenia using the EWGSOP in men (all cut-off points).

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence. EWGSOP2: European Working Group on Sarcopenia in Older People.



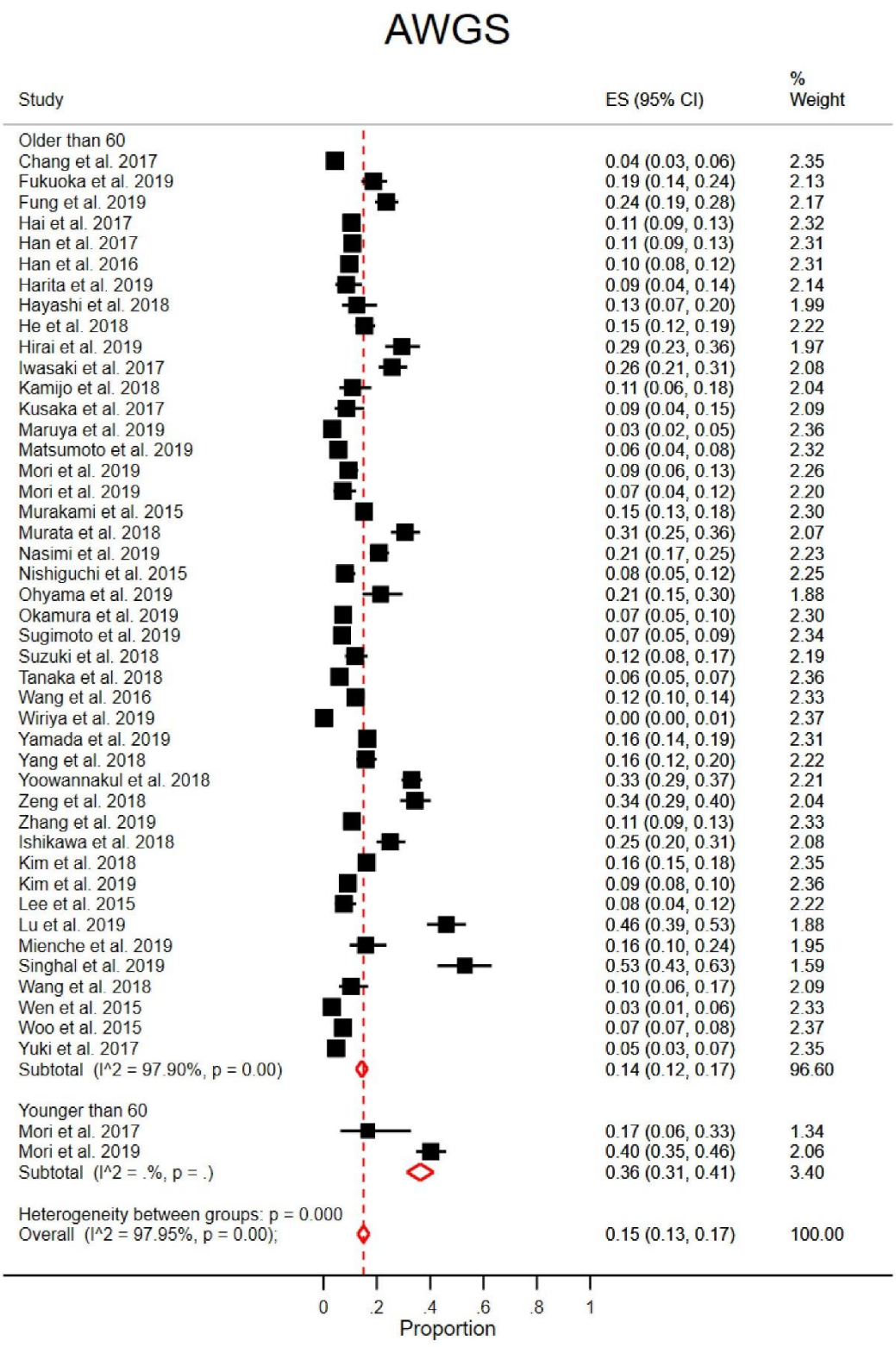
2.1.19 Supplementary Figure 3a. Prevalence of sarcopenia using the AWGS.

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence. AWGS: Asian Working Group for Sarcopenia. DXA: 5.4 kg/m^2 and 7 kg/m^2; BIA: 5.7 kg/m^2 and 7 kg/m^2.



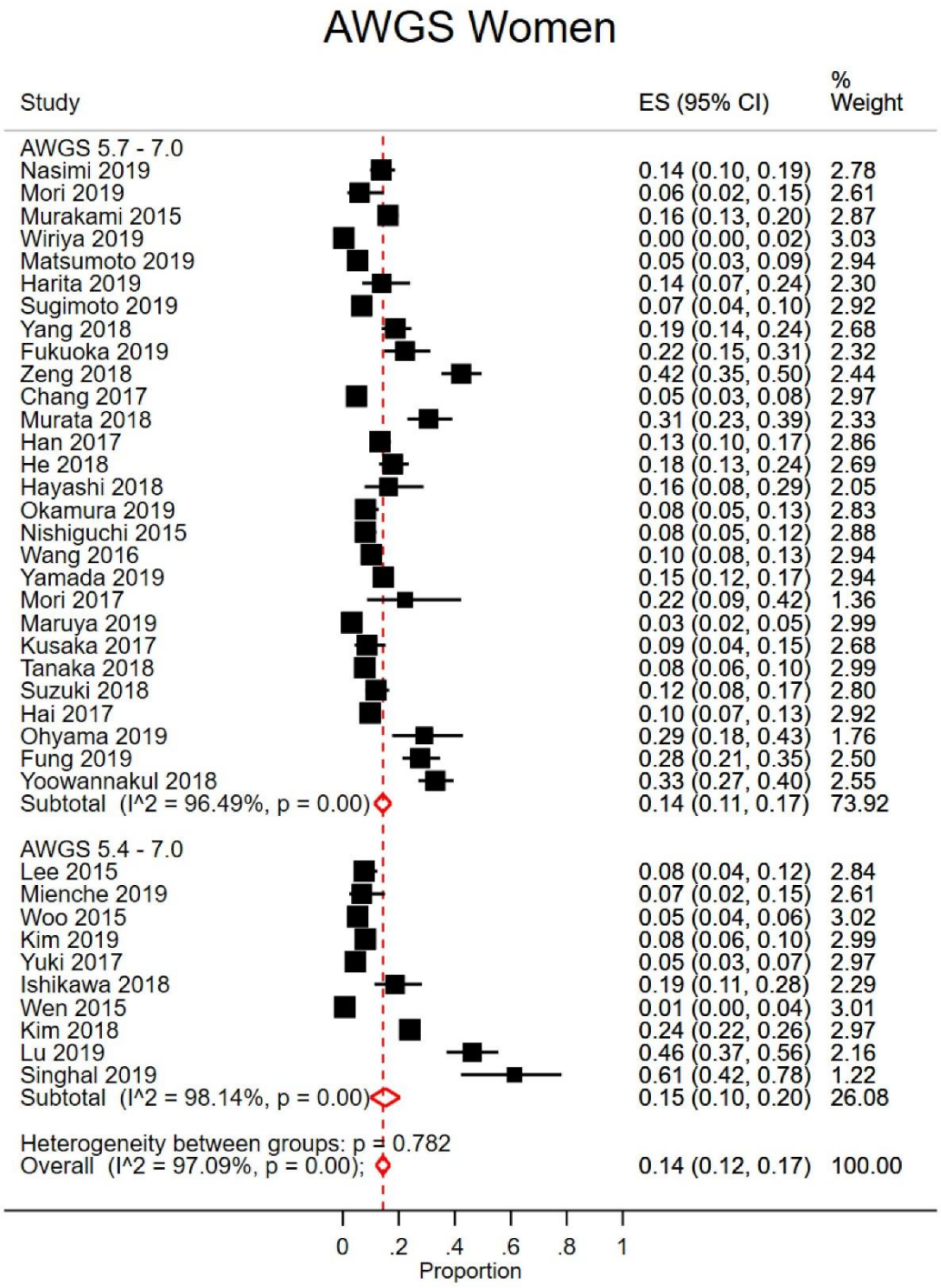
2.1.20 Supplementary Figure 3b. Prevalence of sarcopenia using the AWGS by region of origin.

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence. AWGS: Asian Working Group for Sarcopenia.



2.1.21 Supplementary Figure 3c. Prevalence of sarcopenia using the AWGS by age categories.

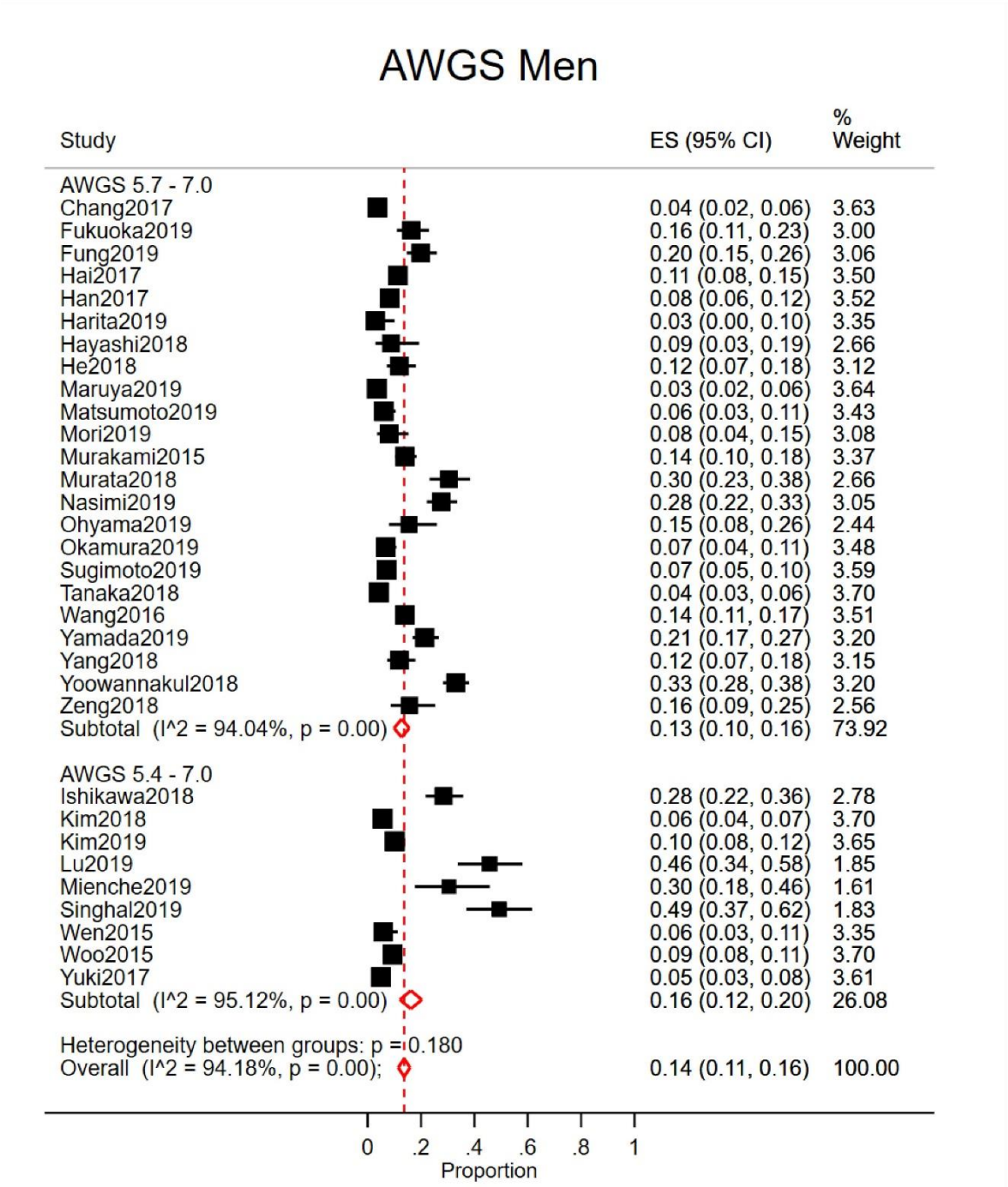
Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence. AWGS: Asian Working Group for Sarcopenia.



2.1.22 Supplementary Figure 3d. Prevalence of sarcopenia using the AWGS in women.

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence. AWGS: Asian Working Group for Sarcopenia.

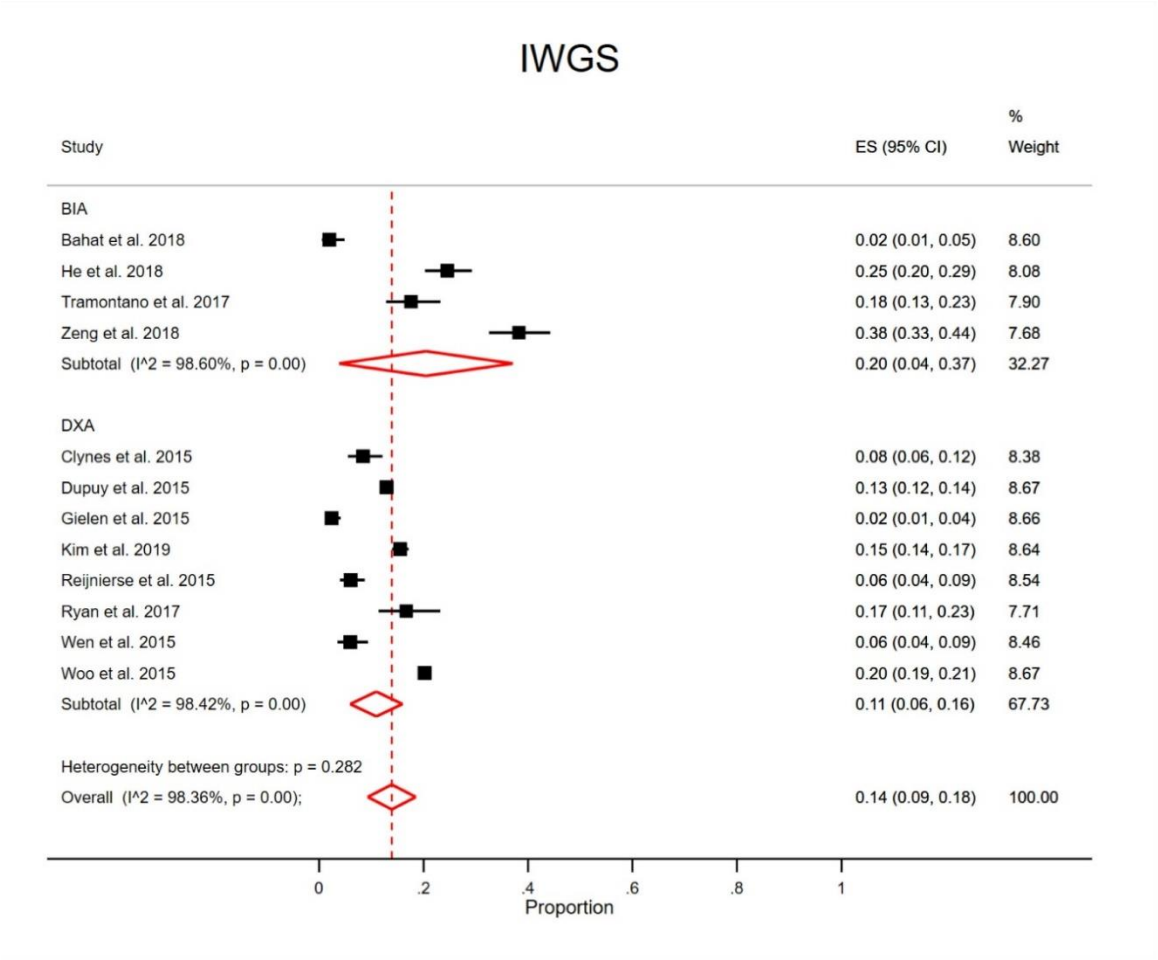
DXA: 5.4 kg/m^2 and 7 kg/m^2; BIA: 5.7 kg/m^2 and 7 kg/m^2.



2.1.23 Supplementary Figure 3e. Prevalence of sarcopenia using the AWGS in men.

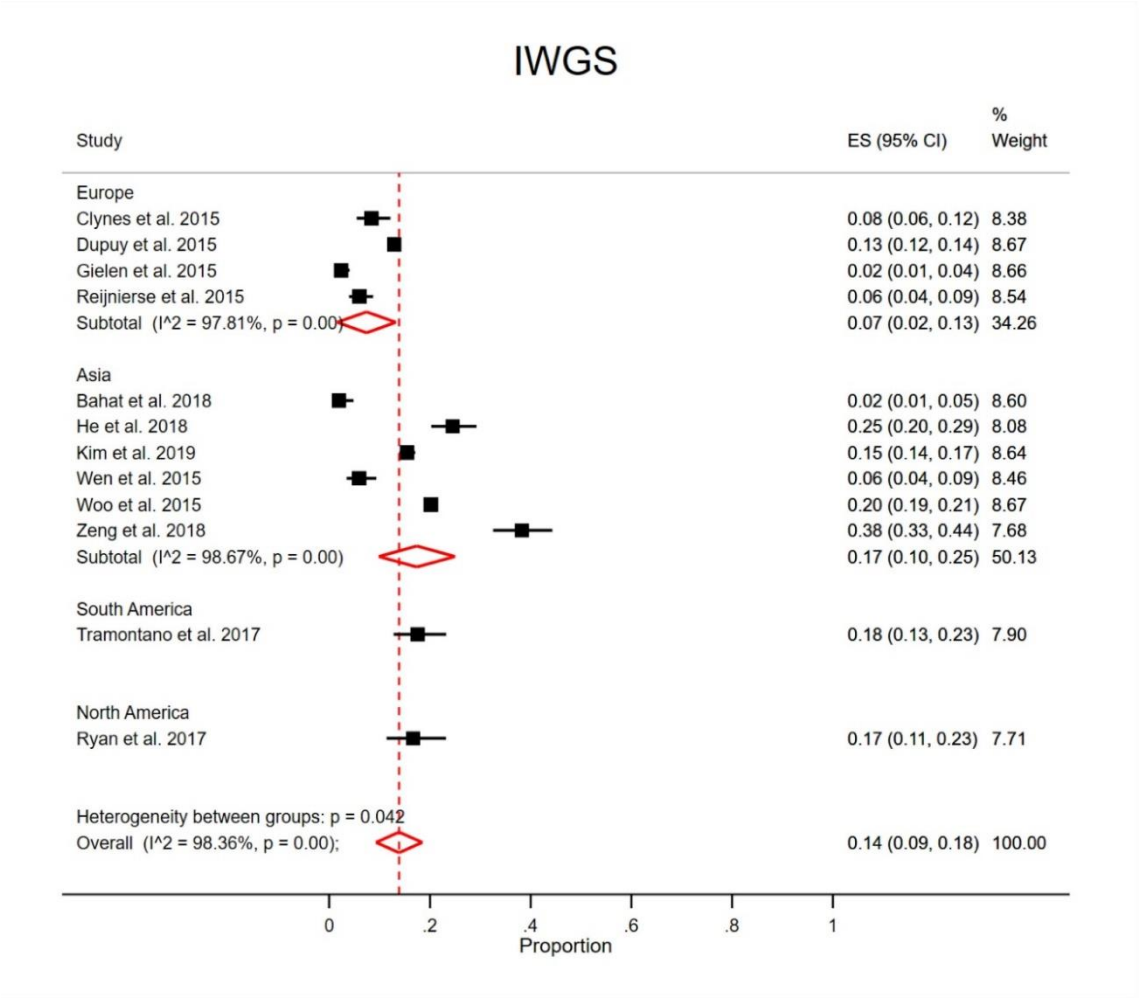
Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence. AWGS: Asian Working Group for Sarcopenia.

DXA: 5.4 kg/m^2 and 7 kg/m^2; BIA: 5.7 kg/m^2 and 7 kg/m^2.



2.1.24 Supplementary Figure 4a. Prevalence of sarcopenia using the IWGS.

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence. IWGS: International Working Group on Sarcopenia.

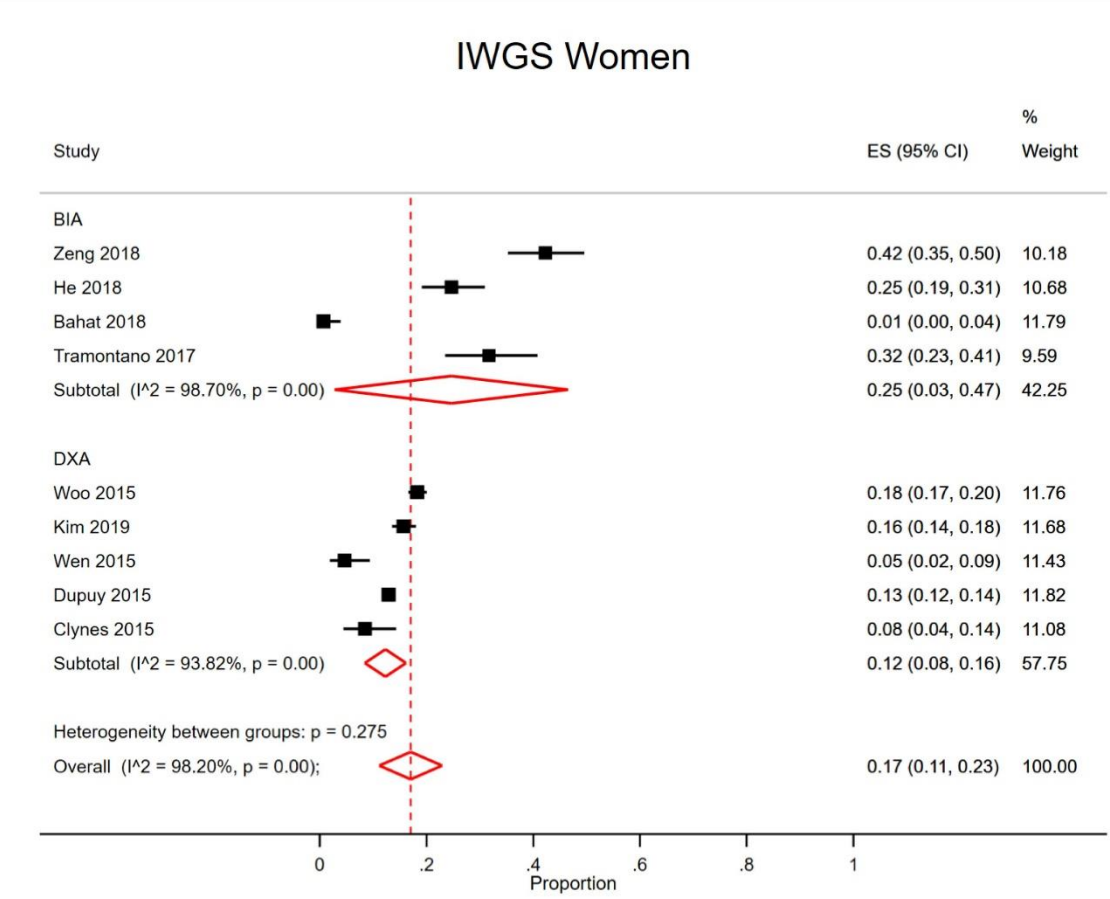


2.1.25 Supplementary Figure 4b. Prevalence of sarcopenia using the IWGS by region of origin.

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence. IWGS: International Working Group on Sarcopenia.

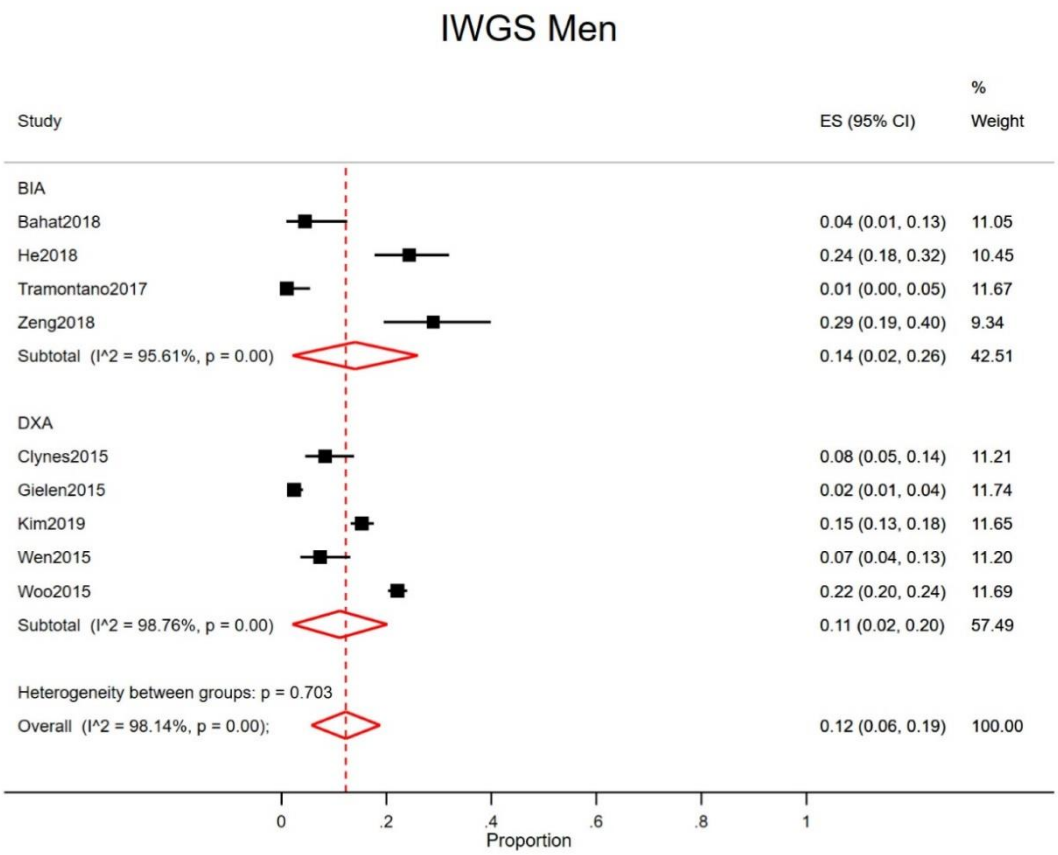
2.1.26 *Supplementary Figure 4c. Prevalence of sarcopenia using the IWGS by age categories.

*There was no data available for individuals younger than 60 years.



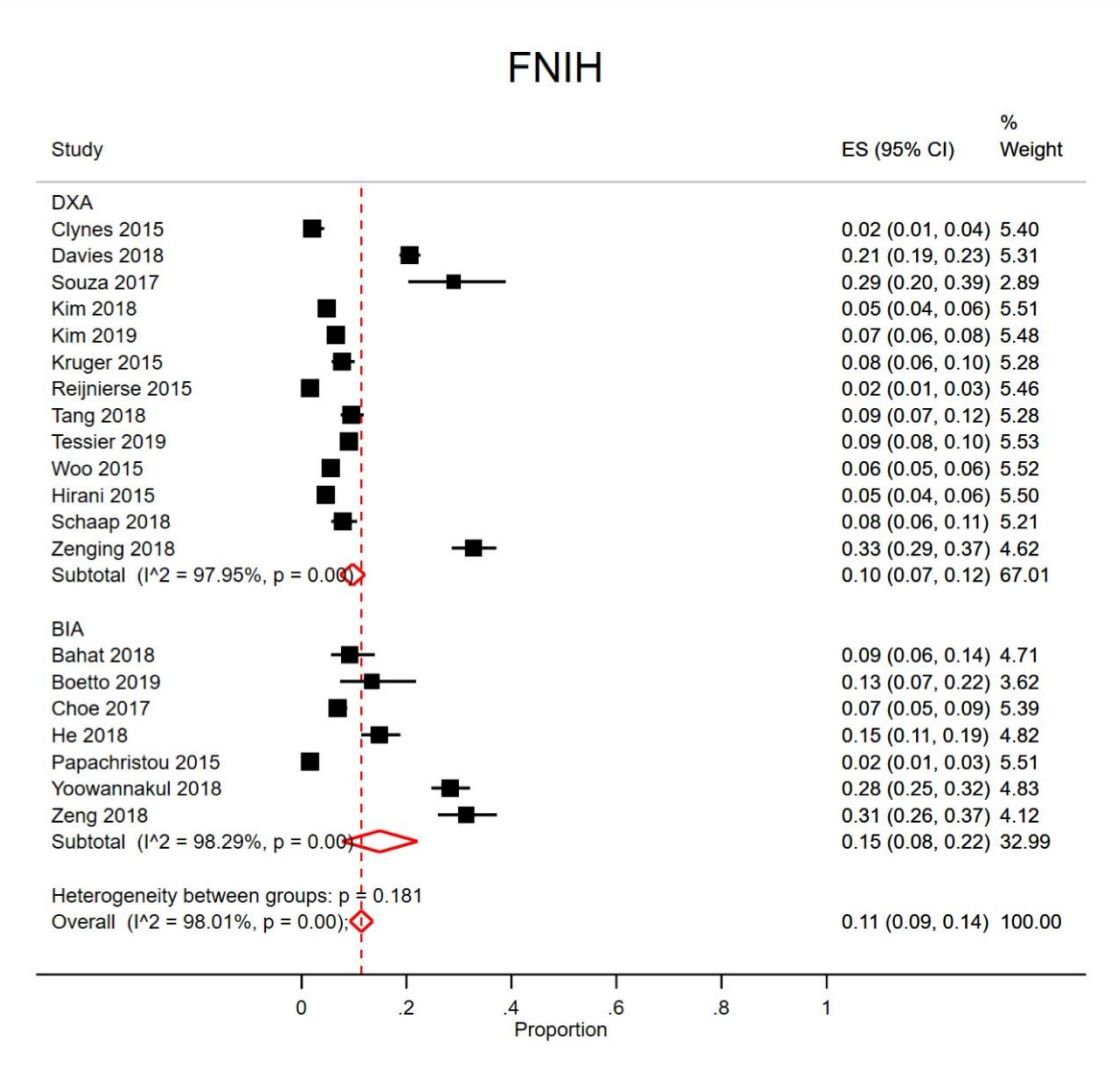
2.1.27 Supplementary Figure 4d. Prevalence of sarcopenia using the IWGS in women.

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence. IWGS: International Working Group on Sarcopenia.



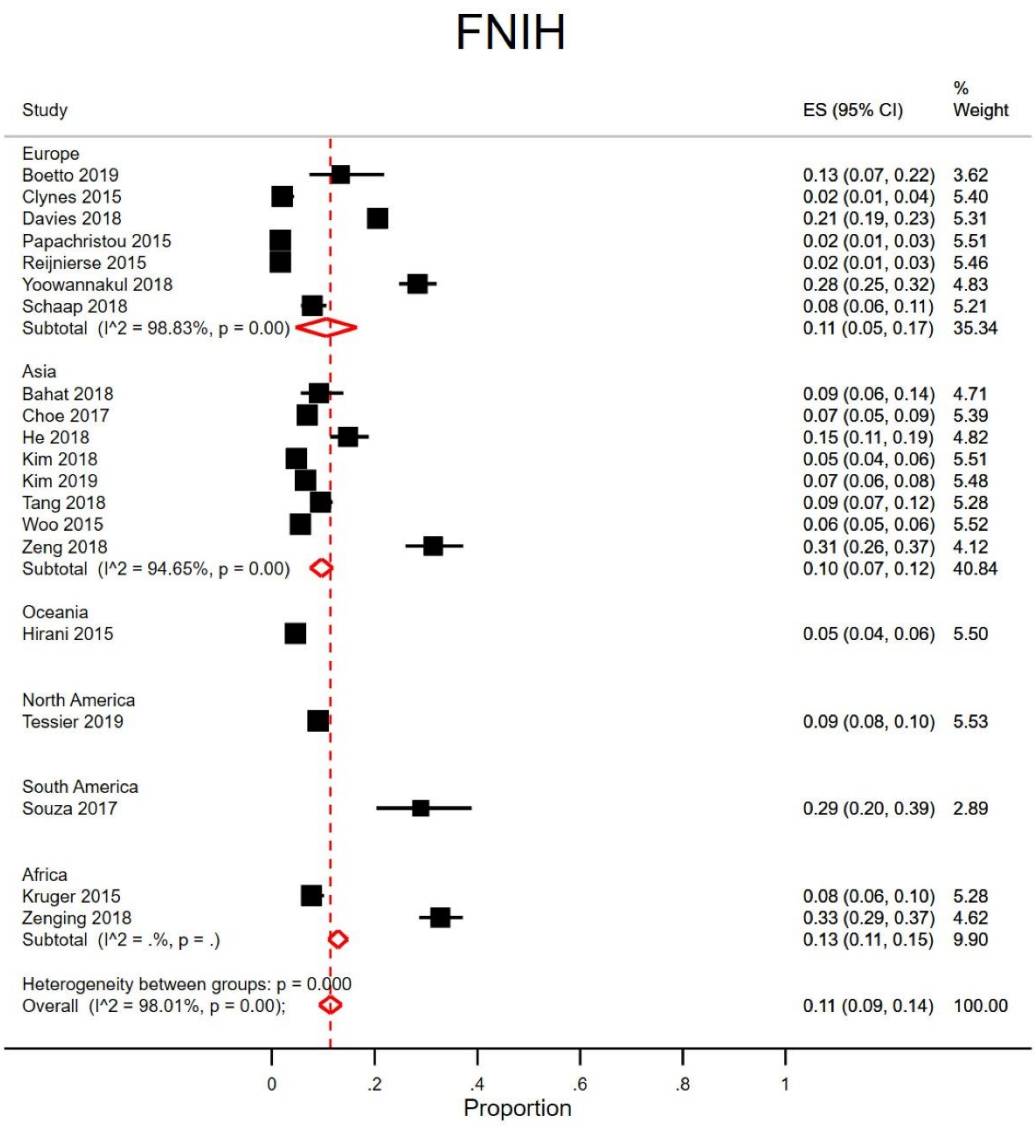
2.1.28 Supplementary Figure 4e. Prevalence of sarcopenia using the IWGS in men.

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence. IWGS: International Working Group on Sarcopenia.



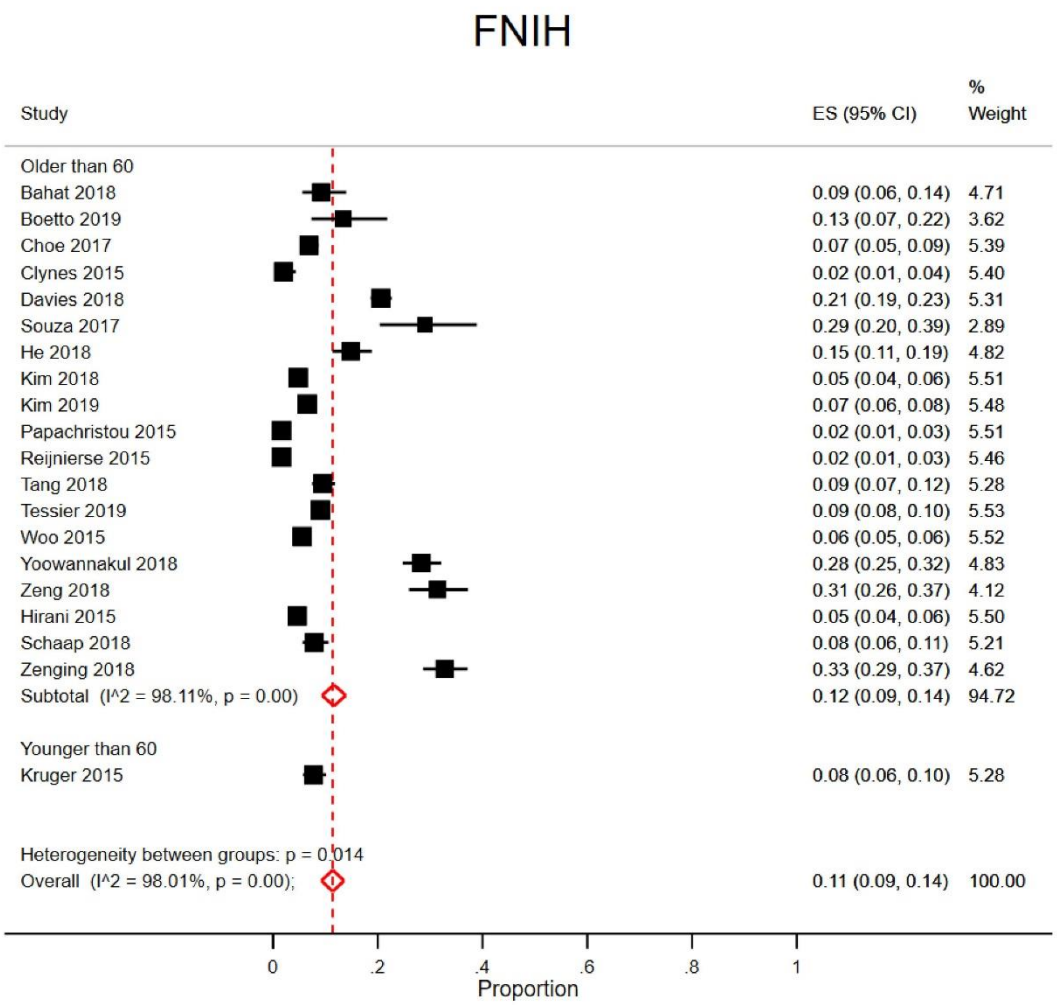
2.1.29 Supplementary Figure 5a. Prevalence of sarcopenia using the FNIH.

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence. FNIH: Foundation for the National Institute of Health.



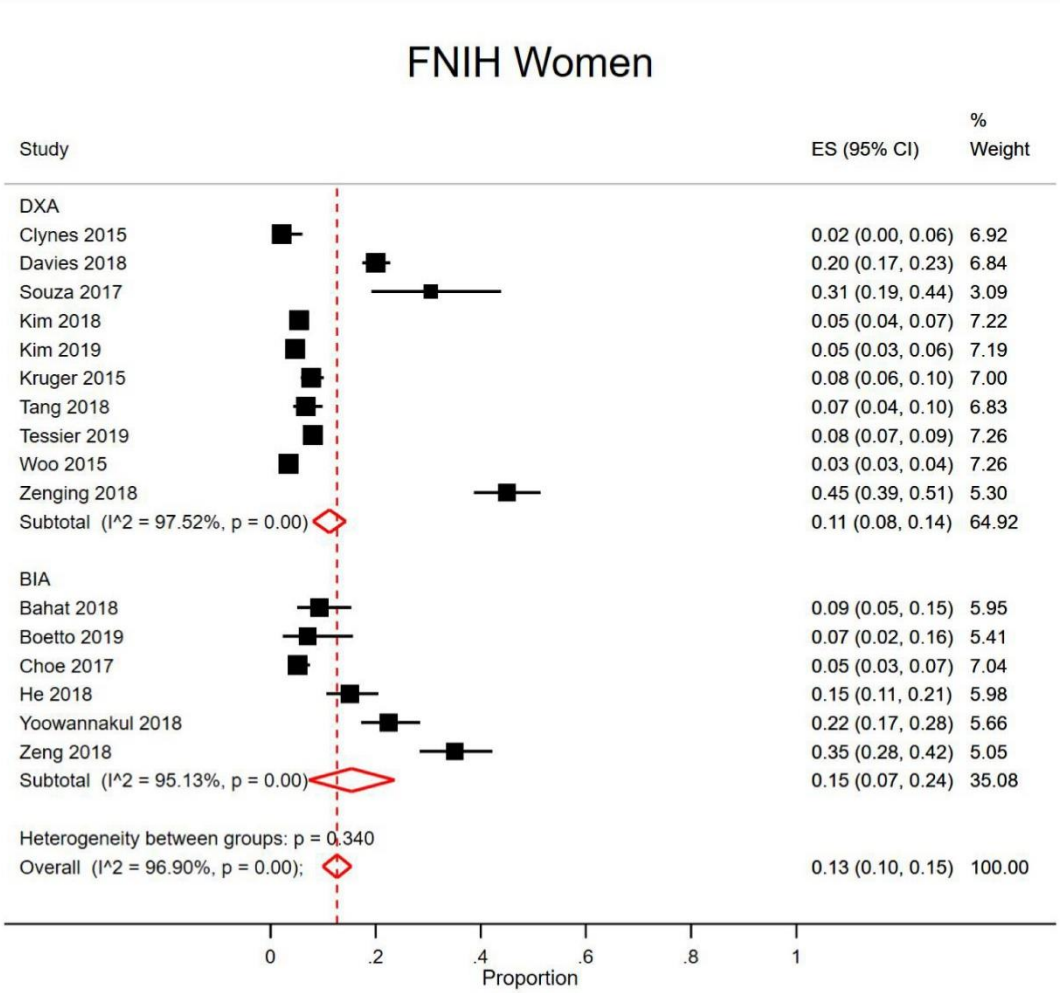
2.1.30 Supplementary Figure 5b. Prevalence of sarcopenia using the FNIH by region of origin.

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence. FNIH: Foundation for the National Institute of Health.



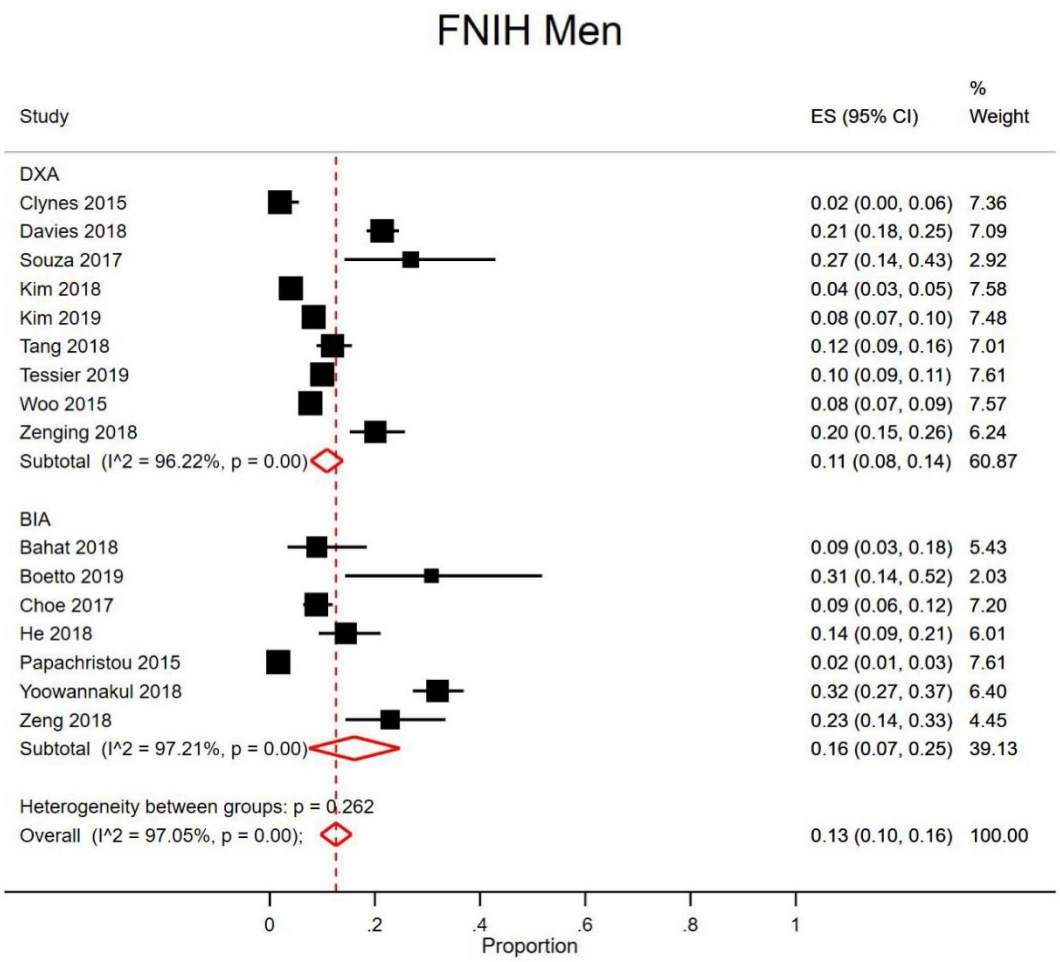
2.1.31 Supplementary Figure 5c. Prevalence of sarcopenia using the FNIH by age categories.

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence. FNIH: Foundation for the National Institute of Health.



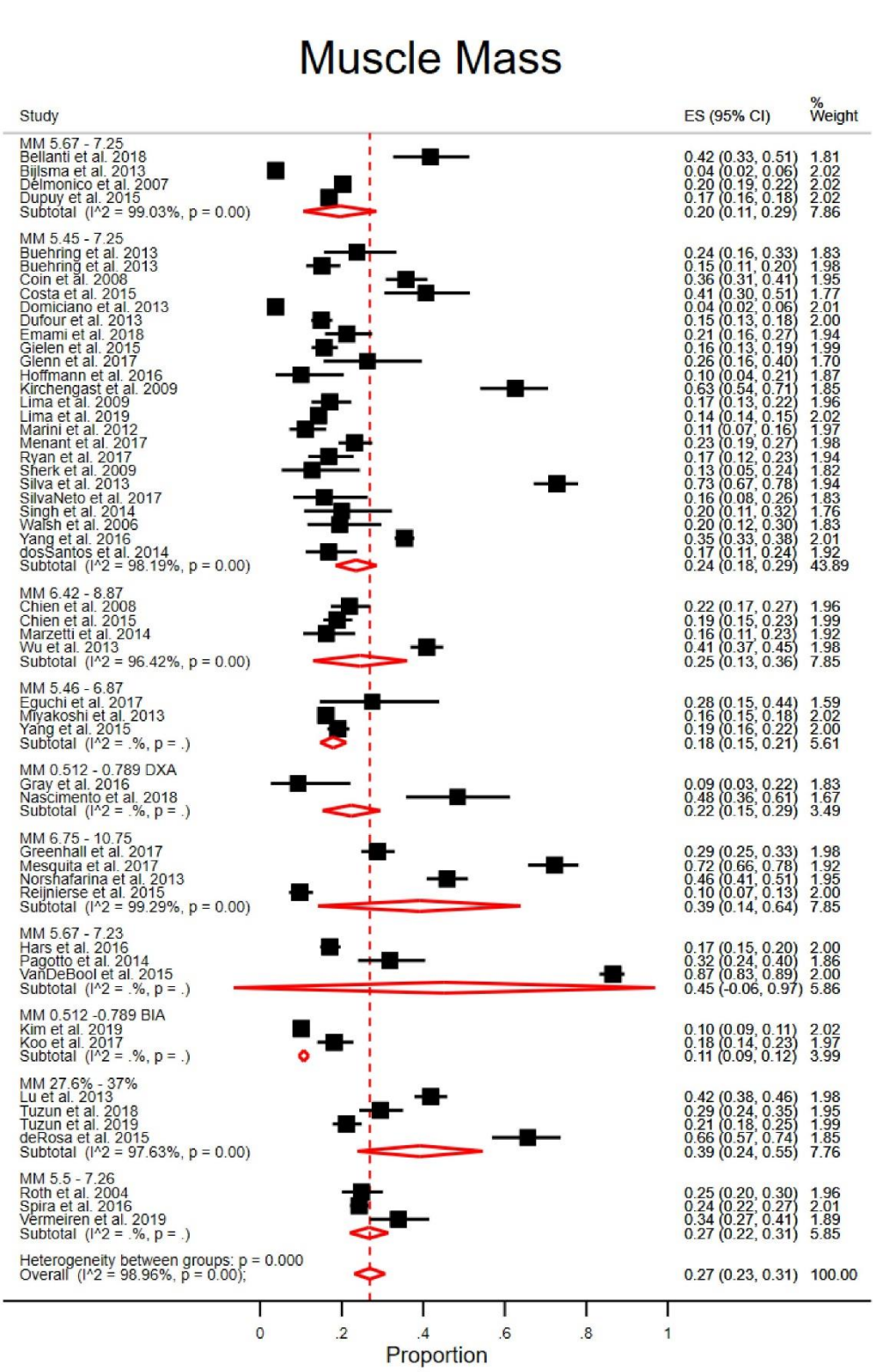
2.1.32 Supplementary Figure 5d. Prevalence of sarcopenia using the FNIH in women.

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence. FNIH: Foundation for the National Institute of Health.



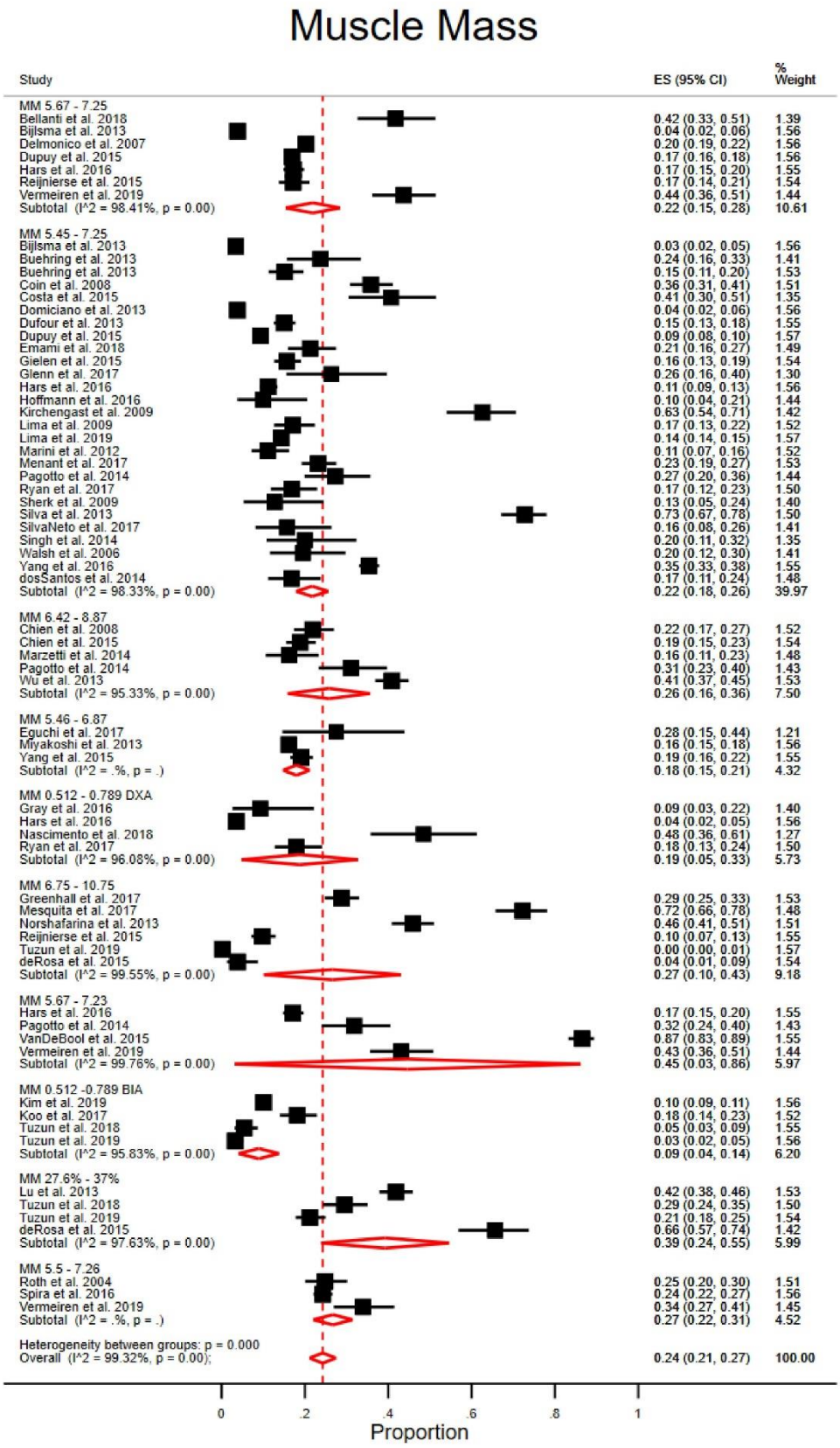
2.1.33 Supplementary Figure 5e. Prevalence of sarcopenia using the FNIH in men.

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence. FNIH: Foundation for the National Institute of Health.



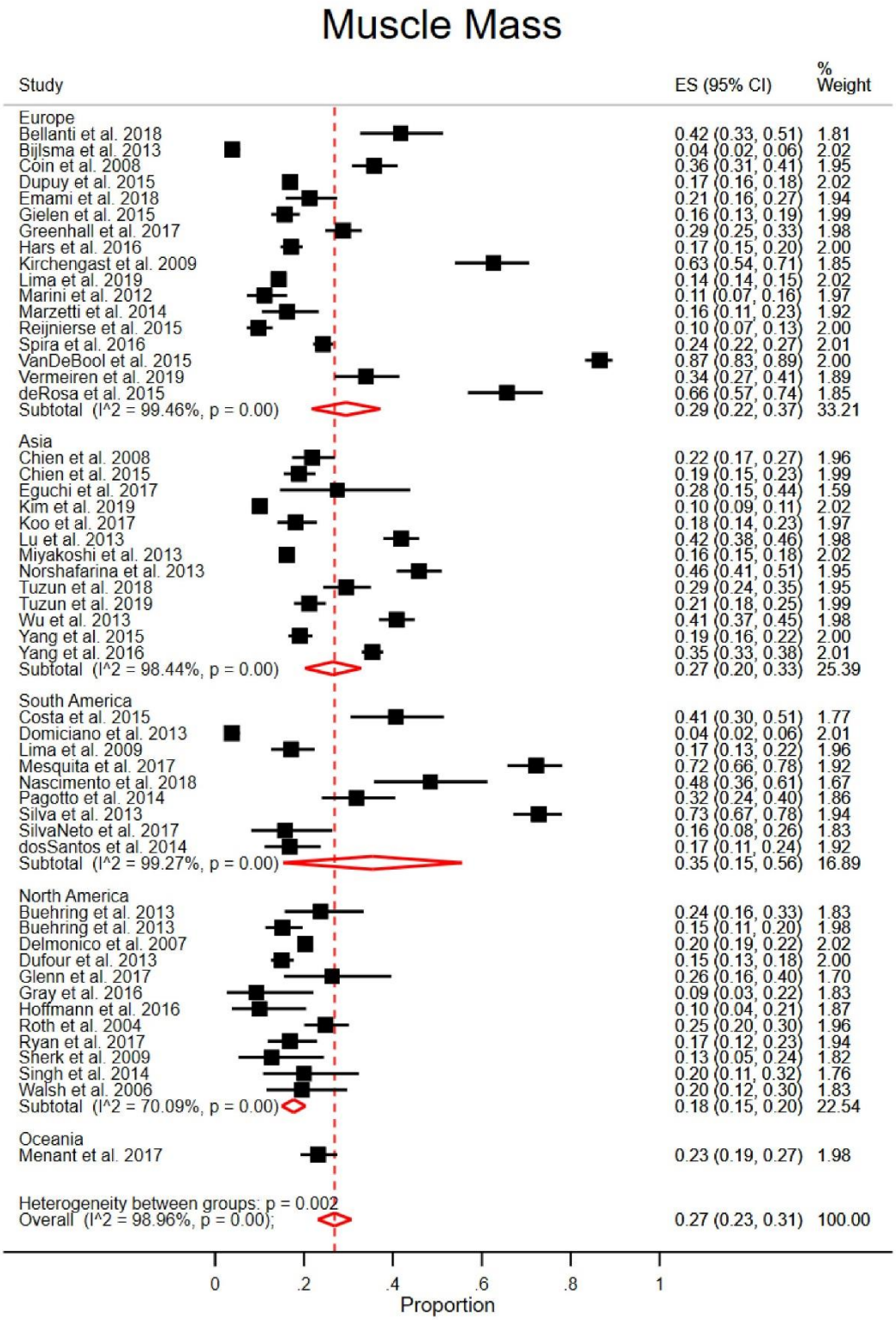
2.1.34 Supplementary Figure 6.a.1. Prevalence of sarcopenia using muscle mass (excluding those who reported the prevalence more than once using different cut-off points).

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence.



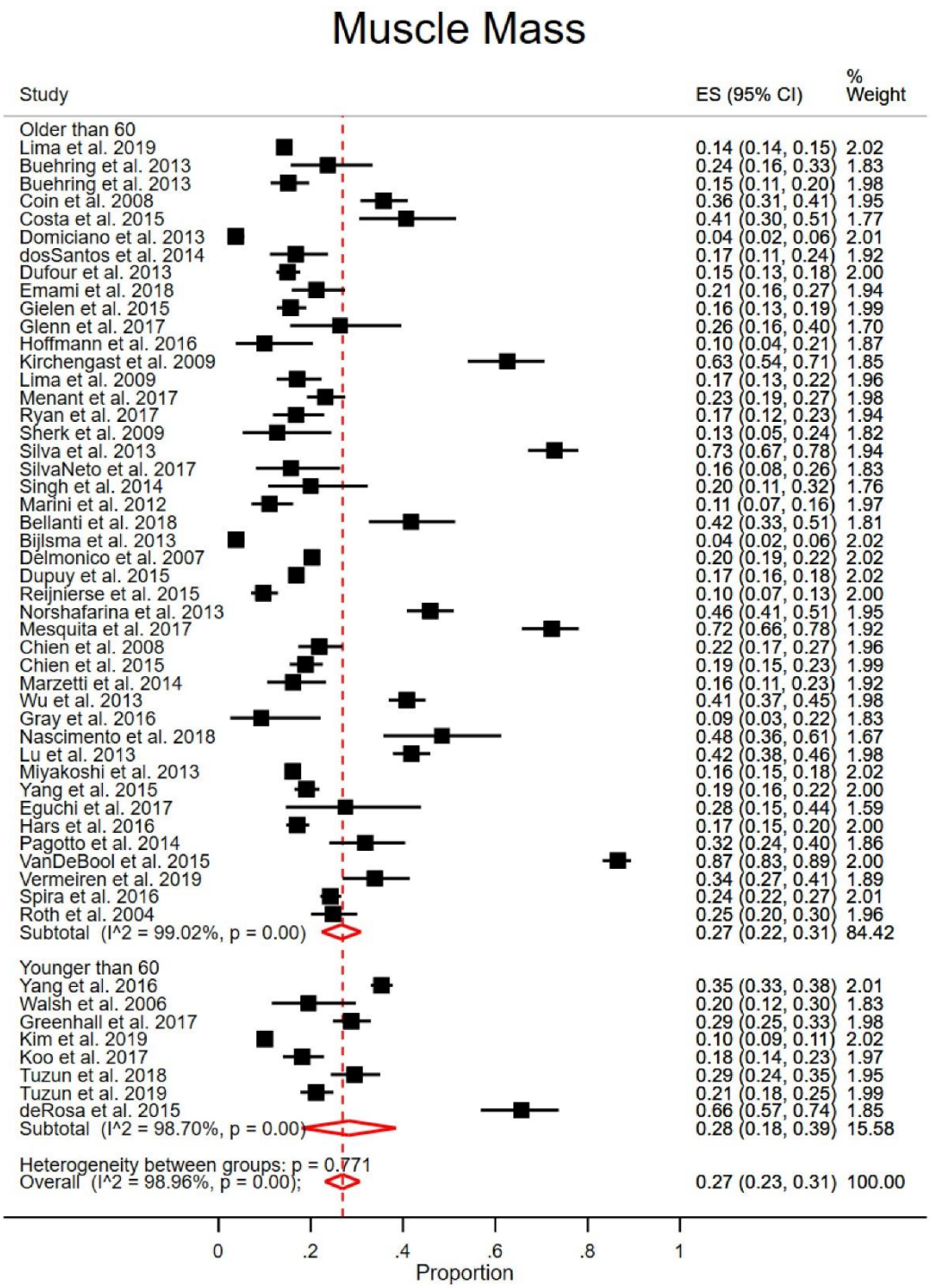
2.1.35 Supplementary Figure 6.a.2. Prevalence of sarcopenia using muscle mass (all cut-off points).

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence.



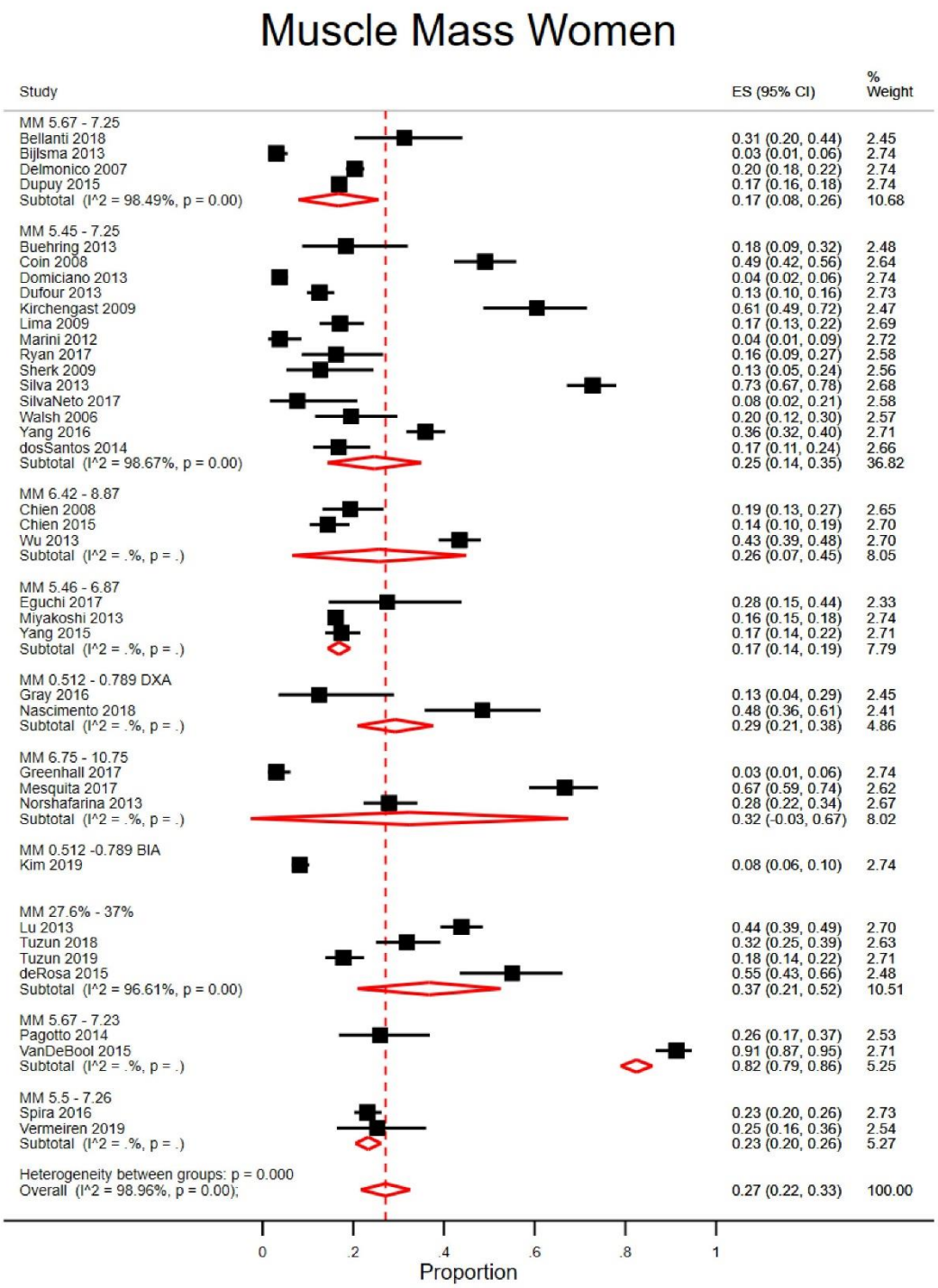
2.1.36 Supplementary Figure 6b. Prevalence of sarcopenia using muscle mass by region of origin (excluding those who reported the prevalence more than once using different cut-off points).

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence.



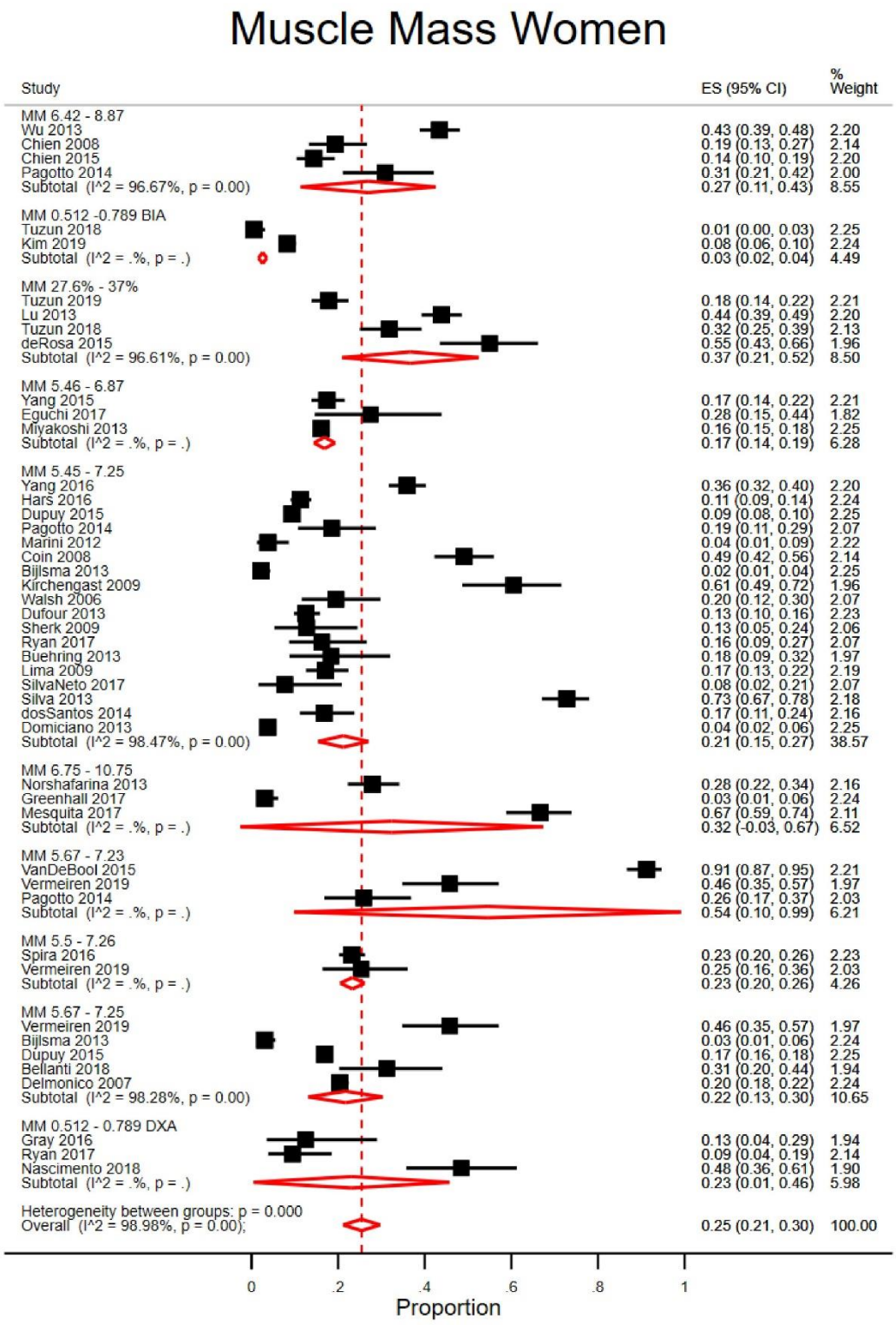
2.1.37 Supplementary Figure 6c. Prevalence of sarcopenia using muscle mass by age categories (excluding those who reported the prevalence more than once using different cut-off points).

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence.



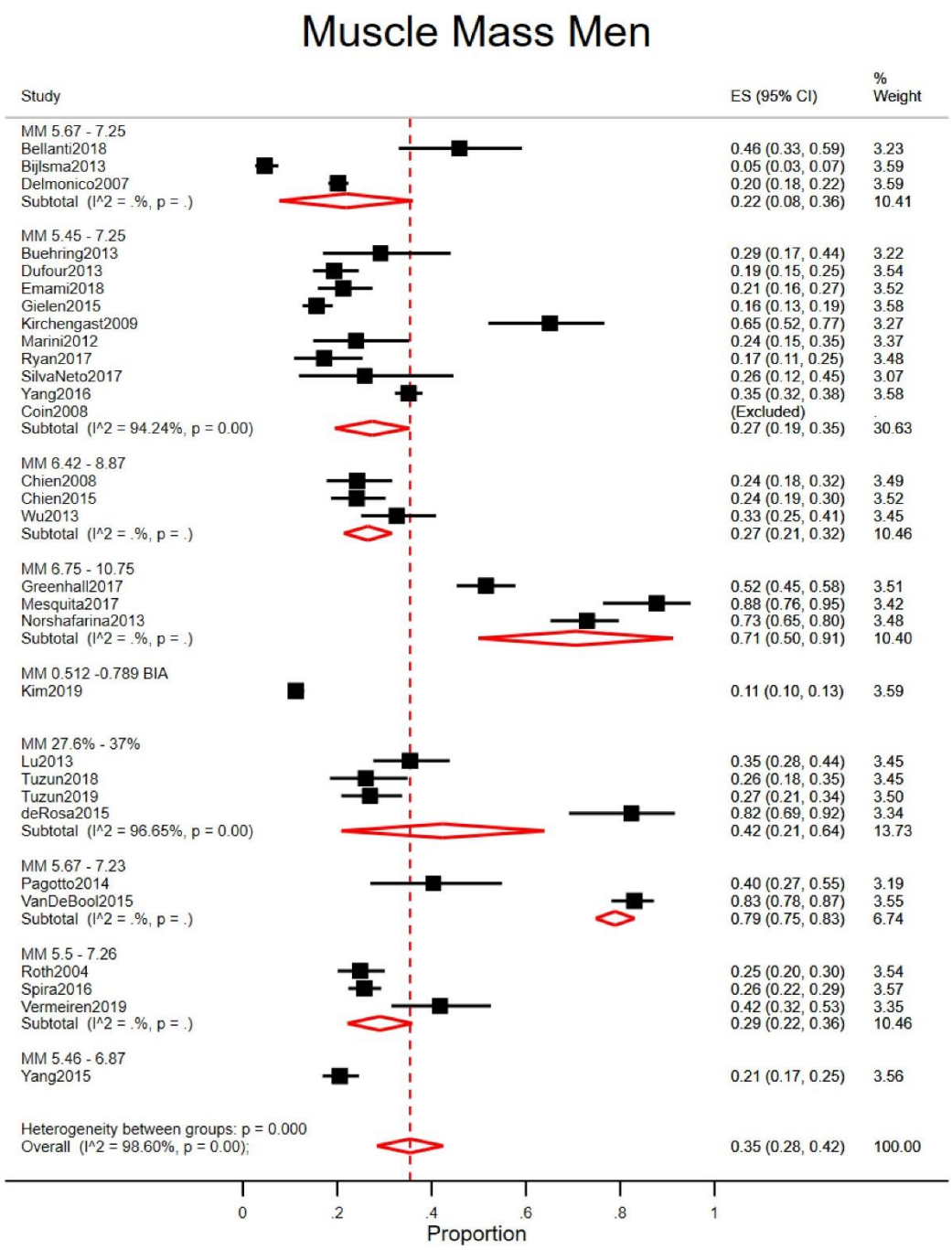
2.1.38 Supplementary Figure 6d.1 Prevalence of sarcopenia using muscle mass in women (excluding those who reported the prevalence more than once using different cut-off points)

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence.



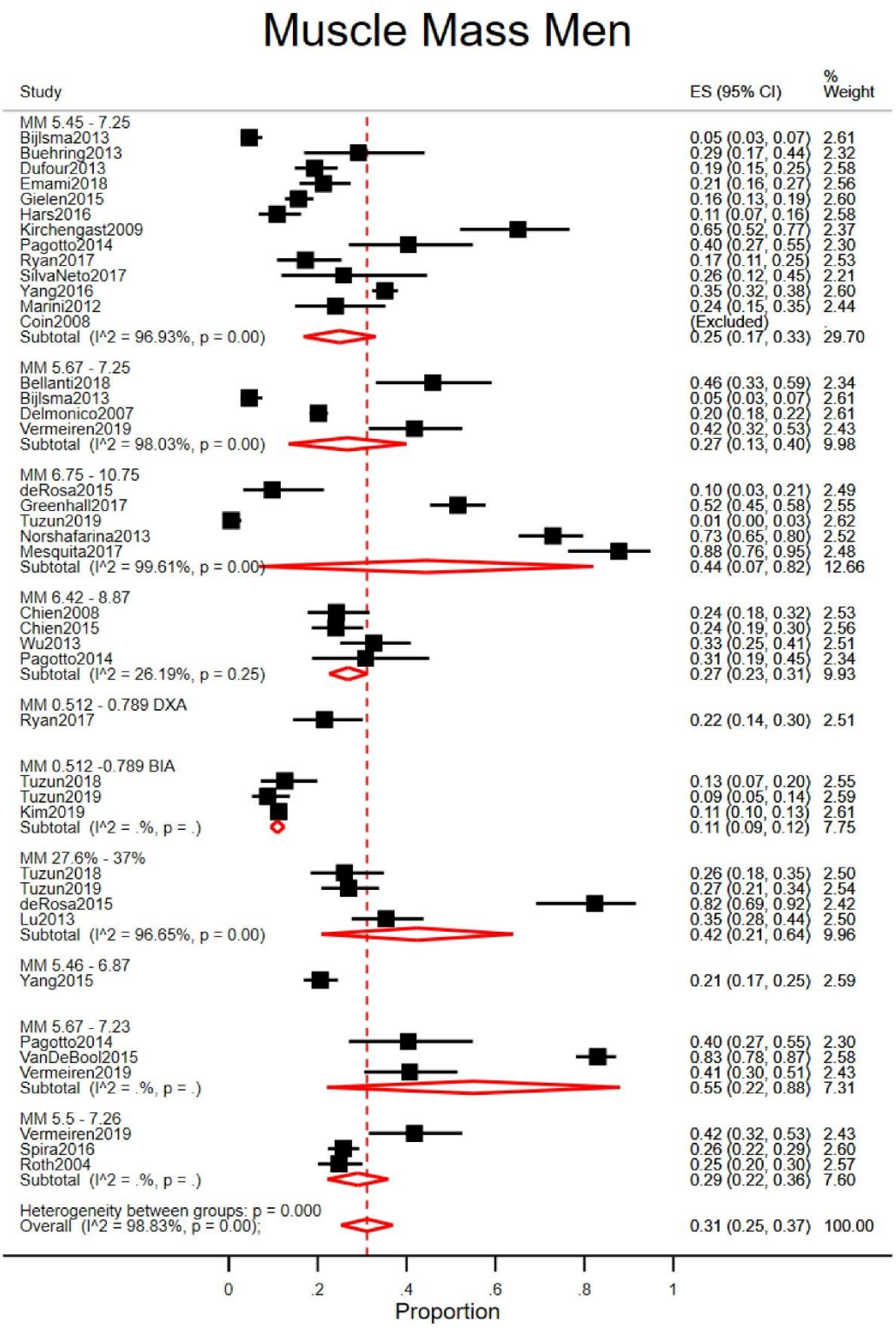
2.1.39 Supplementary Figure 6d.2 Prevalence of sarcopenia using muscle mass in women (all cut-off points).

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence.



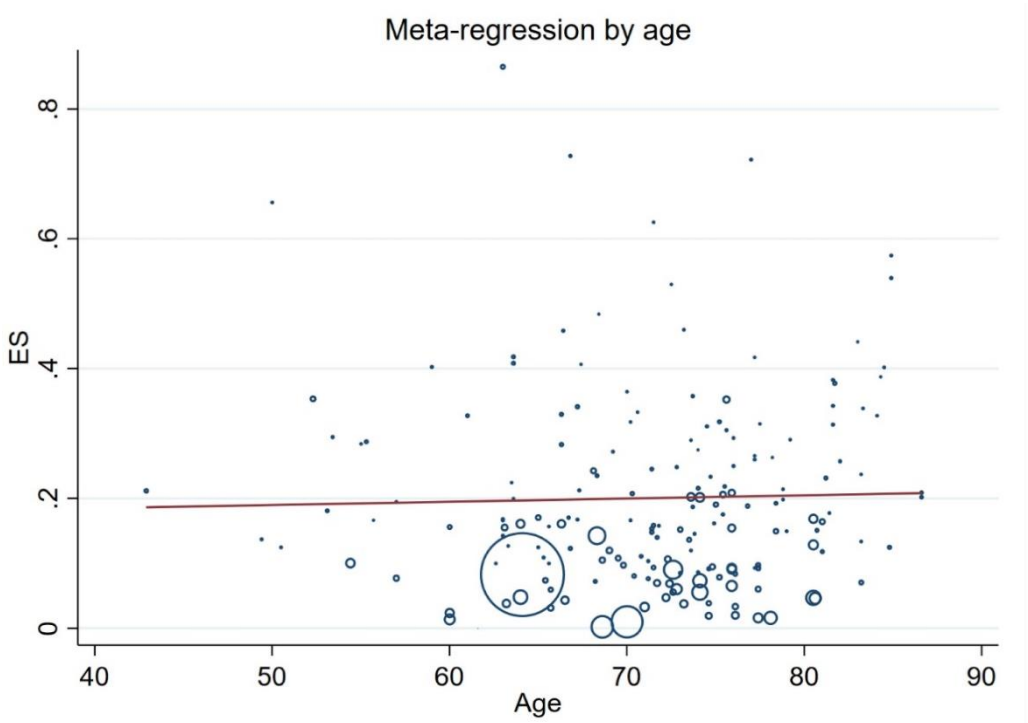
2.1.40 Supplementary Figure 6e.1 Prevalence of sarcopenia using muscle mass in men (excluding those who reported the prevalence more than once using different cut-off points)

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence.

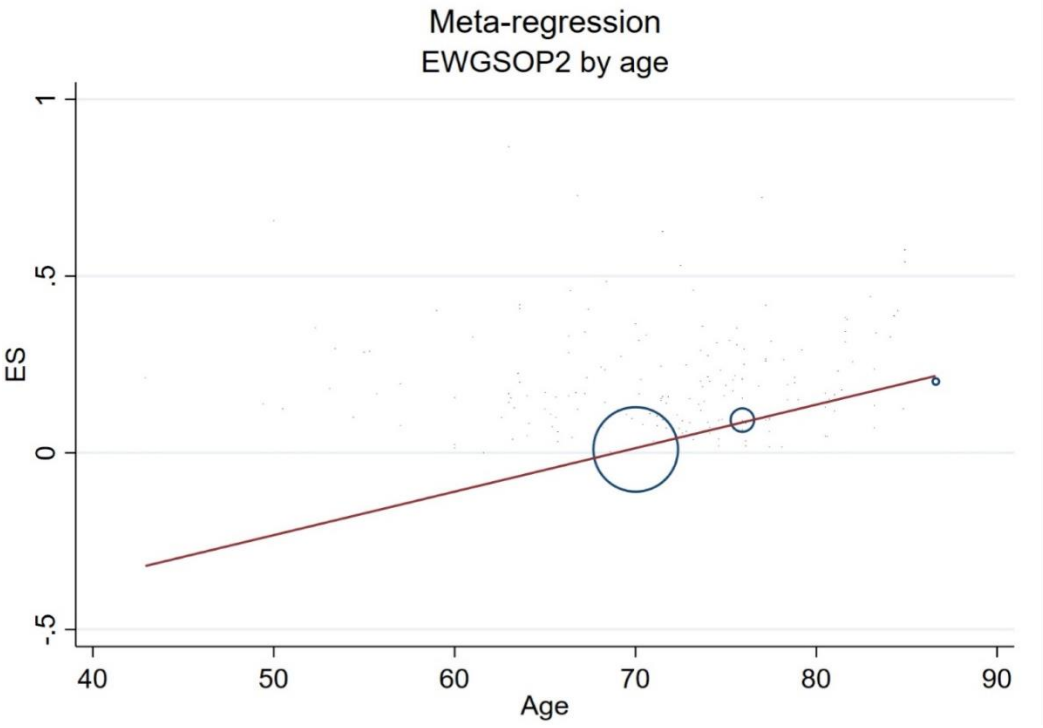


2.1.41 Supplementary Figure 6e.2. Prevalence of sarcopenia using muscle mass in men (all cut-off points).

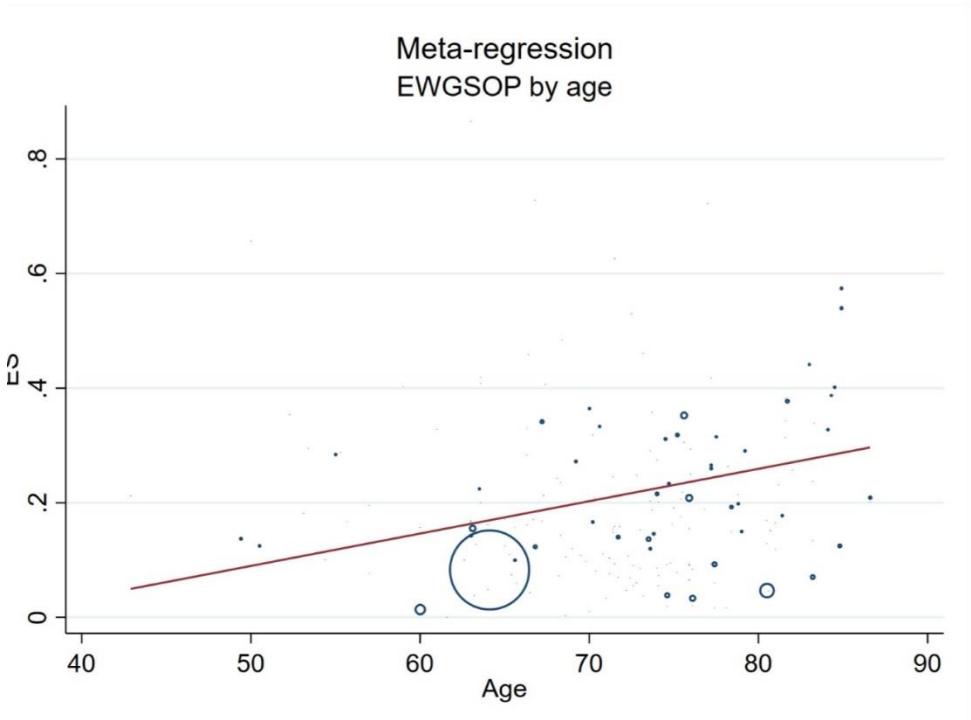
Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence.



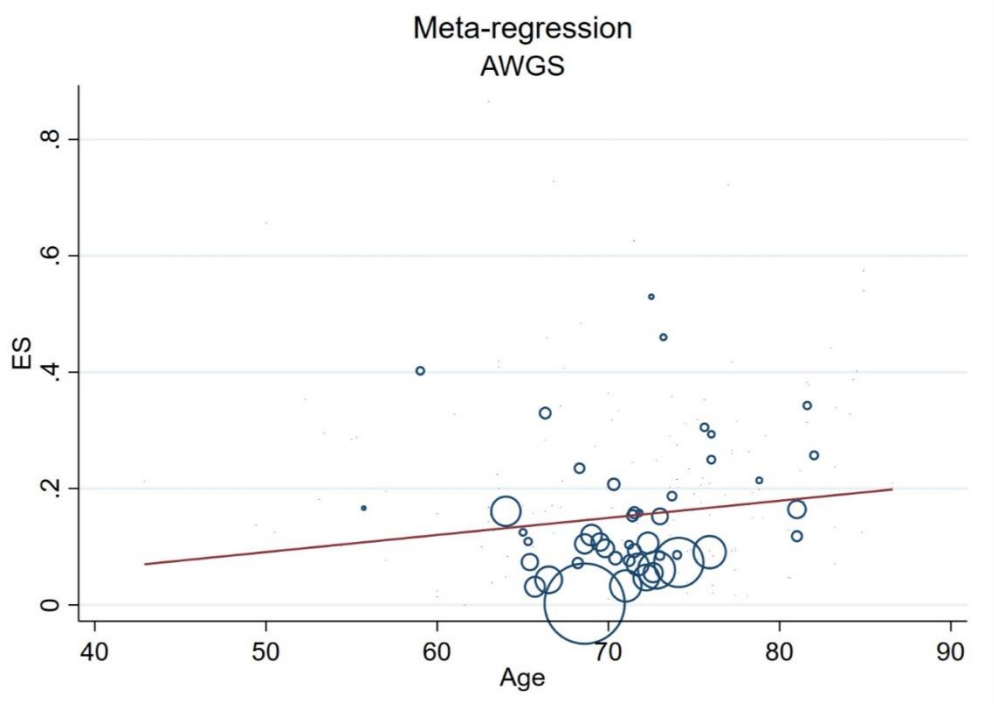
2.1.42 Supplementary Figure 7. Overall meta-regression by age.



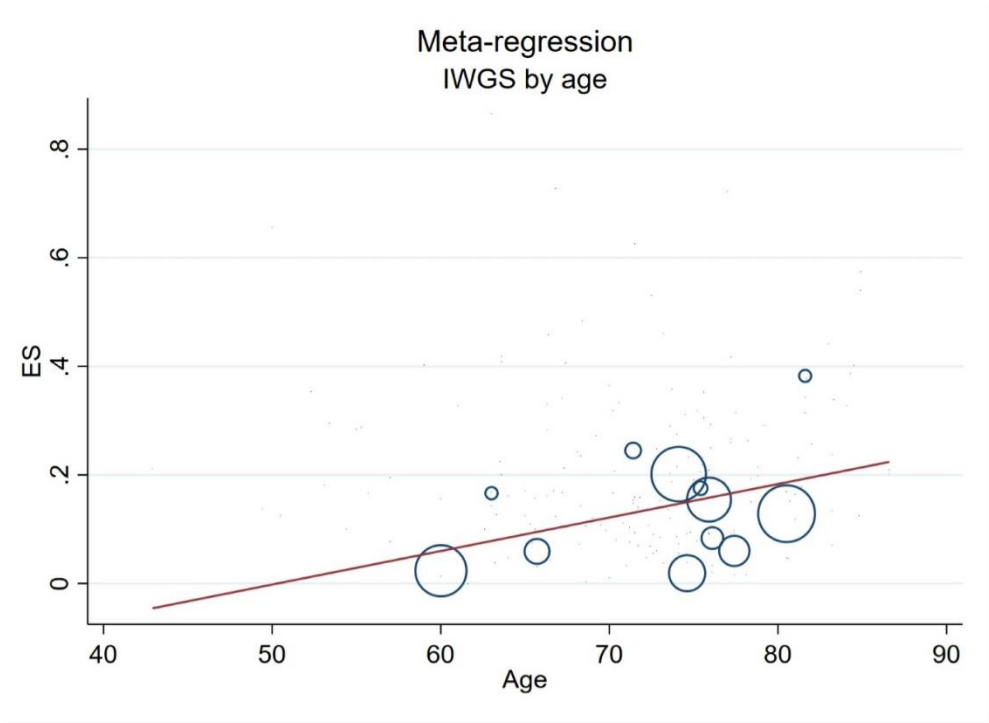
2.1.43 Supplementary Figure 7a. Meta-regression by age using the EWGSOP2



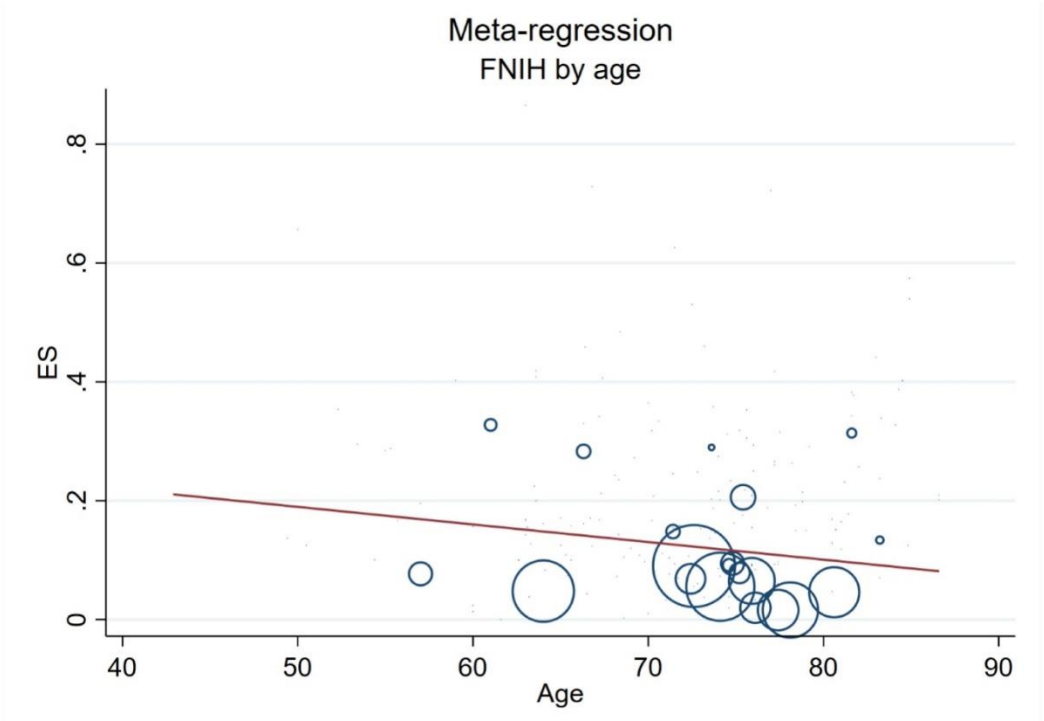
2.1.44 Supplementary Figure 7b. Meta-regression by age using the EWGSOP



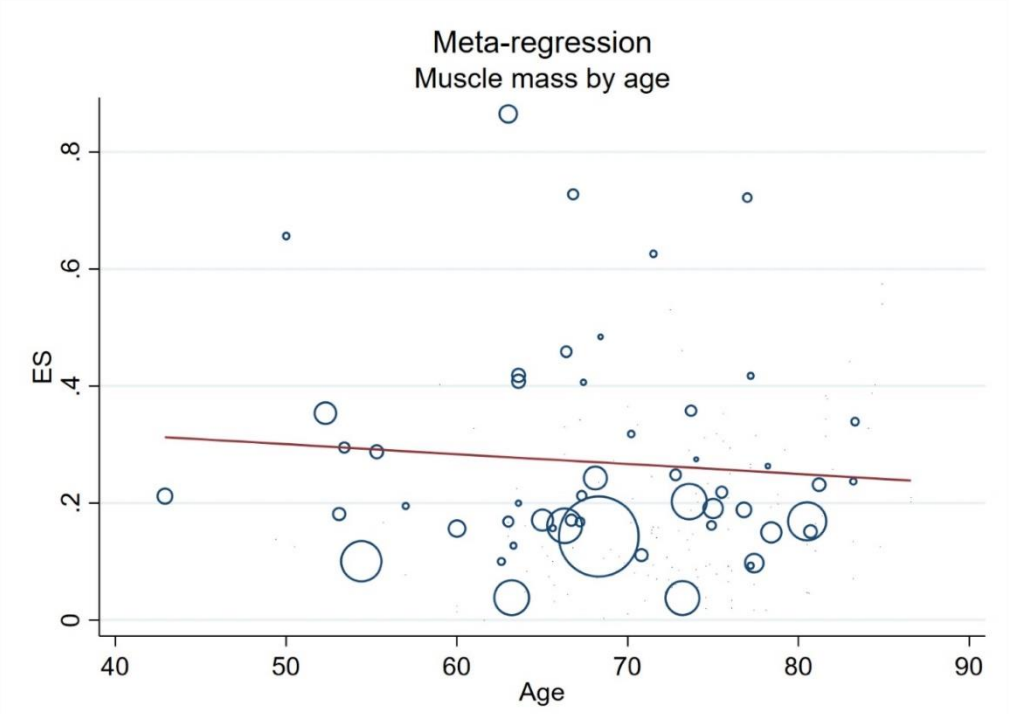
2.1.45 Supplementary Figure 7c. Meta-regression by age using the AWGS



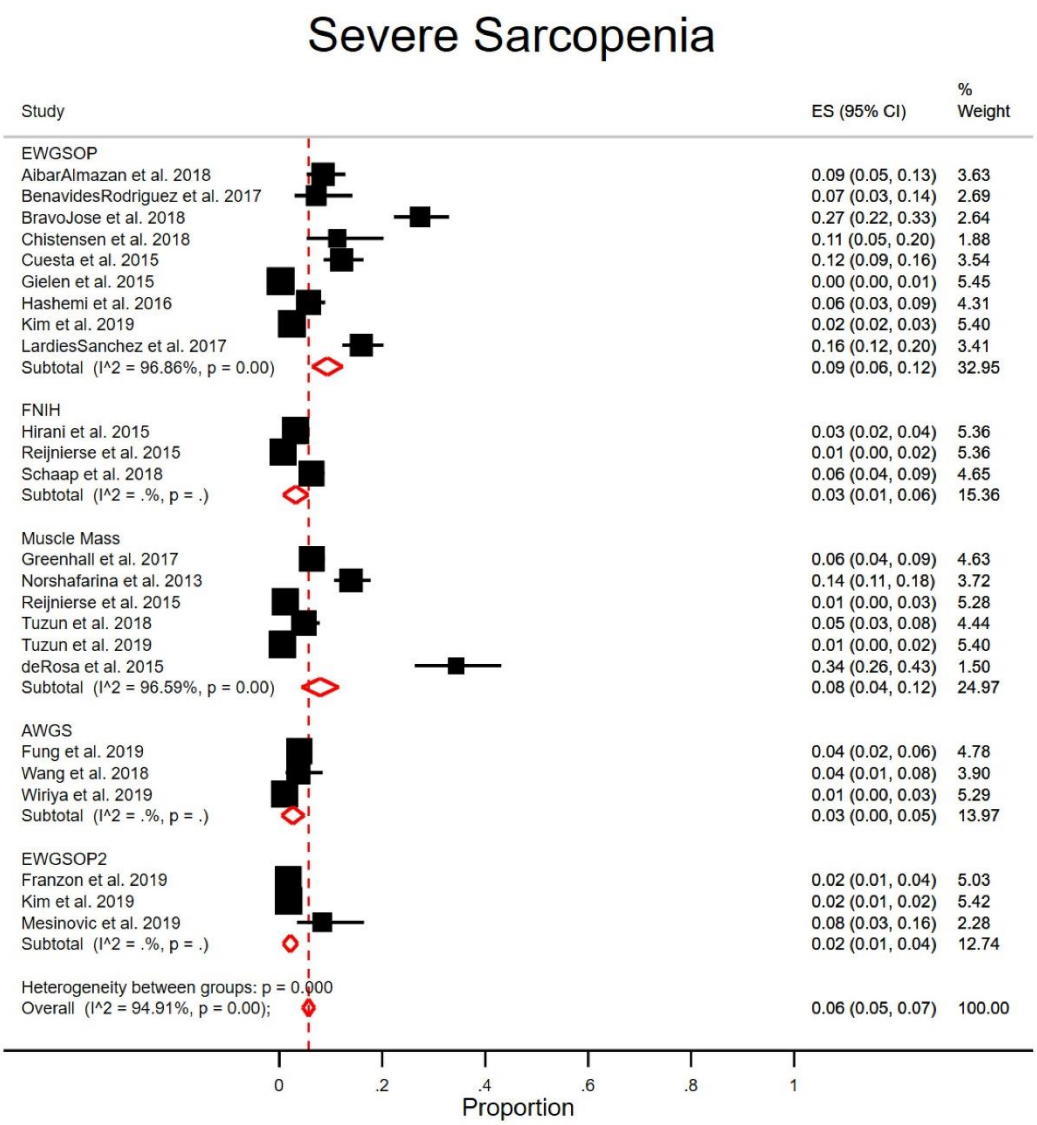
2.1.46 Supplementary Figure 7d. Meta-regression by age using the IWGS



2.1.47 Supplementary Figure 7e. Meta-regression by age using the FNIH

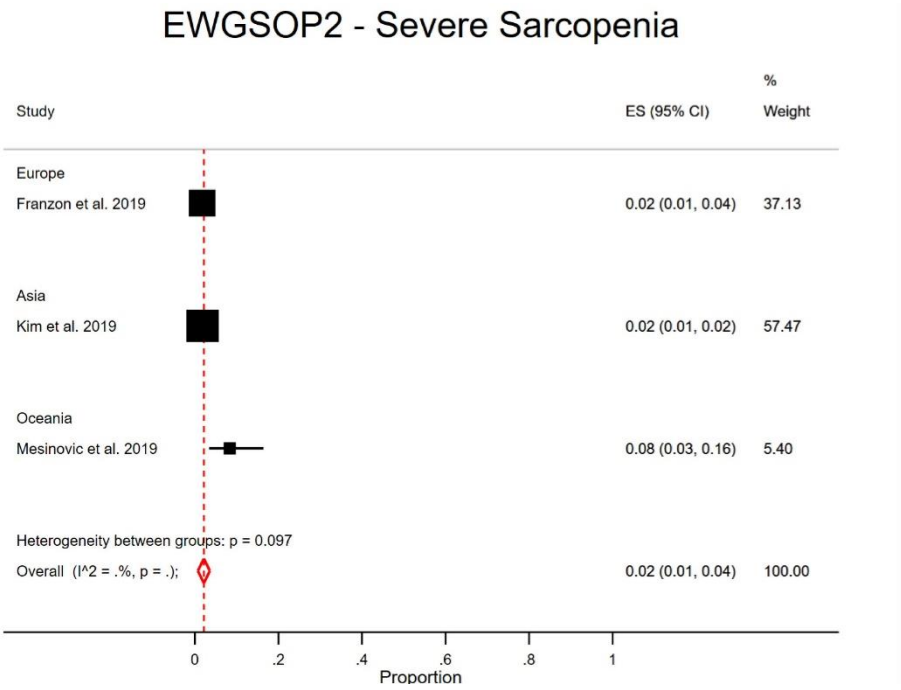


2.1.48 Supplementary Figure 7f. Meta-regression by age using muscle mass



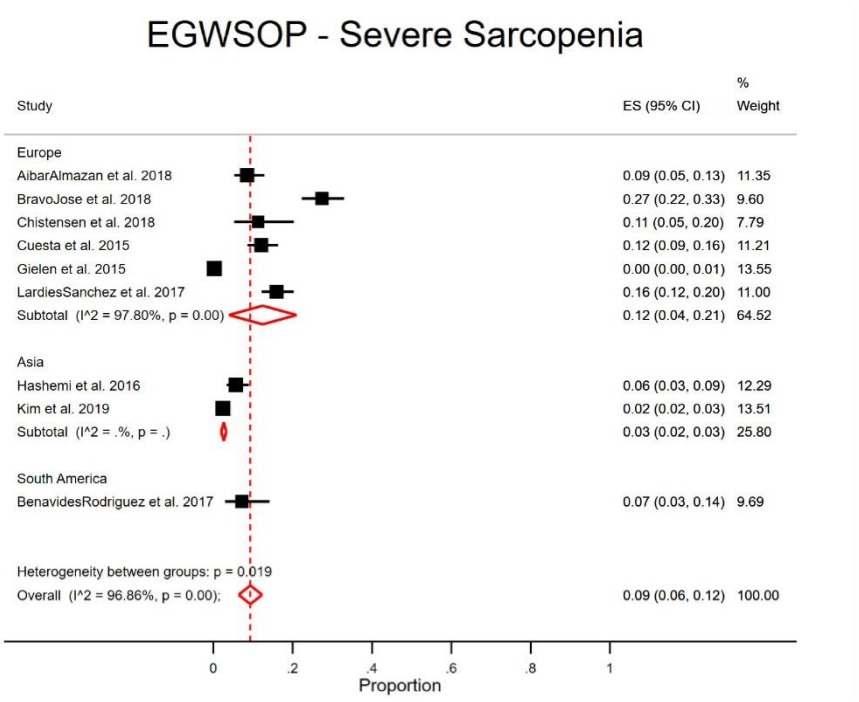
2.1.49 Supplementary Figure 8. Prevalence of severe sarcopenia using different classifications.

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence. EWGSOP2: European Working Group on Sarcopenia in Older People 2; EWGSOP: Asian Working Group for Sarcopenia, AWGS: Asian Working Group for Sarcopenia; FNIH: Foundation for the National Institute of Health.



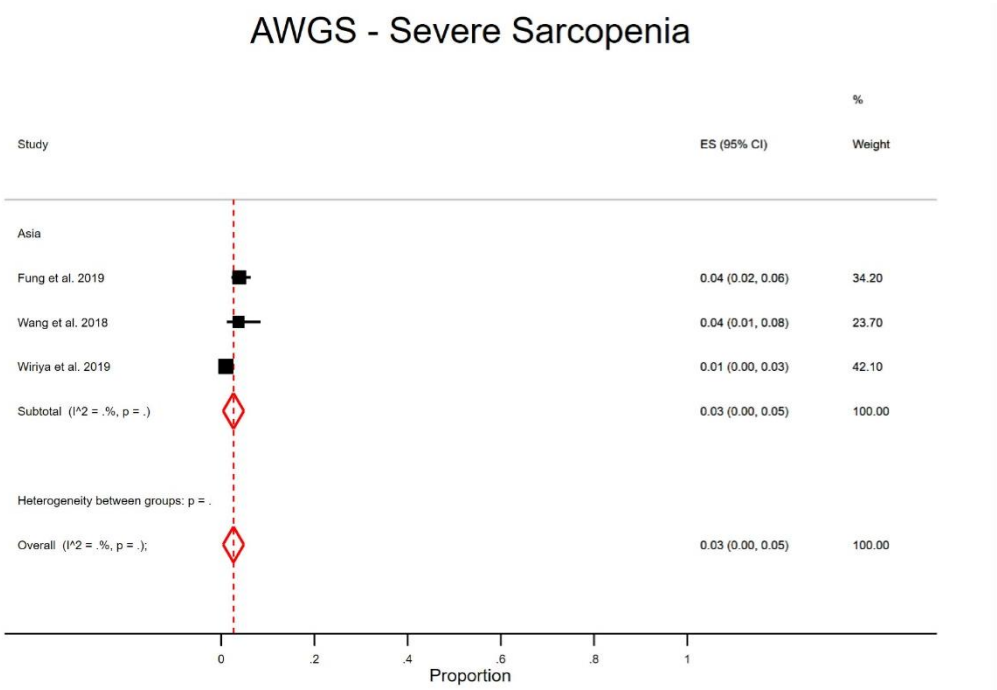
2.1.50 Supplementary Figure 9a. Prevalence of severe sarcopenia using the EWGSOP2.

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence.



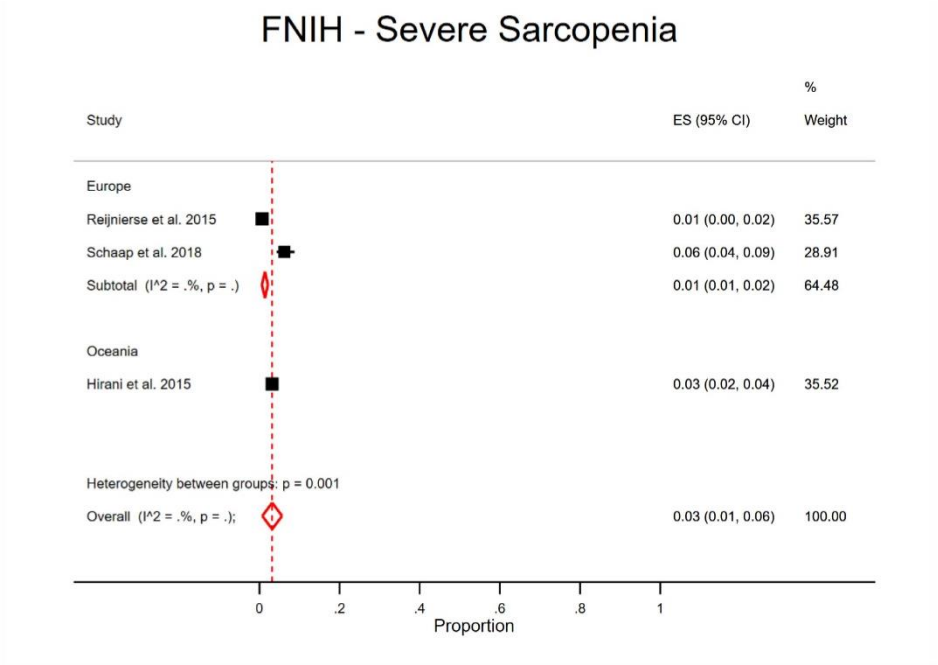
2.1.51 Supplementary Figure 9b. Prevalence of severe sarcopenia using the EWGSOP.

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used.



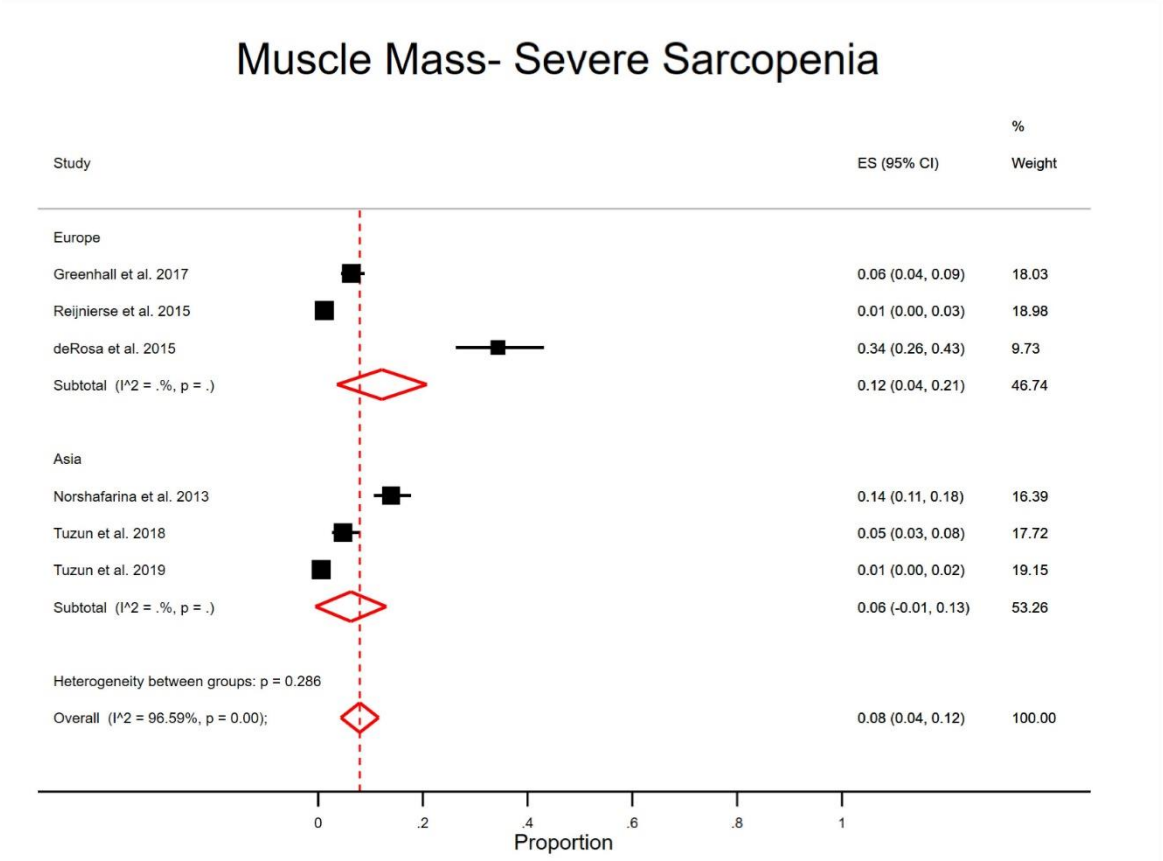
2.1.52 Supplementary Figure 9c. Prevalence of severe sarcopenia using the AWGS.

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence.



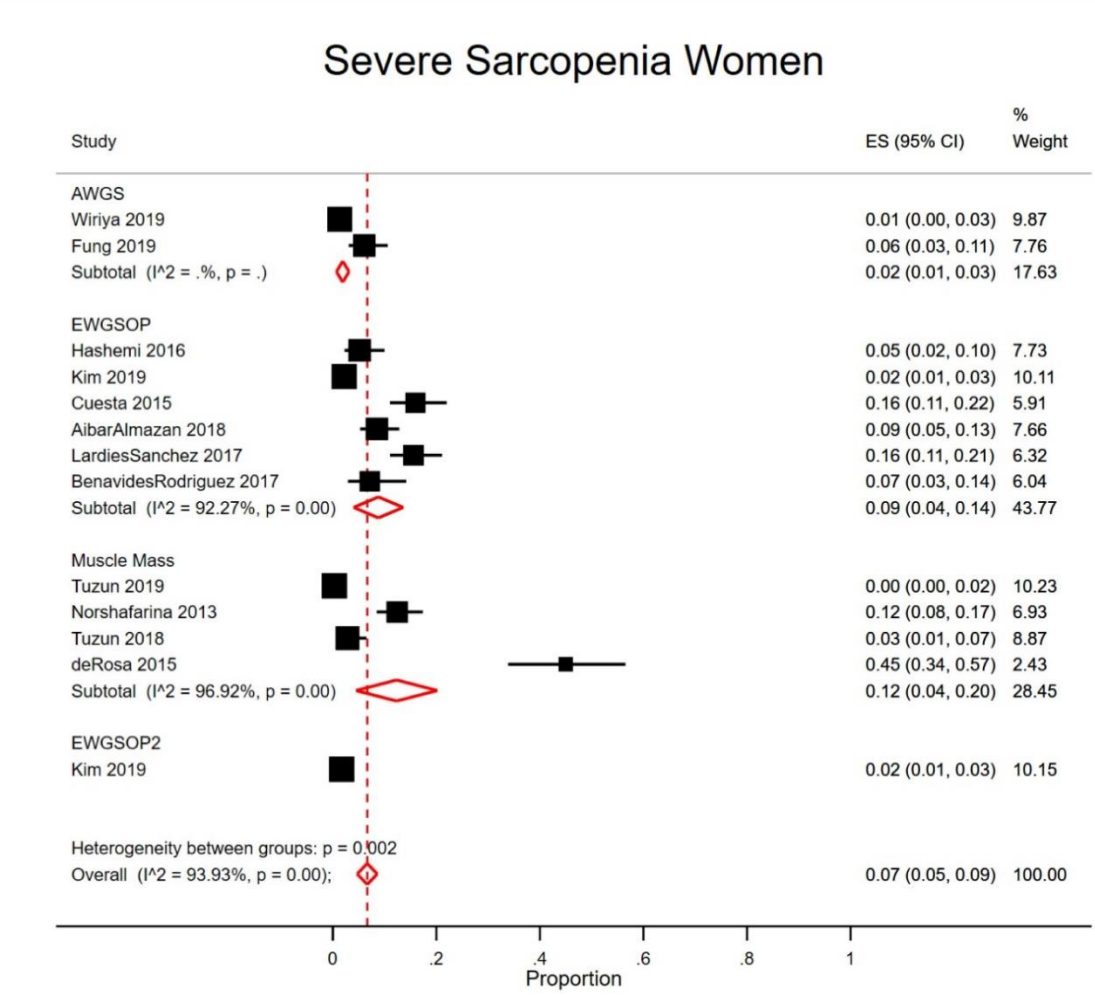
2.1.53 Supplementary Figure 9d. Prevalence of severe sarcopenia using the FNIH.

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used.



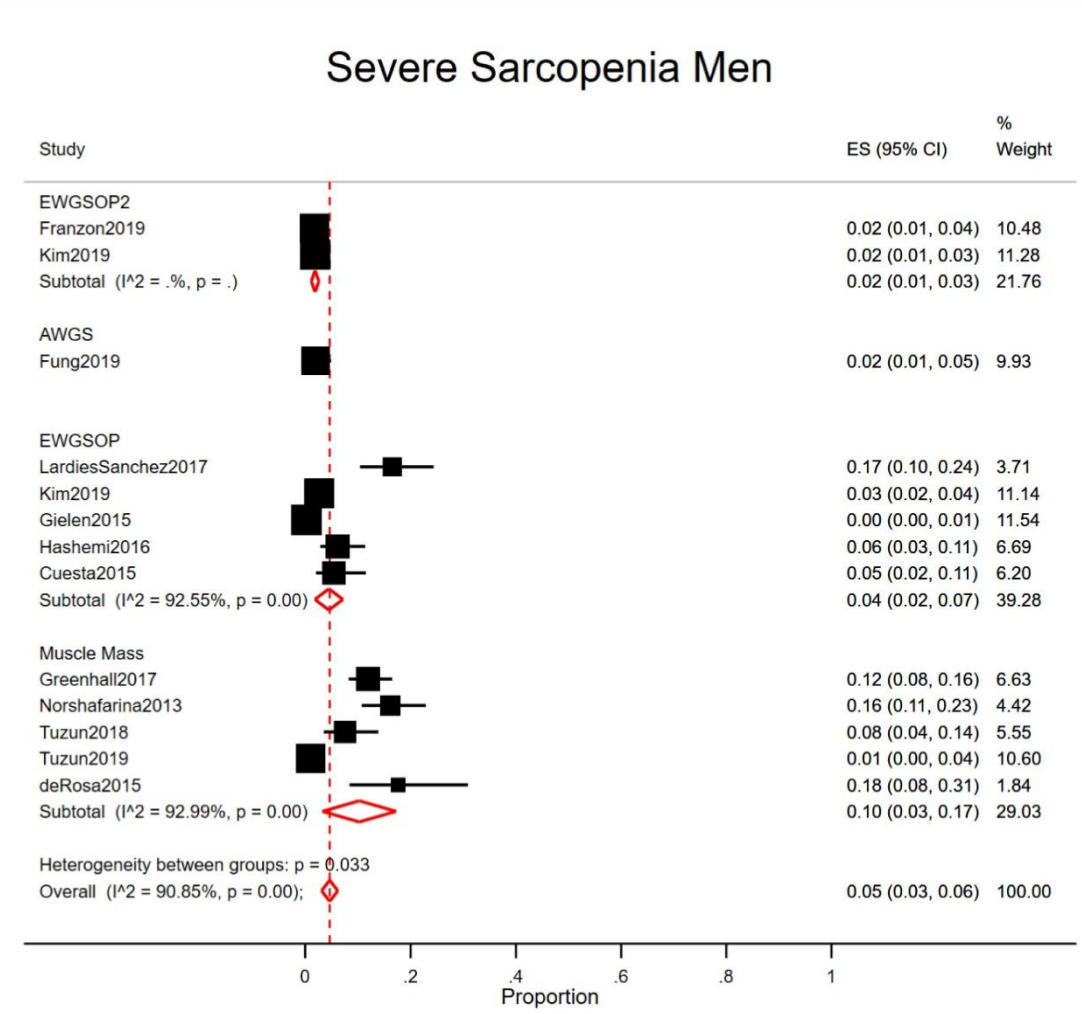
2.1.54 Supplementary Figure 9e. Prevalence of severe sarcopenia using muscle mass.

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence.



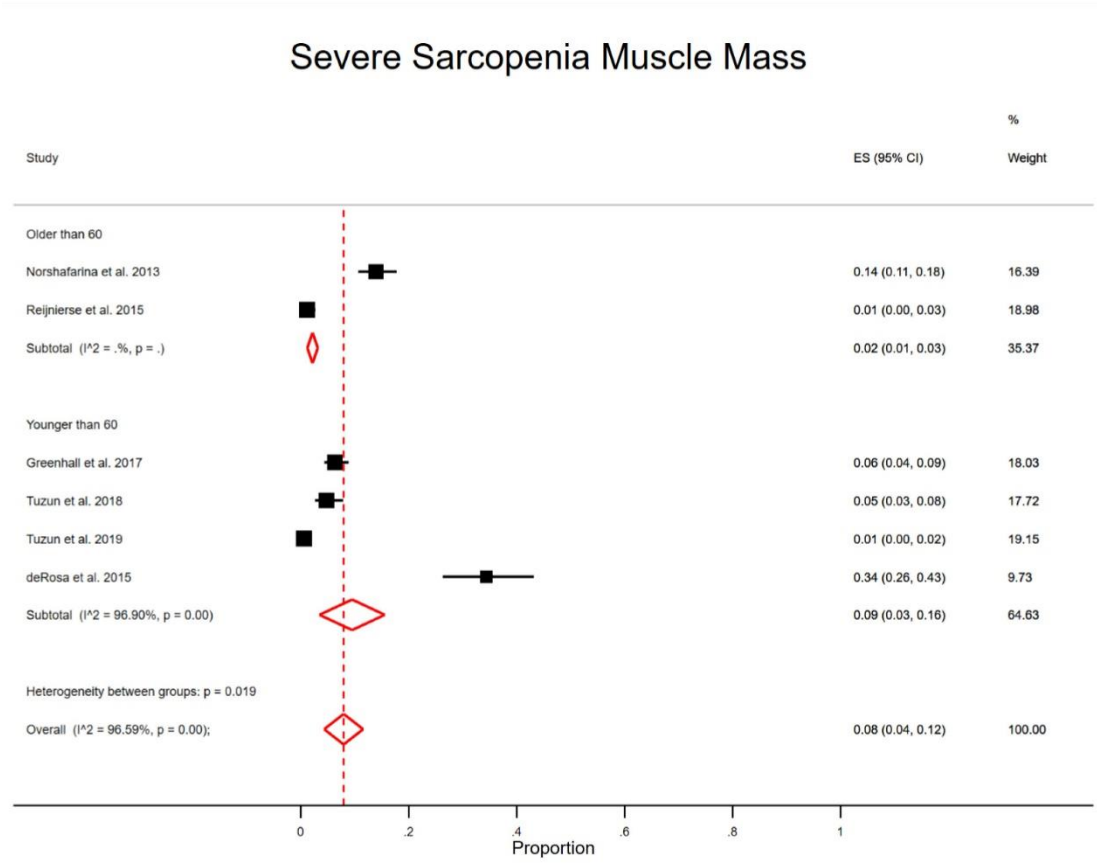
2.1.55 Supplementary Figure 10. Prevalence of severe sarcopenia in women.

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence.



2.1.56 Supplementary Figure 11. Prevalence of severe sarcopenia using in men.

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence.



2.1.57 Supplementary Figure 12. Prevalence of severe sarcopenia by age categories and muscle mass.

Data presented as prevalence (%) with their respectively 95% confidence intervals (CI) by classification used. Overall pooled estimates with inverse-variance weights obtained from a random-effects were estimated for the analyses using *metaprop* in Stata. ES: estimated prevalence.

Chapter 3 The UK Biobank Study

3.1 Introduction to the UK Biobank Study

UK Biobank is an open access and largescale, general population cohort study containing in-depth health information which are widely used by researchers globally. UK Biobank has an international scientific advisory group and is used by international researchers. The main aim of UK Biobank is to enable new scientific discoveries using genetic and health information from half a million UK participants of middle and old ages (Biobank, 2021b).

Although data collection started in 2006, UK Biobank was originally conceived in 1999 as the result of a meeting hosted by the Medical Research Council (MRC) and Wellcome Trust on case-control studies. After consulting more than 150 specialists, and with the support of two expert working groups led by Professor Tom Meade, the project was funded jointly by the MRC, Wellcome Trust and the Department of Health in 2002 (Ollier et al., 2005). In 2003, UK Biobank was formally established as a charitable company, and its framework (including the research standards) was published. Over the next three years, the study protocol was developed, ethics approval obtained, and pilot studies carried out. Recruitment and baseline data collection was planned to start in 2006 with the intention to collect longitudinal data (follow-up outcomes) over the next 20 years (Ollier et al., 2005).

A minimum of 500,000 men and women was required to investigate common causes of morbidity and mortality. The statistical power calculations (with 80% power) demonstrated that the inclusion of a half-million individuals would provide at least 5,000–10,000 incident cases of all major conditions; thereby providing sufficient power to detect the main effects of different exposures with odds ratios (ORs) between 1.3 and 1.5 (based on UK age- and sex-specific rates). For interaction terms, around 20,000 incident cases would be required to obtain ORs of at least 2.0. (Sudlow et al., 2015). To have adequate incident health outcomes during the early years of follow-up and participants sufficiently young for the initial assessment to occur before these events, individuals between 40 and 69 years old were recruited (Palmer, 2007, Sudlow et al., 2015). This age group was selected to be studied since entails people at risk over the next few

years of developing a wide variety of adverse health outcomes (including diabetes, CVD, cancer and dementia). The latter would allow prolonged follow-up of participants across routine medical and other health-related records. The use of this unique rich resource would allow a better understanding of why some people develop outcomes and others do not. Therefore, UK Biobank provides the opportunity to a better understanding of the causes of diseases and, consequently, find new alternative options to prevent and treat these conditions.

Twenty-two assessment centres were set up across England, Wales and Scotland and people aged 40-69 years who lived within a reasonable travelling distance of each assessment centre were invited to participate between 2006 and 2010. Invitation letters were sent to potential participants registered with the National Health Service (NHS) general practitioners. A summary of the invitation and appointment process is shown in Figure 2.1.

Figure 3-1 Schematic of invitation and appointment system

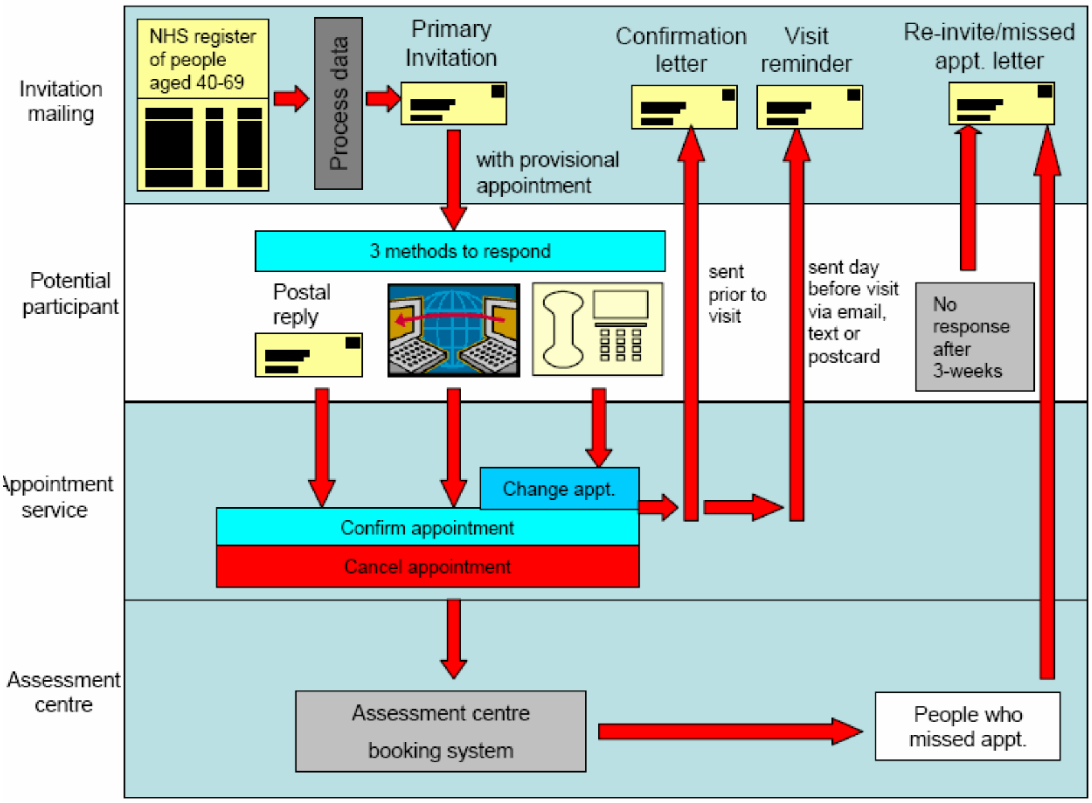


Figure extracted from UK Biobank: Protocol for a large-scale prospective epidemiological resource (Biobank, 2007).

Approximately 9.2 million individuals were invited to participate. The final number of participants included in the baseline assessment was 502,664 (5.5% response rate). All participants completed a touch-screen questionnaire, had physical measurements taken, and provided blood, urine, and saliva samples at baseline. At baseline, the average age was 56.5 years (8.1 years) and 54.4% of the sample were women. Most participants had a white background (94.6%) and around 33% of the sample had a college or University degree. Compared to non-responders, those who were finally enrolled were older, more likely to be women and live in less socioeconomically deprived areas (Fry et al., 2017). On the other hand, Fry et al. demonstrated that compared with the general UK population, UK Biobank participants were less likely to be obese, to smoke, to report fewer self-reported health conditions and to drink alcohol daily (Fry et al., 2017). Of noted, Batty et al. highlighted that even if risk factor levels and mortality rates were more favourable in UK Biobank participants compared with the Health Surveys for England (data from 15 studies) and the Scottish Health Surveys (data from three studies), associations in the UK Biobank study seem generalisable (Batty et al., 2020). Therefore, as UK Biobank is not representative of the general population, these studies suggested that the summary statistics obtained from the UK Biobank study should not be generalised. However, effect sizes estimated from UK Biobank were generally consistent with those from population-representative cohorts, as it was shown for Batty et al. (Batty et al., 2020).

3.2 Data collections, questionnaires, physical assessment and biological samples collection

Full-scale recruitments of volunteers began in 2006 and finished in June 2010. At the baseline assessment visits, evidence about lifestyles, past medical history, medications and other health-related information was collected through self-completed touch-screen questionnaires and face to face interviews. Physical measurements and biological samples were also collected. The baseline assessment took an average of 90 minutes (Biobank, 2007).

3.2.1 Questionnaires

Baseline questionnaires focused on potential risk factors, both in adulthood and early life, for important public health concerns for the adult population were implemented.

a Sociodemographic characteristics

Age at baseline was determined from dates of birth at baseline assessment. Sex was self-reported at baseline. Socioeconomic status was ascertained in terms of material deprivation, social deprivation, socioeconomic class. Deprivation (area-based socioeconomic status) was derived from the postcode of residence, using the Townsend score (Townsend P, 1988). Ethnicity was self-reported and categorised as: white, south Asian, black, Chinese, and mixed ethnic background.

b Lifestyle

Smoking behaviour questions were adapted from previous longitudinal studies and surveys, while alcohol consumption was assessed with quantity-frequency type questions. Self-reported smoking status was categorised as never, former or current smoker. The frequency of alcohol intake was also self-reported at baseline and categorised into: daily/almost daily, 3-4 times a week, once/twice a week, 1-3 times a month, special occasions only, never and prefer not to answer. If participants' alcohol intake varied significantly, they were encouraged to include the average intake over the previous year. Data collection for this variable was performed during four instances (including the baseline assessment). Yet, only at baseline there was information for the whole dataset. This variable was not validated. The self-completed touch-screen questionnaire (completed at baseline) was used to collect the frequency of consumption of food items over the previous year to assess dietary habits. 27 questions related to dietary intake were assessed: cooked vegetables, salad/raw vegetables, fresh fruit, dried fruit, oily fish, non-oily fish, processed meat, poultry, beef, lamb, pork, cheese, milk type used, spread type, bread type, cereal intake, cereal type, salt added to food, tea, coffee, water, age when last ate meat, never eat (eggs, dairy, wheat, sugar), non-butter spread type details, hot drink temperatures, major dietary changes in the last five years and variation in diet.

Except for those variables that had a numerical answer, the other questions were categorised as: never, less than once a week, 2-4 times a week, 5-6 times a week and once or more daily. Even if many of these questions did not have a validation, UK Biobank was expecting a range of feasible responses. For instance, cup/of tea: require ≥0, ≤99, expected ≤20. As per alcohol, data collection was performed during four instances (including the baseline assessment). Yet, only at baseline, there was information for the whole dataset. Self-reported physical activity was estimated using the International Physical Activity Questionnaire, short forms which include time spent in different physical activity domains including, walking, moderate and vigorous physical activity. Other physical activity related questions were also included in the assessment questionnaire which assess physical activity levels across a comprehensive set of domains including (Biobank, 2007). Total time spent in sedentary behaviours was derived from the sum of self-reported time spent driving, using a computer and watching television. Walking pace was also self-reported and categorised into slow, average or brisk. Nonetheless, the majority of the lifestyle variables were self-reported, which are prone to recall bias and misclassification.

c Cognitive assessment

Paired-associated learning questions to assess global cognition and reaction time tests for touch-screen administration, exposure to environmental factors, self-reported information on medical history, reproductivity, disability were also assessed (Biobank, 2007).

d Medical history and other self-reported variables

Medical history (physician diagnosis of depression, stroke, angina, heart attack, hypertension, cancer, diabetes, hypertension, or other illness) was collected from the self-completed baseline assessment questionnaire.

Birth weight, breastfeeding, maternal smoking, childhood body size, residence at birth and family history of common cancers, CVD, and other medical conditions among first degree relatives were included in the questions relating to early childhood exposures and family history (Biobank, 2007).

3.2.2 Physical assessment

All measurements were taken by trained staff using standard operating procedures. Blood pressure and pulse rate were measured, in mmHg and bpm, respectively, using an Omron HEM-7015IT digital blood pressure monitor. In those participants where the electronic blood pressure monitors failed to produce a correct reading, a sphygmomanometer with an inflatable cuff - in conjunction with a stethoscope - was used. Weight (in kg) and body composition were measured, through bioimpedance (BIA), using a Tanita BC-418 MA body composition analyser. Standing and sitting height were measured in cm using a Seca 202 height measure. Waist circumference –at the level of the umbilicus – and hip circumference were measured in cm using a Wessex non-stretchable sprung tape measure. Right- and left-hand grip strengths were measured in kg using a Jamar J00105 hydraulic hand dynamometer. The dynamometer measures grip force isometrically and can be adjusted for hand size in five half-inch increments. Isometric grip force was assessed from a single 3-second maximal grip effort, separately in the right and left arms, with the participant seated upright with their elbow by their side and flexed at 90º so that their forearm was facing forwards and resting on an armrest. The average of the right and left values were expressed in absolute units (kg) and used in subsequent analyses. Muscle mass index was derived from appendicular lean muscle mass (kg) divided by height (m) squared, using the total body composition measured by BIA by trained nurses. Forced expiratory volume in one second (FEV1) was estimated in litres using a Vitalograph Pneumotrac 6800 spirometer. Bone mineral densitometry (grams/cm^2) and T-score (standard deviation [SD]) were estimated based on ultrasound measurement of the calcaneus using the Sahara Clinical Bone Sonometer (Biobank, 2007).

3.2.3 Biological samples collection

Due to the feasibility and cost of collecting and processing samples for over 500,000 individuals, only 40-50 ml of blood and a random urine sample was collected during the baseline assessment visit (Biobank, 2007). Thirty-three biomarkers were obtained using these samples: albumin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, apolipoprotein A, apolipoprotein B, direct bilirubin, total

bilirubin, urea, cholesterol, HDL cholesterol, LDL direct, triglycerides, CRP, cystatin C, glucose, haemoglobin A1c, insulin-like growth factor 1, lipoprotein A, oestradiol, testosterone, phosphate, rheumatoid factor, sex hormone-binding globulin, total protein, urate, vitamin D, calcium, sodium, systolic blood pressure and diastolic blood pressure. The first 29 were analysed from serum and packed red blood cell samples, while calcium and sodium were measured in urine.

3.2.4 Variables included as confounders in the manuscripts

A wide range of potential confounders was included in the analyses. These confounders were selected due to:

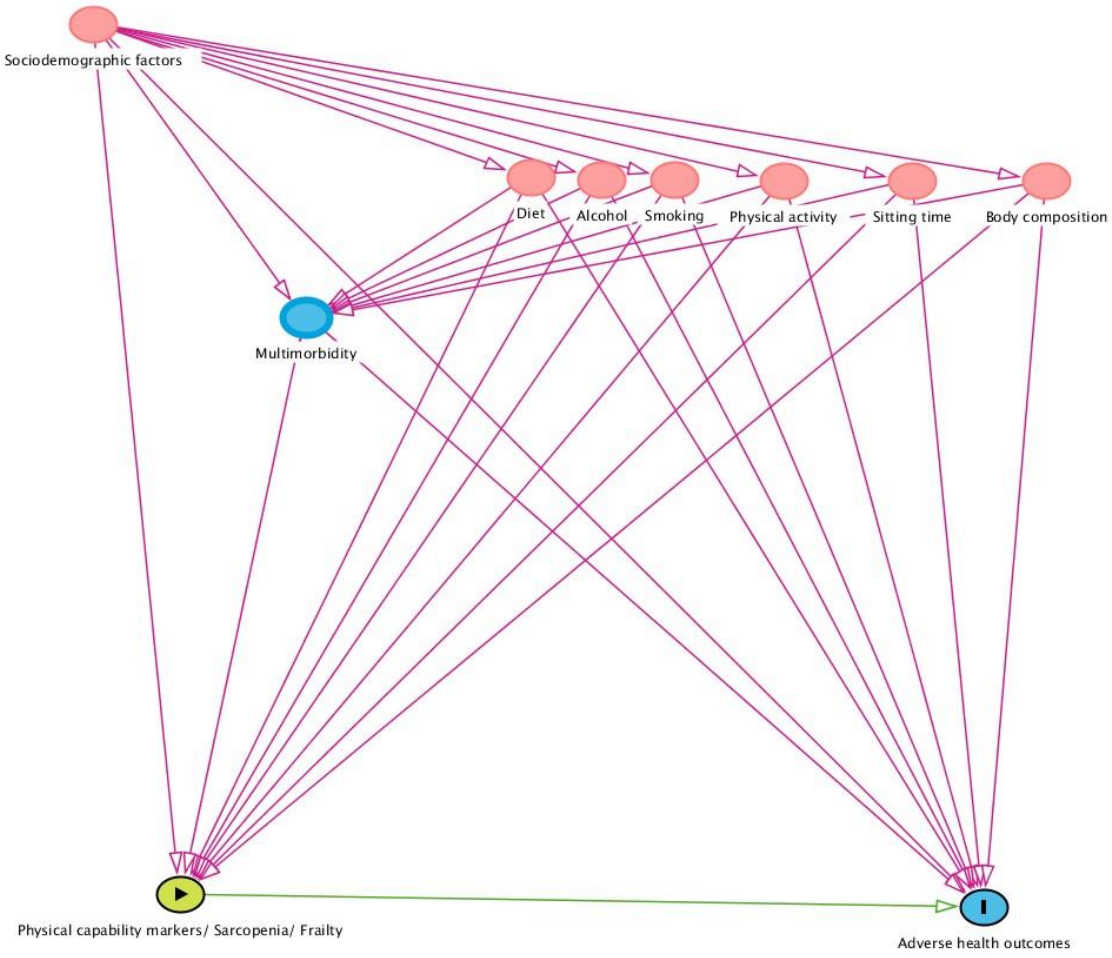
a) They were associated with the exposure

b) They were associated with the disease

c) They were no intermediate factors between the exposure and the outcome.

The list of covariates included in the six manuscripts was selected based on previous literature where they were associated with physical capability markers, sarcopenia and frailty status (Scott et al., 2016b, Docherty et al., 2020, Ho et al., 2020, Niedzwiedz et al., 2020, Lim et al., 2018, Buchman et al., 2008, Liu et al., 2017, Li et al., 2019, Hanlon et al., 2018b), as well as prognosis of the adverse health outcomes included. Therefore, they may potentially confound the relationship between the exposures and outcomes of interest. Figure 3-2 provides an overview of the associations between the exposures, the outcome, and covariates included in the analyses using a directed acyclic graph (DAG).

Figure 3-2 Directed acyclic graph (DAG) explaining the association between the exposures, the outcome, and covariates included in the thesis.



Sociodemographic factors include age, sex, deprivation and ethnicity. This is an original figure created using http://www.dagitty.net/.

3.3 Follow-up assessments

Consent was obtained at enrolment from all participants to access all their past and future medical and other health-related records. Unless participants subsequently decide to withdraw from the study, follow-up continues for everyone (Biobank, 2021b). Up to August 2021, 205 (0.04%) participants have withdrawn from UK Biobank. Individual-level record linkage is used to obtain follow-up information from health records in England and Wales, and Scotland, using the NHS number and the Community Health Index (CHI), respectively.

After completion of the baseline data collection, the first death and cancer registration data were available in June 2013, while the first hospital admission data were released in July 2014, both for the full cohort. Over the follow-up period, date and cause of death have been obtained from death certificates held

by the NHS Information Centre (England and Wales) and the NHS Central Register Scotland. Dates and causes of hospital admissions have been identified via record linkage to Health Episode Statistics (HES) (England and Wales) and the Scottish Morbidity Records (SMR01) (Scotland).

In addition to adverse health outcomes, new data have been collected and released on the following topics:

1. Repeat baseline measures (April 2013)
2. Cognitive function questionnaire (May 2014)
3. Diet questionnaire (June 2014)
4. Imaging study (started in August 2014; released in March 2016)
5. Occupational health questionnaire (February 2015)
6. Mental health questionnaire (May 2016)
7. Genotyping and imputation data (Jun 2017)
8. Active monitor data (August 2017)
9. Digestive health questionnaire (September 2017)
10. Exome sequencing project (started in January 2018; released in March 2019)
11. Whole-genome sequencing study (started in April 2018; released in October 2020)
12. Biochemistry data released (May 2019)
13. Primary care data Released (June 2019)
14. Repeat imaging (started in July 2019; released in February 2020)

15. Food preferences questionnaire (August 2019)
16. Health record linkage for coronavirus research (May 2020)
17. COVID-19 seroprevalence study (May 2020)
18. Pain questionnaire (December 2020)
19. Metabolomic data (March 2021)

3.4 Ethics

UK Biobank was approved by the NHS Northwest Multicentre Research Ethics Committee (Ref: 11/NW/0382). Data and samples are only used for ethically and scientifically approved research and confidentiality of the participants' data and samples are maintaining in all processes. Additionally, UK Biobank has the Ethics Advisory Committee (EAC) who provides advice to the UK Biobank Board and Funders on ethical issues that occurs during the maintenance, development and use for current and future activities of the UK Biobank study. The EAC was established in 2018 and replaced the Ethics and Governance Council (Biobank, 2021a)

3.5 UK Biobank today

UK Biobank is globally accessible to approved researchers and scientists undertaking vital research into the most common and life-threatening diseases. The database is regularly updated with additional biological (more assays on existing blood, urine and saliva samples) and medical data and changes in the lifestyle of participants. Data are then linked to individual's health-related records to provide a deeper understanding of how individuals experience diseases (Biobank, 2021b).

The study has shown that it is feasible to establish a population-based prospective cohort study on a large scale and make the resulting resource openly available to investigators (Allen et al., 2014). In fact, UK Biobank is a major contributor to modern medicine and treatment and has enabled several scientific discoveries (Biobank, 2021b).

Since the first open call for research applications in January 2012, more than 20,000 researchers have registered globally and over 2,800 projects are currently active, continuing to make new scientific discoveries on common and life-threatening diseases to improve public health. All these achievements have been carried out with the support of the Wellcome Trust, the MRC, the Department of Health, the Scottish Government and the Northwest Regional Development Agency (Biobank, 2021b).

Chapter 4 Papers using UK Biobank data

4.1 Physical capability markers used to define sarcopenia and their association with cardiovascular and respiratory outcomes and all-cause mortality: A prospective study from UK Biobank (Paper 2)

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Physical capability markers used to define sarcopenia and their association with cardiovascular and respiratory outcomes and all-cause mortality: A prospective study from UK Biobank

Fanny Petermann-Rocha[a,b], Frederick K Ho[a], Paul Welsh[b], Daniel Mackay[a], Rosemary Brown[b], Jason M.R. Gill[b], Naveed Sattar[b], Stuart R Gray[b,1], Jill P Pell[a,1], Carlos A Celis-Morales[a,b,c,d,*,1]

[a] Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK
[b] British Heart Foundation Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK
[c] Centre of Exercise Physiology Research (CIFE), Universidad Mayor, Chile
[d] Research Group in Education, Physical Activity and Health (GEEAFyS), Universidad Católica del Maule, Talca, Chile

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ABSTRACT

Introduction: It is unclear what combinations of physical capability markers used to define sarcopenia have the strongest associations with health outcomes.
Aim: To compare the associations between different combinations of physical capability markers of sarcopenia with cardiovascular and respiratory outcomes and all-cause mortality.
Study design: 469,830 UK Biobank participants were included in this prospective study. Four groups were derived based on combinations of three physical capability markers used to define sarcopenia or severe sarcopenia: gait speed, grip strength and muscle mass. Outcomes studied were all-cause mortality, as well as incidence and mortality from cardiovascular disease (CVD), respiratory disease and chronic obstructive pulmonary disease (COPD).
Results: All combinations of physical capability markers used to define sarcopenia or severe sarcopenia identified individuals at increased risk of respiratory disease and all-cause mortality. However, the definition most strongly associated with a wide range of adverse health outcomes was the combination of slow gait speed plus low muscle mass, followed by severe sarcopenia, and the combination of slow gait speed plus low grip strength. The current definition of sarcopenia (low grip strength plus low muscle mass) had the weakest associations with all-cause (HR: 1.35 [95% CI: 1.07 to 1.71]) and respiratory mortality (HR: 1.88 [95% CI: 1.15 to 3.10]), as well as respiratory disease (HR: 1.38 [95% CI: 1.11 to 1.73]) and COPD incidence (HR: 2.08 [95% CI: 1.14 to 3.79]).
Conclusions: Associations of sarcopenia with adverse outcomes were strongest when sarcopenia was defined as slow gait speed plus low muscle mass, followed by severe sarcopenia, suggesting that this combination of physical capability markers should be still considered in the diagnosis of sarcopenia.

1. Introduction

Low grip (muscle) strength, low muscle mass and slow walking pace (gait speed) have been shown to be strong independent predictors of morbidity and mortality in middle-aged and old-aged populations [1–3]. These markers of physical capability are all known to decline after the age of ~35 years, and with the rapid growth of ageing populations, the number of individuals with low levels of physical capability is also expected to be increased rapidly. This, in turn, will increase the number of people who are at higher risk of developing non-communicable diseases [4]. Although markers of physical capability are generally investigated in isolation, combinations of these predictors are used to define conditions, such as sarcopenia. In 1989, Irwin Rosenberg was the first to recognise the age-related decline in lean body mass and coined the term “sarcopenia” (from the Greek ‘sarx’ for flesh + ‘penia’ for loss) [5,6]. Nowadays, sarcopenia is defined as a complex syndrome characterised by a progressive loss of muscle strength along with a higher risk of disability and reduction in quality of life [7] and it is one

* Corresponding author at: B.H.F. Glasgow Cardiovascular Research Centre, Institute of, Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, G12 8TA, UK.
E-mail address: carlos.celis@glasgow.ac.uk (C.A. Celis-Morales).
[1] SRG, JPP, CACM contributed equally to this work and are joint senior authors.

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of the 150 musculoskeletal conditions that contribute to disability worldwide [8]. Furthermore, the International Classification of Disease (ICD-10) has recognised sarcopenia as an independent condition since September 2016 [9].

Although sarcopenia has been clinically recognised as a frailty marker, a global consensus on an operational definition has not been reached. This could explain the wide variation in reported sarcopenia prevalence, ranging from 3% to 30% for older adults aged 60 years or older [10]. In the last ten years, there have been several attempts to standardise the operational definition and cut-off points for sarcopenia, most of which have used combinations of measures of muscle mass, muscle strength and gait speed [11–13]. The most recent statement, by the European Working Group on Sarcopenia in Older People 2019 (EWGSOP2), has proposed that sarcopenia should be defined as low muscle strength plus low muscle mass, with severe sarcopenia including the addition of slow gait speed [7].

Although the associations between sarcopenia and all-cause mortality, chronic obstructive pulmonary disease (COPD) [14,15], and cardiovascular diseases (CVD) [16,17] have been previously studied, it is unclear whether a different combination of physical capability markers results in a stronger association with health outcomes. The aim of this study, therefore, was to compare the association of different combinations of physical capability markers used to define sarcopenia with cardiovascular and respiratory outcomes as well as all-cause mortality in UK Biobank, a large prospective cohort study of middle-aged adults.

2. Methods

Between April 2007 and December 2010, UK Biobank recruited over 500,000 participants (5.5% response rate), aged 37 to 73 years from the general population [18]. Participants attended one of 22 assessment centres across England, Wales and Scotland [19,20] where they completed a touch-screen questionnaire, had physical measurements taken, and provided biological samples, as described in detail elsewhere [19,20].

The outcomes in the current study were all-cause mortality and incidence and mortality for CVD and respiratory diseases, and the exposures were different combinations of physical capability markers used to define sarcopenia. Due to ethnic differences in the reference values for these markers, inclusion in the study was restricted to participants of a white European background.

2.1. Procedures

Date of death was obtained from death certificates held by the National Health Service (NHS) Information Centre (England and Wales) and the NHS Central Register Scotland (Scotland). Dates and causes of hospital admissions were identified via record linkage to Health Episode Statistics (HES) (England and Wales) and the Scottish Morbidity Records (SMR01) (Scotland). Details of the linkage procedure can be found at http://www.ic.nhs.uk/services/medical-research-information-service. Follow-up data started in March 2008 and were available until 31 January 2018 for participants in England or Wales, and 30 May 2017 for participants in Scotland. Follow-up was censored on these for deaths.

Incident CVD was defined as a hospital admission or death with ICD10 (International Classification of Diseases, 10th revision) codes I60, I61, I63, I64, I21, I21.4, and I21.9. Respiratory disease was defined as ICD10 codes J09-J98, and COPD was defined as ICD10 code J44.

2.2. Physical capability markers groups

The 2019 EWGSOP2 statements define sarcopenia as the combination of low grip strength plus low muscle mass and severe sarcopenia as both in combination with slow gait speed [7]. To compare the association of different combinations of physical capability markers used to define sarcopenia with the health outcomes of interest, we derived four groups, two of which were the current EWGSOP2 definition of sarcopenia and severe sarcopenia and the other two being the remaining combinations of physical capability markers (Supplementary Fig. 1). The four groups were therefore as follows: a) slow gait speed plus low grip strength only (gait-grip group), b) slow gait speed plus low muscle mass only (gait-muscle group), c) low grip strength plus low muscle mass only (grip-muscle group or current sarcopenia definition), and d) low grip strength plus low muscle mass plus slow gait speed (severe sarcopenia). The four groups were mutually exclusive.

Details about measures and the cut-off points for each physical capability marker as well as other sociodemographic, lifestyle and health measures are available in supplementary methods.

2.3. Statistical analyses

Associations of the combination of physical capability markers with cause-specific incidence and mortality were investigated using Cox-proportional hazard models (individuals with a normal range for all physical capability markers were used as the reference group). Associations between individual physical capability markers and cause-specific incidence and mortality are also reported. The results are reported as hazard ratios (HR) and their 95% confidence intervals (CIs). The proportional hazard assumption was checked by tests based on Schoenfeld residuals. All analyses were performed using a 2-year landmark analysis. The models for CVD and respiratory incidence and mortality were performed excluding participants with medical diagnoses of CVD, or respiratory disease, respectively.

We produced three models that included an increasing number of covariates: “model 1” (minimally adjusted) included sociodemographic covariates (age, sex and deprivation); “model 2” (maximally adjusted) was adjusted as in model 1, but also included prevalent diseases (hypertension, diabetes, depression, major illness, cancer, as well as CVD and respiratory disease when these were not the outcome) and lifestyle factors (smoking, sleep duration, waist circumference [WC], total physical activity, total discretionary sedentary time and dietary intake including alcohol, fruit and vegetable, oily fish, red meat and processed meat intake). Sensitivity analyses, where all 71,778 participants with comorbidities at baseline (such as CVD, cancer, COPD, diabetes and depression) were excluded from the analyses irrespective of the outcome, were conducted to evaluate the association between combinations of physical capability markers and health outcomes among apparently “healthy” individuals (model 3).

To investigate whether the association between combinations of physical capability markers used to define sarcopenia and health outcomes differed by age and sex, we fitted a multiplicative interaction term between sarcopenia and these sociodemographic variables. Where these were statistically significant, subgroup analyses were performed, stratified by age category (below and above 60 years) and sex as appropriate.

All analyses were performed using STATA 16 statistical software (StataCorp LP). P-values below 0.05 were regarded as statistically significant.

3. Results

Of the 502,535 participants recruited to UK Biobank, 469,830 (93.5%) had full data available on exposure, outcomes and covariates. The mean follow-up period was 6.9 years (interquartile range: 6.3 to 7.5) after the landmark period for all-cause and cause-specific mortality, and 6.0 years (interquartile range: 5.4 to 6.7) for cardiovascular and respiratory disease incidence. Over the follow-up period, 14,786 (3.1%) participants died; 2548 (0.5%) from CVD and 2577 (0.5%) from respiratory diseases. Additionally, 19,332 (4.1%) participants developed cardiovascular disease, 16,105 (3.4%) respiratory disease, and 1605 (0.3%) COPD. The specific numbers of deaths/events for each

Table 1
Baseline characteristics by different combinations of physical capability markers.

	Without sarcopenia (normal)	Gait-grip group	Gait-muscle group	Grip-muscle group *	Severe Sarcopenia
Socio-demographics					
Total n	394,583	8731	564	1678	424
Sex (Female), n (%)	207,782 (52.7)	5378 (61.6)	505 (89.5)	1604 (95.6)	386 (91.0)
Age (years), mean (SD)	56.1 (8.1)	60.2 (6.8)	62.0 (5.9)	63.0 (5.3)	62.0 (6.3)
Age categories, n (%)					
< 56 years	173,200 (43.9)	1953 (22.4)	77 (13.7)	167 (9.9)	67 (15.8)
56 to 65 years	169,368 (42.9)	4589 (52.5)	294 (52.1)	855 (51.0)	198 (46.7)
> 65 years	52,037 (13.2)	2192 (25.1)	193 (34.2)	656 (39.1)	159 (37.5)
Deprivation, n (%)					
Lower	141,660 (35.9)	1748 (20.0)	150 (26.6)	542 (32.3)	114 (26.9)
Middle	135,979 (34.5)	2412 (27.7)	184 (32.6)	611 (36.5)	136 (32.1)
Higher	116,509 (29.6)	4559 (52.3)	230 (40.8)	524 (31.2)	174 (41.0)
Smoking status, n (%)					
Never	215,924 (54.9)	3750 (43.3)	236 (41.9)	993 (59.5)	200 (47.4)
Previous	138,609 (35.2)	3414 (39.5)	190 (33.8)	529 (31.7)	133 (31.5)
Current	38,877 (9.9)	1490 (17.2)	137 (24.3)	147 (8.8)	89 (21.1)
Obesity-related markers					
Height (metres), mean (SD)	1.69 (0.09)	1.64 (0.09)	1.63 (0.08)	1.61 (0.07)	1.62 (0.08)
Body weight (kg), mean (SD)	78.0 (15.2)	83.8 (18.6)	62.4 (11.0)	59.6 (8.3)	61.3 (10.3)
BMI, mean (SD)	27.1 (4.4)	31.2 (6.4)	23.6 (4.0)	22.9 (2.9)	23.5 (3.5)
BMI Categories, n (%)					
Underweight (<18.5 kg.m^{-2})	1480 (0.4)	43 (0.5)	41 (7.3)	102 (6.1)	28 (6.6)
Normal weight (18.5-24.9 kg.m^{-2})	131,731 (33.5)	1268 (14.7)	347 (61.5)	1171 (69.8)	274 (64.6)
Overweight (25.0 to 29.9 kg.m^{-2})	173,553 (44.1)	2750 (31.9)	147 (26.1)	392 (23.3)	106 (25.0)
Obese (≥ 30.0 kg.m^{-2})	86,692 (22.0)	4560 (52.9)	29 (5.1)	13 (0.8)	16 (3.8)
Waist Circumference (cm)	89.7 (12.9)	99.2 (15.2)	81.7 (10.6)	78.2 (8.8)	81.4 (10.2)
Central Obesity, n (%)	121,990 (31.0)	5638 (64.7)	120 (21.3)	224 (13.4)	99 (23.4)
% Body fat, mean (SD)	30.7 (8.3)	37.2 (9.0)	37.0 (8.1)	36.1 (6.4)	36.9 (7.5)
Fitness and Physical activity					
Total PA (MET-h.week^{-1}), mean (SD)	3018.2 (3286.7)	1889.2 (2359.2)	1821.2 (2214.9)	2609.6 (2744.5)	1560 (1904.5)
Cardiorespiratory fitness (MET), mean (SD)	9.8 (2.8)	8.0 (2.5)	7.2 (1.7)	7.6 (1.8)	7.6 (1.4)
Grip Strength (kg), mean (SD)	32.5 (10.3)	14.5 (6.2)	22.2 (5.8)	12.7 (3.7)	10.9 (5.0)
TV viewing (h.day^{-1}), mean (SD)	2.7 (1.5)	4.0 (2.2)	3.8 (2.0)	3.2 (1.7)	4.0 (2.1)
Total Sedentary behaviour (h.day^{-1}), mean (SD)	5.0 (2.2)	5.6 (2.8)	5.3 (2.5)	4.6 (2.0)	5.2 (2.4)
Health status, n (%)					
Diabetes	15,062 (3.8)	1470 (17.0)	15 (2.7)	28 (1.7)	14 (3.3)
CVDs	106,513 (27.0)	5022 (57.8)	232 (41.3)	443 (26.5)	176 (41.6)
High blood pressure	88,983 (22.6)	3046 (35.0)	163 (29)	343 (20.5)	110 (26.0)
Fractures/ broken bones last 5 years	35,648 (9.1)	1350 (15.6)	104 (18.6)	52 (15.1)	87 (20.6)
Falls, n (%)					
No falls	326,585 (82.9)	4256 (49.2)	351 (62.3)	1189 (70.9)	230 (54.4)
One fall	49,217 (12.5)	1515 (17.5)	99 (17.6)	354 (21.2)	87 (20.6)
More than one fall	18,288 (4.6)	2886 (33.3)	113 (20.1)	133 (7.9)	106 (25.1)

Gait-grip group: slow gait speed plus low grip strength only. Gait-muscle group: slow gait speed plus low muscle mass only. Grip-muscle group or current sarcopenia definition*: low grip strength plus low muscle mass only. Severe sarcopenia: having low grip strength plus low muscle mass plus slow gait speed. BMI: body mass index; n: number; PA: physical activity; MET: metabolic-equivalent; TE: total energy; SD: standard deviation; CVD: cardiovascular disease.

physical capability marker and their combinations are presented in the Supplementary Table 1.

The study population's characteristics by the four physical capability markers groups are summarised in Table 1. Overall, in comparison to people without any form of sarcopenia, people with any combination of physical capability markers were older, more deprived and more likely to be female. For all groups, other than the grip-muscle group (current sarcopenia definition), participants were more likely to be current smokers and were less physically active. Those defined by low grip strength plus low muscle mass had the lowest body weight, and WC and those defined by slow gait speed plus low grip strength had the highest prevalence of obesity, central obesity, diabetes, CVD and hypertension. However, people with severe sarcopenia had the highest prevalence of fractures and falls in the last 5-years and 1-year, respectively. The main characteristics of the population by individual physical capability markers (gait speed or grip strength or muscle mass) are presented in Supplementary Table 2.

The associations between the individual physical capability markers used to define sarcopenia and health outcomes are presented in Fig. 1 and Supplementary Table 3. These results show that slow gait speed had the strongest associations with health outcomes. Low grip strength and low muscle mass were associated with similar risk estimate for outcomes except for COPD, whereas individuals with low muscle mass had similar risks to those observed for slow gait speed.

As shown in Fig. 2, severe sarcopenia had the strongest association with all-cause mortality (HR: 3.02 [95% CI: 2.34 to 3.91]), whilst the combination of slow gait speed plus low muscle mass (gait-muscle group) showed the strongest association with CVD (HR: 3.47 [95% CI: 2.03 to 5.91]), and respiratory mortality (HR: 5.73 [95% CI: 3.83 to 8.57]). Severe sarcopenia and the combination of slow gait speed plus low grip strength were also associated with CVD and respiratory mortality, but the magnitude of these associations were lower in comparison to the gait-muscle group (Fig. 2). However, the combination of low grip strength plus low muscle mass, i.e. the current sarcopenia definition, had the lowest magnitude of associations compared to other combinations of physical capability markers. Individuals with low grip plus low muscle mass had a 35% and 88% higher risk of all-cause and respiratory diseases mortality compared to the reference group. No

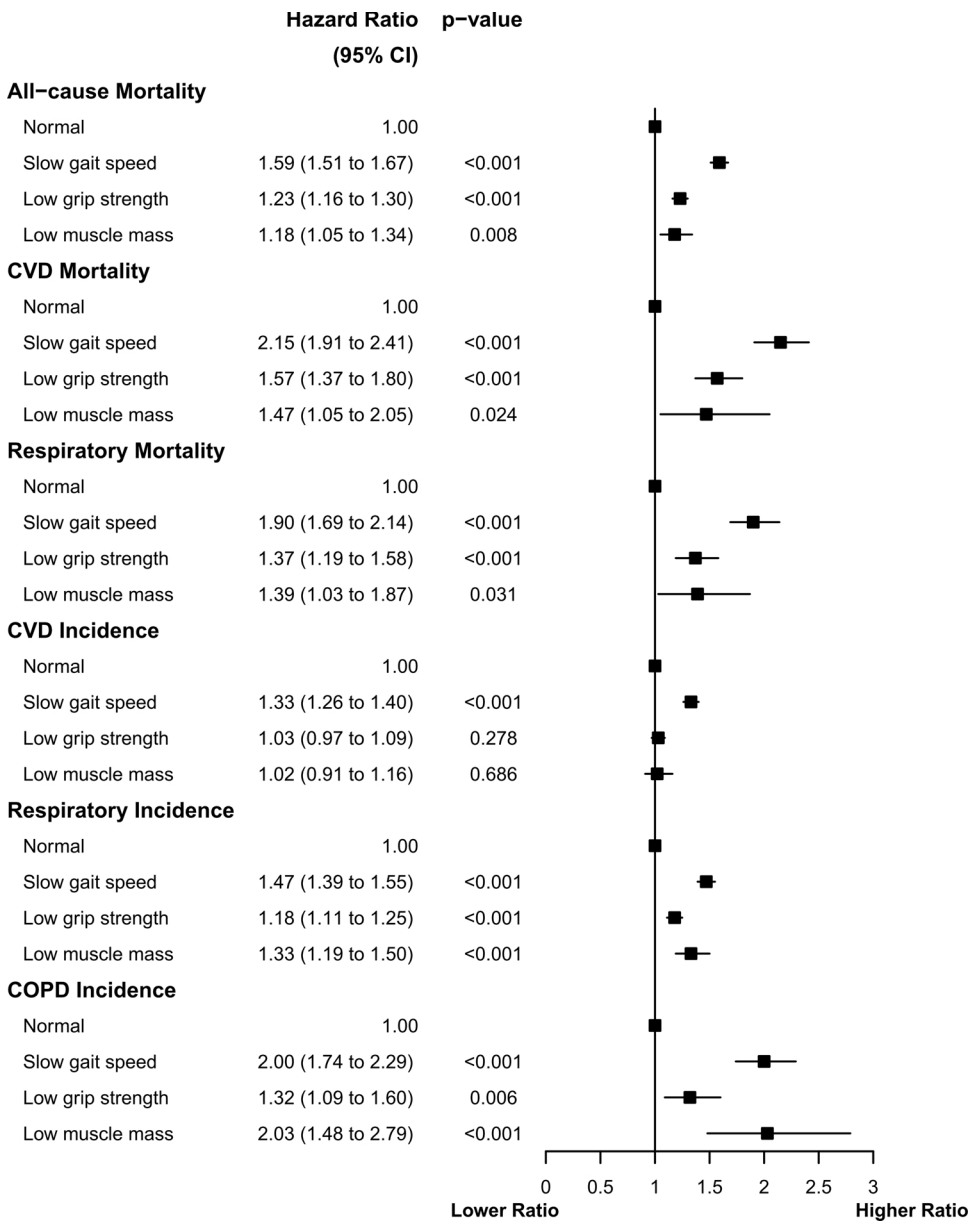

Fig. 1. Association of physical capability markers with incidence and mortality.
Data presented as adjusted hazard ratio (HR) and its 95 % confidence interval (95 % CI) by different combinations of physical capability markers. People with a normal range for all physical capability markers were used as the reference group for the analyses.
All analyses were conducted using a 2-year landmark analyses and for Model 2, were adjusted for age, sex, deprivation, smoking status, sleep duration, WC, total physical activity, discretionary sedentary time, dietary intake (alcohol, fruit and vegetable, oily fish, red meat and processed meat intake), hypertension, diabetes, depression, comorbidities, cancer, as well as CVD and respiratory disease when these were not the outcome.

associations were observed between this group and CVD mortality.

All combinations of physical capability markers were associated with a higher incidence risk of respiratory diseases (Fig. 3), with the strongest association observed for those classified as severely sarcopenic (HR: 2.74 [95% CI: 2.06 to 3.65]). In terms of COPD incidence, the gait-muscle group had 4.16 times higher risk than people with normal physical capability markers (HR: 4.16 [95% CI 2.59 to 6.70]), followed by those with severe sarcopenia (HR: 3.85 [95% CI: 2.24 to 6.62]) and the gait-grip group (HR: 2.42 [95% CI: 2.01 to 2.91]). A lower magnitude of association was found for CVD incidence in the gait-muscle group (HR: 1.62 [95% CI: 1.20 to 2.17]), followed by the gait-grip group (HR: 1.38 [95% CI: 1.27 to 1.50]). However, no associations with CVD were found for the severe sarcopenia group and the grip-muscle group. When participants with major comorbidities at baseline were excluded from the analyses, the magnitude of the associations with all health outcomes increased for the gait-muscle group and the gait-grip group.

There were significant interactions between age and the gait-grip group for all-cause mortality, and respiratory mortality and incidence, and between age and severe sarcopenia in relation to CVD incidence. In these cases, the magnitude of the associations was slightly bigger for younger individuals compared to older individuals (Supplementary Table 6). Interactions were also observed in relation to sex (Supplementary Table 7). Associations for all-cause mortality and respiratory incidence with all physical capability groups were stronger in men than women. However, women had stronger associations with CVD mortality for all physical capability groups (except grip-muscle group) (Supplementary Table 7).

4. Discussion

Sarcopenia is a progressive and complex disorder associated with the development of a number of diseases and contributes to frailty, disability, morbidity and mortality. As detailed previously, there are many diagnostic criteria used to define sarcopenia [11–13]. In this study, we used the three physical capability markers (gait speed, grip strength and muscle mass) used in EWGSOP2 to derive four different combinations of physical capability markers, including the current definition of sarcopenia and severe sarcopenia [7].

The main finding of this study was that all combinations of physical

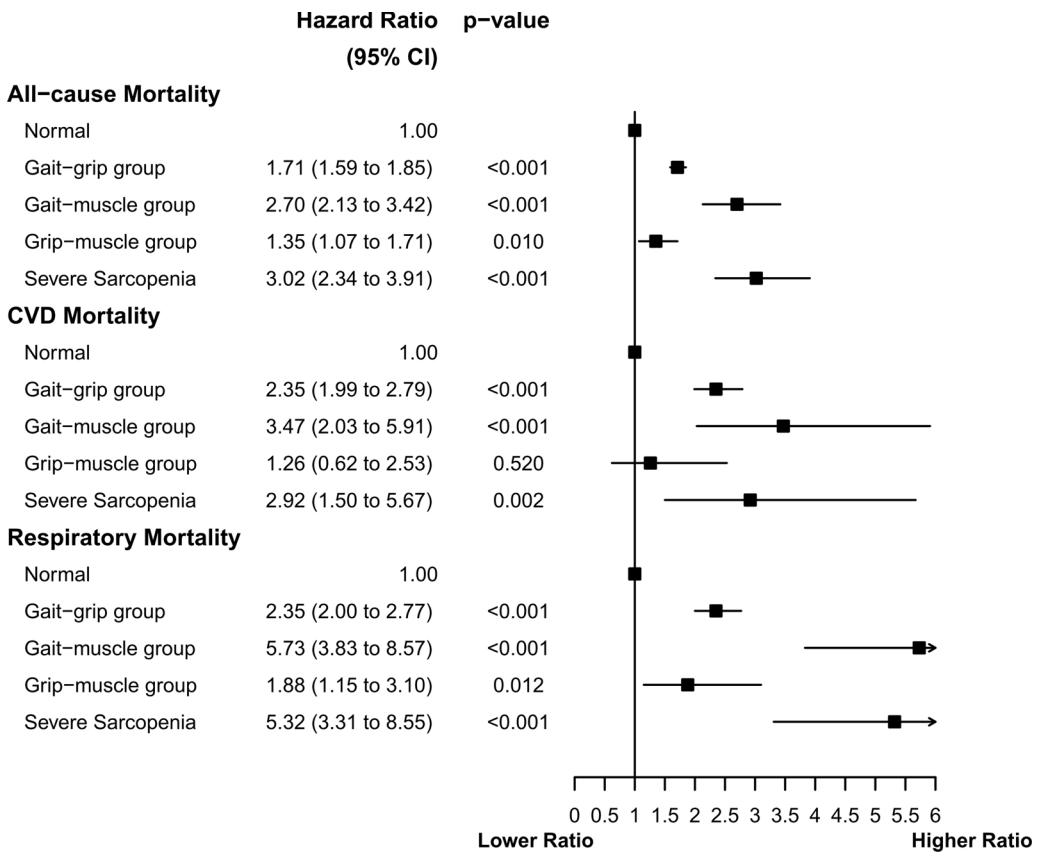

Fig. 2. Association between different combinations of physical capability markers and all- and cause-specific mortality.
Data presented as adjusted hazard ratio (HR) and its 95 % confidence interval (95 % CI) by different combinations of physical capability markers.
People with a normal range for all physical capability markers were used as the reference group for the analyses.
Gait-grip group: having slow gait speed plus low grip strength only. Gait-muscle group: having slow gait speed plus low muscle mass only. Grip-muscle group or current sarcopenia definition: having low grip strength plus low muscle mass only. Severe sarcopenia: having low grip strength plus low muscle mass plus slow gait speed.
All analyses were conducted using a 2-year landmark analyses and for Model 2 were adjusted for age, sex, deprivation, smoking status, sleep duration, WC, total physical activity, discretionary sedentary time, dietary intake (alcohol, fruit and vegetable, oily fish, red meat and processed meat intake), hypertension, diabetes, depression, comorbidities, cancer, as well as CVD and respiratory disease when these were not the outcome.

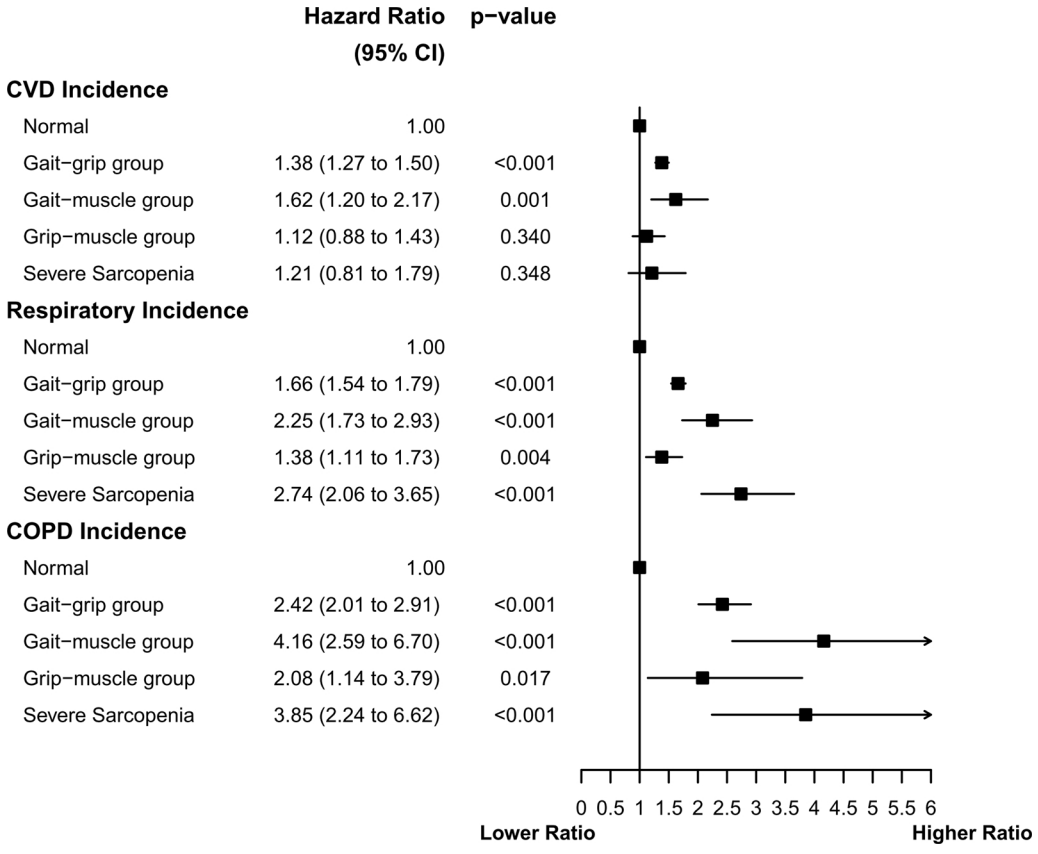

Fig. 3. Association between different combinations of physical capability markers and cause-specific incidence.
Data presented as adjusted hazard ratio (HR) and its 95 % confidence interval (95 % CI) by different combinations of physical capability markers. People with a normal range for all physical capability markers were used as the reference group for the analyses.
Gait-grip group: having slow gait speed plus low grip strength only. Gait-muscle group: having slow gait speed plus low muscle mass only. Grip-muscle group or current sarcopenia definition: having low grip strength plus low muscle mass only. Severe sarcopenia: having low grip strength plus low muscle mass plus slow gait speed.
All analyses were conducted using a 2-year landmark analyses and for Model 2 were adjusted for age, sex, deprivation, smoking status, sleep duration, WC, total physical activity, discretionary sedentary time, dietary intake (alcohol, fruit and vegetable, oily fish, red meat and processed meat intake), hypertension, diabetes, depression, comorbidities, cancer, as well as CVD and respiratory disease when these were not the outcome.

capability markers used to define sarcopenia or severe sarcopenia identified individuals at increased risk of respiratory disease and all-cause mortality. However, the definition most strongly associated with a wide range of adverse health outcomes was the combination of slow gait speed plus low muscle mass, followed by severe sarcopenia, and the combination of slow gait speed plus low grip strength. Individuals with these characteristics were at significantly higher risk of developing CVD, respiratory disease and COPD incidence as well as all-cause, CVD and respiratory mortality. Nevertheless, the new EWGSOP2 guidelines proposed that low muscle strength (or grip strength) plus low muscle mass should be used to diagnose sarcopenia [7].

Whilst the loss of muscle mass was the first and is the most widely recognised characteristic of sarcopenia, strength and gait may be better measures of sarcopenia severity and its risk to health. In fact, Bachettini el al. showed that gait speed was the only criterion independently associated with mortality in the definition of sarcopenia using the EWGSOP2 definition (76 % higher risk of mortality) [21] and Ganna & Ingelsson demonstrated that the self-reported walking pace – along with the self-reported health – was the strongest predictor of mortality in both men and women [22]. Therefore, a definition, and diagnosis, based on slow gait speed and/or low grip strength may be more meaningful for use in clinical practice and research since both are quick tests for the sarcopenia diagnosis. In particular, slow gait speed and low grip strength appeared to be the main drivers of the observed associations with health outcomes more than low muscle mass. In fact, Sim et al. demonstrated that different definitions of sarcopenia were not associated with falls-related hospitalisations in older Australian women; however, when each physical capability marker was examined individually, both grip strength and physical function, but not muscle mass, were associated with falls-related hospitalisation [23]. Comparable results were observed for mortality in the same cohort [24]. However, despite its potential as a diagnostic tool, grip strength may not respond to treatment well, and its use in the continual monitoring of sarcopenic patients can be limited [25].

In terms of muscle mass, we should note that other measurements on muscle mass could provide a better prognostic value. For instance, Cawthon et al. highlighted that when muscle mass was determined by creatine concentration, people in the lowest quartile of muscle mass had a higher risk of mortality for all-cause, cancer and CVD [26]. However, this method is still not recognised as a measurement of muscle mass by the EWGSOP2 [7].

In our study, the current definition of sarcopenia and severe sarcopenia were both more prevalent in women; however, were associated with a stronger risk of adverse health outcomes in men. Women experience an earlier loss of muscle mass and a major decline in sex-specific hormones that are important for the muscle maintenance, and therefore they could be more susceptible to experiencing sarcopenia early in life; however, men have a greater decline in skeletal muscle mass with advancing age [27]. This muscle loss is accompanied by a significant decrease in muscle strength which is intensified when there is poor nutrition (e.g. low intake of protein) and lower levels of physical activity [27].

Sarcopenia was initially considered a disease of ageing but is now understood to begin before older ages [7]. In our study, we demonstrated that the associations were slightly stronger in participants aged < 60 years. Our findings, therefore, reinforce the need for earlier detection of sarcopenia and altered physical capability markers in clinical practice.

In terms of health outcomes, other studies have identified similar associations between different combinations of physical capability markers used to define sarcopenia and health outcomes [14–17]. Zhang et al. showed that sarcopenia was associated with an increased risk for all-cause mortality among older nursing home residents (HR: 1.86 [95% CI: 1.42 to 2.45]) [28]. By contrast, Kittiskulnam et al. determined that neither sarcopenia nor low muscle mass were a good predictor of mortality among patients on haemodialysis; however, when gait speed or grip strength were used, a positive association was identified [29]. These findings are similar to our study because, although we found a positive association with a different classification of sarcopenia, low grip strength and slow gait speed, no associations between low muscle mass (the previously more important criterion) and the outcomes were identified.

Finally, the majority of the strongest associations were with respiratory outcomes. It has been postulated that both ageing and sarcopenia may be associated with reduced power of the diaphragm muscle, which, in turn, impairs expulsive airway clearance [30]. Jones et al., after studying 622 stable patients with COPD, determined that sarcopenia, defined by EWGSOP criteria, has an impact on the functional and health status in these patients, specifically those with reduced functional performance, exercise capacity and quality of life [14].

4.1. Strengths and limitations

UK Biobank is not representative of the UK population in terms of lifestyle and prevalent disease [31]. Therefore, whilst estimates of effect sizes can be generalised, summary statistics should not be. However, the use of UK Biobank allowed us to test our research question in a very large general population cohort as well as the opportunity to work with information collected using validated and standardised methods. On the other hand, dual-energy X-ray absorptiometry (DXA) is the most commonly used method for deriving muscle mass because it can provide a reproducible estimation of the appendicular skeletal muscle mass in a few minutes. In the UK Biobank study, muscle mass was measured using bioimpedance, but this method has been shown to correlate well with DXA ($r = 0.868$, $p < 0.0001$). Finally, walking pace was self-reported. Whilst this is potentially a source of bias, it is more easily replicated in clinical practice. Future studies are needed to establish whether it is a reasonable proxy of objectively measured gait speed.

In conclusion, even though different combinations of physical capability markers were associated with CVD, respiratory, COPD incidence and all-cause, CVD and respiratory mortality, there were differences in the strength of association. Notably, the EWGSOP2 definition was not significantly associated with both fatal and nonfatal CVD. The strongest associations were observed for the combination of slow gait speed plus low muscle mass. These findings suggest that slow gait speed, which was omitted in defining sarcopenia in the current EWGSOP2, may be an important physical capability marker of sarcopenia and its use should not be limited to the definition of severe sarcopenia.

5. Contributors

Fanny Petermann-Rocha contributed to the conception and design of the study, advised on all statistical aspects, interpreted the data, performed the literature search and the analyses, and contributed to critical revision of the article.

Frederick K Ho contributed to critical revision of the article.

Paul Welsh contributed to critical revision of the article.

Daniel Mackay contributed to critical revision of the article.

Rosemary Brown contributed to critical revision of the article.

Jason M. R. Gill contributed to critical revision of the article.

Naveed Sattar contributed to critical revision of the article.

Stuart R Gray contributed to the conception and design of the study, advised on all statistical aspects, interpreted the data, supported the analyses, and contributed to critical revision of the article.

Jill P Pell contributed to the conception and design of the study, advised on all statistical aspects, interpreted the data, supported the analyses, and contributed to critical revision of the article.

Carlos A Celis-Morales contributed to the conception and design of the study, advised on all statistical aspects, interpreted the data, supported the analyses, and contributed to critical revision of the article.

All authors approved the final draft for submission. Stuart R Gray,

Jill P Pell and Carlos A Celis-Morales contributed equally to this work and are joint senior authors. Carlos A Celis-Morales is the guarantor.

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Ethical approval

UK Biobank was approved by the North West Multi-Centre Research Ethics Committee (REC reference: 11/NW/03820) and all participants provided written informed consent to participate in the UK Biobank study. The study protocol is available online (http://www.ukbiobank.ac.uk/). This work was conducted under the UK Biobank application number 7155.

Research data (data sharing and collaboration)

All UK Biobank information is available online on the webpage www.ukbiobank. Data access are available through applications. This research was conducted using the application number 7155.

Provenance and peer review

This article has undergone peer review.

Conflict of intereset

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.maturitas.2020.04.017.

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4.1.1 Appendix B

4.1.2 Physical capability markers

Grip strength was measured using a Jamar J00105 hydraulic hand dynamometer. Isometric grip force was assessed from a single 3-second maximal grip effort, separately in the right and left arms, with the participant seated upright with their elbow by their side and flexed at 90º so that their forearm was facing forwards and resting on an armrest. The average of the right and left values were expressed in absolute units (kg) and used in subsequent analyses. The cut-off points used to define low grip strength was <27 kg in men and <16 kg in women (Cruz-Jentoft et al., 2019a).

Muscle mass index was derived from appendicular lean muscle mass (kg) divided by height (m) squared. To estimate the appendicular lean muscle mass, the Janssen equation was utilized (Janssen et al., 2000) using the total body composition measured by bioimpedance by trained nurses. The cut-off points used to define low muscle mass were <7.0 $kg.m^{-2}$ in men and < 5.5 $kg.m^{-2}$ for women (Cruz-Jentoft et al., 2019a). Finally, self-reported walking speed was utilized as a proxy of gait speed. Participants categorised their usual walking pace as slow, average or brisk and, in order to derive a proxy for the EWGSOP-2019 definition of walking pace, this was then dichotomised into slow or normal (average or brisk pace).

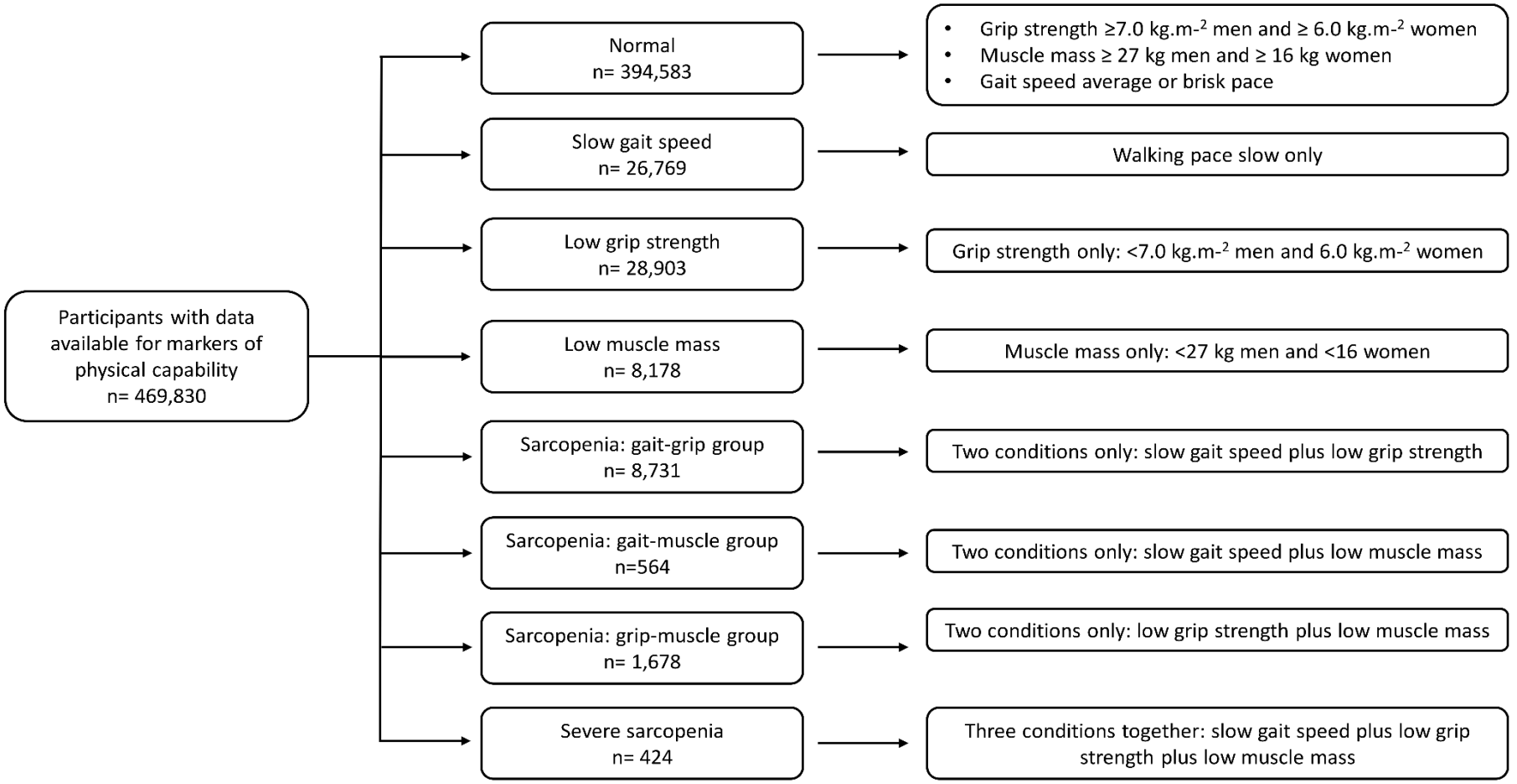
Socio-demographics, lifestyle and health measures

Age was calculated from dates of birth and baseline assessment. Area-based socioeconomic status was derived from the postcode of residence, using the Townsend score (Townsend P, 1988). Physical activity was based on self-reported data, collected using the IPAQ short form (Guo et al., 2015) and total physical activity was computed as the sum of walking, moderate and vigorous activity, measured as metabolic equivalents (MET-hours/week). Total time spent in sedentary behaviours was derived from the sum of self-reported time spent driving, using a computer and watching television. Dietary information was collected via the Oxford WebQ; a web-based 24-hour recall questionnaire which was developed specifically for use in large population studies (Liu et al., 2011,

Anderson et al., 2017). Self-reported smoking status was categorised as never, former or current smoker. Fractures or broken bone in the last 5-years and falls in the last year were self-reported via touchscreen at baseline. Medical history (physician diagnosis of depression, stroke, angina, heart attack, hypertension, cancer, diabetes, hypertension, COPD or other illness) was collected from the self-completed, baseline assessment questionnaire. Height and body weight were measured by trained nurses during the initial assessment. BMI was calculated as (weight/height^2) and the WHO criteria were applied to categorise participants into underweight <18·5 kg.m^{-2}, normal weight 18·5-24·9 kg.m^{-2}, overweight 25·0-29·9 kg.m^{-2} and obese ≥30·0 kg.m^{-2}(WHO, 2000). Waist circumference was used to derive central obesity, defined as ≥88 cm for women and ≥102 cm for men(WHO, 2000). Further details of these measurements can be found in the UK Biobank online protocol (http://www.ukbiobank.ac.uk).

Ethical Approval

UK Biobank was approved by the North West Multi-Centre Research Ethics Committee and all participants provided written informed consent to participate in the UK Biobank study. The study protocol is available online (http://www.ukbiobank.ac.uk/). This work was conducted under the UK Biobank application number 7155.



4.1.3 Supplementary Figure 1. Operational classification and cut-off points for different combinations of physical capability markers.

4.1.4 Table S1. Specific death/event by different combination of physical capability markers

	Normal		Slow gait speed		Low grip strength		Low muscle mass		Gait-grip group		Gait-muscle group		Sarcopenia (grip-muscle group)		Severe sarcopenia	
	Total n	death-events	Total n	death-events	Total n	death-events	Total n	death-events	Total n	death-events	Total n	death-events	Total n	death-events	Total n	death-events
All-cause mortality	359,656	10,142	23,283	2,132	26,439	1,219	7,433	261	7,553	828	497	71	1,528	73	369	60
CVD mortality	351,020	1,564	21,046	489	25,404	241	7,302	37	6,632	186	471	14	1,476	8	338	9
Respiratory mortality	356, 808	1,586	22,103	455	26,052	227	7,069	46	7,069	204	441	25	1,482	16	328	18
CVD incidence	346,973	14,866	20,378	2,028	25,012	1,340	7,227	265	6,385	695	459	45	1,454	68	332	25
Respiratory incidence	354,271	11,527	21,598	2,000	25,773	1,276	7,230	315	6,859	804	432	57	1,465	78	312	48
COPD incidence	356,862	836	22,100	384	26,062	123	7,304	42	7,082	177	442	18	1,484	11	328	14

Gait-grip group: having slow gait speed plus low grip strength only. Gait-muscle group: having slow gait speed plus low muscle mass only. Grip-muscle group or current sarcopenia definition: having low grip strength plus low muscle mass only. Severe sarcopenia: having low grip strength plus low muscle mass plus slow walking speed.

4.1.5 Table S2. Cohort characteristics by individual components of sarcopenia

	Without sarcopenia (normal)	Low Gait speed	Low grip strength	Low muscle mass
Socio-demographics				
Total n	394,583	26,769	28,903	8,178
Sex (Female), n (%)	207,782 (52.7)	13,863 (51.8)	18,475 (63.9)	7,939 (97.1)
Age (years), mean (SD)	56.1 (8.1)	59.0 (7.4)	60.0 (7.1)	61.2 (6.1)
Age categories				
<56 years	173,200 (43.9)	7,779 (29.1)	6,938 (24.0)	1,387 (17.0)
56 to 65 years	169,368 (42.9)	13,251 (49.5)	14,643 (50.7)	4,525 (55.3)
>65 years	52,037 (13.2)	5,740 (21.4)	7,323 (25.3)	2,267 (27.7)
Deprivation				
Lower	141,660 (35.9)	6,545 (24.5)	8,841 (30.6)	3,120 (38.2)
Middle	135,979 (34.5)	8,049 (30.1)	9,633 (33.4)	2,823 (34.6)
Higher	116,509 (29.6)	12,136 (45.4)	10,401 (36.0)	2,223 (27.2)
Smoking status, n (%)				
Never	215,924 (54.9)	10,897 (41.0)	15,952 (55.5)	4,862 (59.6)
Previous	138,609 (35.2)	10,851 (40.8)	10,174 (35.4)	2,520 (30.9)
Current	38,877 (9.9)	4,853 (18.2)	2,635 (9.1)	771 (9.5)
Obesity-related markers				
Height (meters), mean (SD)	1.69 (0.09)	1.67 (0.09)	1.64 (0.09)	1.64 (0.07)
Body weight (kg), mean (SD)	78.0 (15.2)	88.8 (19.7)	74.5 (14.6)	60.4 (8.3)
BMI, mean (SD)	27.1 (4.4)	31.6 (6.5)	27.5 (4.6)	22.6 (2.8)
BMI Categories, n (%)				
Underweight (<18.5 $kg.m^{-2}$)	1,480 (0.4)	86 (0.3)	178 (0.6)	449 (5.5)
Normal weight (18.5-24.9 $kg.m^{-2}$)	131,731 (33.5)	3,414 (12.9)	8,916 (30.9)	6,251 (76.4)
Overweight (25.0 to 29.9 $kg.m^{-2}$)	173,553 (44.1)	8,442 (32.0)	12,491 (43.3)	1,387 (17.0)
Obese (≥30.0 $kg.m^{-2}$)	86,692 (22.0)	14,482 (54.8)	7,282 (25.2)	92 (1.1)
Waist Circumference (cm)	89.7 (12.9)	100.9 (15.3)	89.9 (13.1)	77.2 (8.5)
Central Obesity, n (%)	121,990 (31.0)	17,168 (64.6)	10,979 (38)	893 (10.9)
% Body fat, mean (SD)	30.7 (8.3)	36.0 (9.3)	33.2 (8.3)	35.8 (6.1)
Fitness and Physical activity				
Total PA ($MET.h^{-1}.week^{-1}$), mean (SD)	3,018.2 (3,286.7)	2,135.3 (2,643.2)	2,807.2 (3,130.2)	2,596.4 (2,716.8)
Cardiorespiratory fitness (MET), mean (SD)	9.8 (2.8)	8.3 (2.5)	8.9 (2.6)	8.0 (2.1)
Grip Strength (kg), mean (SD)	32.5 (10.3)	29.9 (9.6)	16.2 (5.7)	22.5 (4.7)
TV viewing ($h.day^{-1}$), mean (SD)	2.7 (1.5)	3.7 (2.1)	3.1 (1.6)	3.0 (1.5)
Total Sedentary behaviour ($h.day^{-1}$) , mean (SD)	5.0 (2.2)	5.8 (2.7)	4.9 (2.2)	4.6 (1.9)
Health status, n (%)				
Diabetes	15,062 (3.8)	3,774 (14.2)	1,999 (6.9)	86 (1.0)
CVDs	106,513 (27.0)	14,139 (53)	10,098 (35.0)	1,954 (23.9)
High blood pressure	88,983 (22.6)	9,475 (35.5)	7,924 (27.5)	1,664 (20.4)
Fractures	35,648 (9.1)	3,202 (12.1)	3,459 (12.0)	991 (12.2)
Falls, n (%)				
No falls	326,585 (82.9)	16,899 (63.5)	21,227 (73.7)	6,407 (78.4)
Only one fall	49,217 (12.5)	4,351 (16.4)	4,967 (17.2)	1,356 (16.6)
More than one fall	18,288 (4.6)	5,347 (20.1)	2,626 (9.1)	408 (5.0)

BMI: body mass index; n: number; PA: physical activity; MET: metabolic-equivalent; TE: total energy; SD: standard deviation; CVD: cardiovascular disease.

4.1.6 Supplementary Table 3. Association between individual physical capability markers and all-cause and cause-specific mortality and incidence

	Total n	death-events	Normal	Slow gait Speed	p-value	Low Grip strength	p-value	Low muscle mass	p- value
Model 2			**HR (95%CI)**	**HR (95% CI)**		**HR (95% CI)**		**HR (95% CI)**	
All-cause mortality	426,758	14,786	1.00 (Ref.)	1.59 (1.51; 1.67)	<0.001	1.23 (1.16; 1.30)	<0.001	1.18 (1.05; 1.34)	0.008
CVD mortality	413,689	2,548	1.00 (Ref.)	2.15 (1.91; 2.41)	<0.001	1.57 (1.37; 1.80)	<0.001	1.47 (1.05; 2.05)	0.024
Respiratory mortality	421,586	2,577	1.00 (Ref.)	1.90 (1.69; 2.14)	<0.001	1.37 (1.19; 1.58)	<0.001	1.39 (1.03; 1.87)	0.031
CVD incidence	408,220	19,332	1.00 (Ref.)	1.33 (1.26; 1.40)	<0.001	1.03 (0.97; 1.09)	0.278	1.02 (0.91; 1.16)	0.686
Respiratory incidence	417,940	16,105	1.00 (Ref.)	1.47 (1.39; 1.55)	<0.001	1.18 (1.11; 1.25)	<0.001	1.33 (1.19; 1.50)	<0.001
COPD incidence	421,664	1,605	1.00 (Ref.)	2.00 (1.74; 2.29)	<0.001	1.32 (1.09; 1.60)	0.006	2.03 (1.48; 2.79)	<0.001

Data presented as adjusted hazard ratio (HR) and its 95% confidence interval (95% CI) by different combinations of physical capability markers. People without any form of sarcopenia were used as the reference group for the analysis. All analyses were conducted using a 2-years landmark analyses and adjusted for Model 2 including age, sex, deprivation, smoking status, sleep duration, waist circumference, total physical activity, discretionary sedentary time, dietary intake (alcohol, fruit and vegetable, oily fish, red meat and processed meat intake), hypertension, diabetes, depression, comorbidities, cancer, as well as CVD and respiratory disease when these were not the outcome.

4.1.7 Table S4. Association between different combinations of physical capability markers and all- and cause-specific mortality

	Total n	death-events	Normal	gait-grip group	p-value	Gait-muscle group	p-value	Sarcopenia (grip-muscle group)	p- value	Severe Sarcopenia	p-value
			HR (95%CI)	HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)	
All-cause mortality											
Model 1	426,758	14,786	1.00 (Ref.)	2.95 (2.74; 3.17)	<0.001	4.23 (3.35; 5.35)	<0.001	1.44 (1.14; 1.82)	0.002	5.36 (4.16; 6.92)	<0.001
Model 2	426,758	14,786	1.00 (Ref.)	1.71 (1.59; 1.85)	<0.001	2.70 (2.13; 3.42)	<0.001	1.35 (1.07; 1.71)	0.010	3.02 (2.34; 3.91)	<0.001
Model 3	368,234	9,628	1.00 (Ref.)	1.90 (1.71; 2.12)	<0.001	2.35 (1.62; 3.40)	<0.001	1.32 (0.98; 1.77)	0.067	2.70 (1.79; 4.09)	<0.001
CVD mortality											
Model 1	413,689	2,548	1.00 (Ref.)	4.56 (3.91; 5.33)	<0.001	5.82 (3.43; 9.87)	<0.001	1.27 (0.63; 2.55)	0.505	5.61 (2.91; 10.8)	<0.001
Model 2	413,689	2,548	1.00 (Ref.)	2.35 (1.99; 2.79)	<0.001	3.47 (2.03; 5.91)	<0.001	1.26 (0.62; 2.53)	0.520	2.92 (1.50; 5.67)	0.002
Model 3	369,026	1,847	1.00 (Ref.)	2.80 (2.28; 3.43)	<0.001	4.73 (2.43; 9.16)	<0.001	1.55 (0.73; 3.27)	0.252	2.85 (1.06; 7.66)	0.038
Respiratory Mortality											
Model 1	421,586	2,577	1.00 (Ref.)	4.36 (3.76; 5.05)	<0.001	10.4 (6.96; 15.4)	<0.001	2.14 (1.30; 3.57)	0.003	11.2 (7.05; 17.9)	<0.001
Model 2	421,586	2,577	1.00 (Ref.)	2.35 (2.00; 2.77)	<0.001	5.73 (3.83; 8.57)	<0.001	1.88 (1.15; 3.10)	0.012	5.32 (3.31; 8.55)	<0.001
Model 3	369,129	1,749	1.00 (Ref.)	2.81 (2.30; 3.44)	<0.001	6.92 (2.25; 11.2)	<0.001	1.68 (0.90; 3.14)	0.104	5.11 (2.71; 9.62)	<0.001

Data presented as adjusted hazard ratio (HR) and its 95% confidence interval (95% CI) by different combinations of physical capability markers. People without any form of sarcopenia were used as the reference group for the analysis. All analyses were conducted using a 2-years landmark analyses. Gait-grip group: having slow gait speed plus low grip strength only. Gait-muscle group: having slow gait speed plus low muscle mass only. Grip-muscle group or current sarcopenia definition: having low grip strength plus low muscle mass only. Severe sarcopenia: having low grip strength plus low muscle mass plus slow walking speed. Model 1 was adjusted by age, sex and deprivation,. Model 2, as in model 1, but including, smoking status, sleep duration, waist circumference, total physical activity, discretionary sedentary time, dietary intake (alcohol, fruit and vegetable, oily fish, red meat and processed meat intake), hypertension, diabetes, depression, comorbidities, cancer, as well as CVD and respiratory disease when these were not the outcome. Model 3 excluded 71,781 participants with major comorbidities at baseline.

4.1.8 Table S5. Association between different combinations of physical capability markers and cause-specific incidence

	Total n	death-events	Normal	gait-grip group	p-value	gait-muscle group	p-value	Sarcopenia (grip-muscle group)	p- value	Severe Sarcopenia	p-value
			HR (95%CI)	HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)	
CVD incidence											
Model 1	408,220	19,332	1.00 (Ref.)	2.19 (2.03; 2.36)	<0.001	2.14 (1.59; 2.87)	<0.001	1.10 (0.87; 1.40)	0.432	1.74 (1.17; 2.57)	0.006
Model 2	408,220	19,332	1.00 (Ref.)	1.38 (1.27; 1.50)	<0.001	1.62 (1.20; 2.17)	0.001	1.12 (0.88; 1.43)	0.340	1.21 (0.81; 1.79)	0.348
Model 3	365,328	15,279	1.00 (Ref.)	1.36 (1.24; 1.51)	<0.001	1.83 (1.27; 2.63)	0.001	1.26 (0.97 1.64)	0.077	1.44 (0.89; 2.32)	0.133
Respiratory Incidence											
Model 1	417,940	16,105	1.00 (Ref.)	2.90 (2.70; 3.12)	<0.001	3.26 (2.51; 4.24)	<0.001	1.43 (1.14; 1.78)	0.002	4.44 (3.34; 5.90)	<0.001
Model 2	417,940	16,105	1.00 (Ref.)	1.66 (1.54; 1.79)	<0.001	2.25 (1.73; 2.93)	<0.001	1.38 (1.11; 1.73)	0.004	2.74 (2.06; 3.65)	<0.001
Model 3	366,780	11,925	1.00 (Ref.)	1.88 (1.71; 2.07)	<0.001	2.65 (1.94; 3.62)	<0.001	1.51 (1.18; 1.94)	0.001	2.44 (1.66; 3.60)	<0.001
COPD Incidence											
Model 1	421,664	1,605	1.00 (Ref.)	6.46 (5.47; 7.63)	<0.001	11.1 (6.95; 17.8)	<0.001	2.53 (1.39; 4.60)	0.002	13.7 (8.04; 23.3)	<0.001
Model 2	421,664	1,605	1.00 (Ref.)	2.42 (2.01; 2.91)	<0.001	4.16 (2.59; 6.70)	<0.001	2.08 (1.14; 3.79)	0.017	3.85 (2.24; 6.62)	<0.001
Model 3	366,978	1,112	1.00 (Ref.)	2.32 (1.84; 2.94)	<0.001	5.51 (3.21; 9.45)	<0.001	2.38 (1.23; 4.63)	0.010	3.75 (1.91; 7.34)	0.001

Data presented as adjusted hazard ratio (HR) and its 95% confidence interval (95% CI) by different combinations of physical capability markers. People without any form of sarcopenia were used as the reference group for the analysis. All analyses were conducted using a 2-years landmark analyses. Gait-grip group: having slow gait speed plus low grip strength only. Gait-muscle group: having slow gait speed plus low muscle mass only. Grip-muscle group or current sarcopenia definition: having low grip strength plus low muscle mass only. Severe sarcopenia: having low grip strength plus low muscle mass plus slow walking speed. Model 1 was adjusted by age, sex and deprivation,.Model 2, as in model 1, but including, smoking status, sleep duration, waist circumference, total physical activity, discretionary sedentary time, dietary intake (alcohol, fruit and vegetable, oily fish, red meat and processed meat intake), hypertension, diabetes, depression, comorbidities, cancer, as well as CVD and respiratory disease when these were not the outcome. Model 3 excluded 71,781 participants with major comorbidities at baseline.

4.1.9 Table S6. Association between different combinations of physical capability markers and all-cause and cause-specific mortality and incidence by age

	Total n	Deaths /events	Normal	Gait-grip group	p-value	Gait-muscle group	p-value	Sarcopenia (grip-muscle group)	p- value	Severe Sarcopenia	p-value
			HR (95%CI)	HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)	
All-cause mortality Interaction (Model 2)					0.001*		0.166		0.199		0.482
< 60 years	237,019	4,297	1.00 (Ref.)	1.95 (1.66; 2.28)	<0.001	3.68 (2.20; 6.14)	<0.001	2.13 (1.14; 3.96)	0.017	3.71 (1.98; 6.93)	0.001
≥ 60 years	189,739	10,489	1.00 (Ref.)	1.84 (1.68; 2.01)	<0.001	2.98 (2.29; 3.89)	<0.001	1.49 (1.16; 1.91)	0.002	3.53 (2.66; 4.68)	<0.001
CVD mortality Interaction (Model 2)					0.382		0.591		-		0.260
< 60 years	233,298	633	1.00 (Ref.)	2.58 (1.77; 3.77)	<0.001	2.41 (0.33; 17.3)	0.382	-	-	7.88 (1.93; 32.2)	0.004
≥ 60 years	180,391	1,915	1.00 (Ref.)	2.59 (2.14; 3.13)	<0.001	4.24 (2.44; 7.39)	<0.001	1.48 (0.74; 2.98)	0.270	3.10 (1.46; 6.56)	0.003
Respiratory mortality Interaction (Model 2)					<0.001*		0.112		0.982		0.797
< 60 years	235,171	554	1.00 (Ref.)	3.85 (2.76; 5.38)	<0.001	10.9 (4.42; 26.8)	<0.001	1.96 (0.27; 14.0)	0.503	5.91 (1.45; 24.1)	0.036
≥ 60 years	186,415	2,023	1.00 (Ref.)	2.40 (1.99; 2.89)	<0.001	6.41 (4.09; 10.0)	<0.001	2.26 (1.35; 3.77)	0.002	6.91 (4.17; 11.4)	<0.001
CVD incidence Interaction (Model 2)					0.069		0.109		0.910		0.016*
< 60 years	231,614	6,565	1.00 (Ref.)	1.58 (1.35; 1.86)	<0.001	0.79 (0.25; 2.46)	0.686	1.34 (0.64; 2.81)	0.442	3.18 (1.59; 6.39)	0.001
≥ 60 years	176,606	12,767	1.00 (Ref.)	1.46 (1.33; 1.61)	<0.001	1.97 (1.45; 2.67)	<0.001	1.20 (0.93; 1.54)	0.163	1.06 (0.66; 1.72)	0.799
Respiratory incidence Interaction (Model 2)					<0.001*		0.910		0.856		0.166

< 60 years	233,893	5,532	1.00 (Ref.)	2.17 (1.89; 2.49)	<0.001	2.48 (1.29; 4.78)	0.007	1.42 (0.71; 2.84)	0.322	4.20 (2.32; 7.62)	<0.001
≥ 60 years	184,573	10,573	1.00 (Ref.)	1.66 (1.52; 1.83)	<0.001	2.48 (1.85; 3.32)	<0.001	1.55 (1.23; 1.97)	<0.001	2.90 (2.09; 4.01)	<0.001
COPD incidence Interaction (Model 2)					0.059		0.393		0.413		0.466
< 60 years	235,186	456	1.00 (Ref.)	2.88 (2.03; 4.08)	<0.001	6.42 (2.59; 15.9)	<0.001	4.27 (1.05; 17.3)	0.042	6.39 (2.01; 20.3)	0.004
≥ 60 years	186,478	1,149	1.00 (Ref.)	2.67 (2.15; 3.31)	<0.001	4.50 (2.58; 7.87)	<0.001	2.28 (1.17; 4.42)	0.015	4.88 (2.65; 8.99)	<0.001

Data presented as adjusted hazard ratio (HR) and its 95% confidence interval (95% CI) by different combinations of physical capability markers. People without any form of sarcopenia were used as the reference group for the analysis. All analyses were conducted using a 2-years landmark analyses and adjusted for Model 2 including age, sex, deprivation, smoking status, sleep duration, waist circumference, total physical activity, discretionary sedentary time, dietary intake (alcohol, fruit and vegetable, oily fish, red meat and processed meat intake), hypertension, diabetes, depression, comorbidities, cancer, as well as CVD and respiratory disease when these were not the outcome.*p-interaction between physical capability markers groups and age groups.

4.1.10 Table S7. Association between different combinations of physical capability markers and all-cause and cause-specific mortality and incidence by sex

	Total n	Deaths /events	Normal	Gait-grip group	p-value	Gait-muscle group	p-value	Sarcopenia (grip-muscle group)	p- value	Severe Sarcopenia	p-value
			HR (95%CI)	HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)	
All-cause mortality Interaction (Model 2)					0.005*		0.009*		0.108		0.097
Females	233,554	6,031	1.00 (Ref.)	1.61 (1.43; 1.82)	<0.001	2.47 (1.88; 3.25)	<0.001	1.29 (1.01; 1.65)	0.039	2.84 (2.14; 3.79)	<0.001
Males	193,204	8,755	1.00 (Ref.)	1.79 (1.62; 1.99)	<0.001	4.61 (2.85; 7.43)	<0.001	2.27 (1.08; 4.77)	0.030	4.58 (2.52; 8.30)	<0.001
CVD mortality Interaction (Model 2)					0.369		0.257		0.838		0.574
Females	230,101	786	1.00 (Ref.)	2.35 (1.78; 3.10)	<0.001	3.85 (2.14; 6.94)	<0.001	1.20 (0.56; 2.54)	0.637	2.96 (1.38; 6.34)	0.005
Males	183,588	1,762	1.00 (Ref.)	2.34 (1.89; 2.89)	<0.001	1.87 (0.46; 7.52)	0.379	1.58 (0.22; 11.3)	0.646	2.28 (0.56; 9.24)	0.247
Respiratory mortality Interaction (Model 2)					0.084		0.280		0.440		0.312
Females	230,833	902	1.00 (Ref.)	2.31 (1.79; 2.98)	<0.001	4.65 (2.84; 7.62)	<0.001	1.82 (1.07; 3.11)	0.028	5.20 (3.11; 8.72)	<0.001
Males	190,753	1,675	1.00 (Ref.)	2.30 (1.86; 2.85)	<0.001	9.15 (4.50; 18.6)	<0.001	3.12 (0.78; 12.5)	0.108	3.14 (0.78; 12.7)	0.108
CVD incidence Interaction (Model 2)					0.036*		0.036*		0.188		0.523
Females	228,242	7,050	1.00 (Ref.)	1.32 (1.18; 1.49)	<0.001	1.69 (1.25; 2.30)	0.001	1.14 (0.89;1.45)	0.293	1.14 (0.75; 1.74)	0.544
Males	179,978	12,282	1.00 (Ref.)	1.39 (1.24; 1.56)	<0.001	0.60 (0.19; 1.86)	0.373	0.47 (0.12; 1.90)	0.292	0.94 (0.30; 2.91)	0.912
Respiratory incidence Interaction (Model 2)					0.025*		0.486		0.133		0.999
Females	229,258	7,096	1.00 (Ref.)	1.63 (1.46; 1.81)	<0.001	2.15 (1.61; 2.87)	<0.001	1.35 (1.06; 1.70)	0.013	2.54 (1.87; 3.46)	<0.001
Males	188,682	9,009	1.00 (Ref.)	1.65 (1.48; 1.84)	<0.001	3.03 (1.57; 5.84)	0.001	2.46 (1.17; 5.16)	0.018	2.94 (1.32; 6.58)	0.008

COPD incidence Interaction (Model 2)					0.023*		0.100		0.154		0.593
Females	230,831	712	1.00 (Ref.)	2.44 (1.88; 3.17)	<0.001	4.66 (2.79; 7.81)	<0.001	1.95 (0.99; 3.80)	0.050	3.51 (1.93; 6.40)	<0.001
Males	190,833	893	1.00 (Ref.)	2.33 (1.79; 3.03)	<0.001	2.18 (0.54; 8.84)	0.276	6.00 (1.49; 24.1)	0.012	3.42 (0.84; 13.9)	0.085

Data presented as adjusted hazard ratio (HR) and its 95% confidence interval (95% CI) by different combinations of physical capability markers. People without any form of sarcopenia were used as the reference group for the analysis. All analyses were conducted using a 2-years landmark analyses and adjusted for Model 2 including age, sex, deprivation, smoking status, sleep duration, waist circumference, total physical activity, discretionary sedentary time, dietary intake (alcohol, fruit and vegetable, oily fish, red meat and processed meat intake), hypertension, diabetes, depression, comorbidities, cancer, as well as CVD and respiratory disease when these were not the outcome. *p-interaction between physical capability markers groups and sex.

4.2 Association of sarcopenia with incident osteoporosis: A prospective study of 168,682 UK Biobank participants (Paper 3)

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Association of sarcopenia with incident osteoporosis: a prospective study of 168,682 UK biobank participants

Fanny Petermann-Rocha[1,2], Lyn D. Ferguson[2], Stuart R. Gray[2], Irene Rodríguez-Gómez[3,4], Naveed Sattar[2], Stefan Siebert[5], Frederick K. Ho[1†], Jill P. Pell[1†] & Carlos Celis-Morales[2,6,7*†]

[1]*Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK;* [2]*British Heart Foundation Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK;* [3]*GENUD Toledo Research Group, Universidad de Castilla-La Mancha, Toledo, Spain;* [4]*CIBER of Frailty and Healthy Aging (CIBERFES), Madrid, Spain;* [5]*Institute of Infection, Immunity & Inflammation, University of Glasgow, Glasgow, UK;* [6]*Centre of Exercise Physiology Research (CIFE), Universidad Mayor, Santiago, Chile;* [7]*Human Performance Lab, Education, Physical Activity and Health Research Unit, University Católica del Maule., Talca, 3466706, Chile*

Abstract

Background Sarcopenia often co-occurs with osteoporosis in cross-sectional studies. However, this association has rarely been studied in prospective studies. This study aimed to investigate the association between sarcopenia categories—along with its individual components—and incident osteoporosis in both middle-aged and older men and women from the UK Biobank study.

Methods A total of 168,682 participants (48.8% women, aged 37 to 70 years at baseline) were included in this prospective study. Categories of sarcopenia (pre-sarcopenia and sarcopenia), and its individual components, were defined according to the EWGSOP2 criteria (2019). Associations with incident osteoporosis by sex were investigated using Cox-proportional hazard models adjusted for socio-demographic, lifestyle and health-related factors, and morbidity count. Associations between categories of sarcopenia and incident osteoporosis were also investigated by age-groups and subtype of osteoporosis (with and without pathological fractures).

Results After a median follow-up of 7.4 years, 6296 participants were diagnosed with osteoporosis. When the analyses were adjusted for a range of relevant confounding factors, pre-sarcopenia was associated with 1.3-times higher risk of osteoporosis in men (HR: 1.30 [95% CI: 1.03 to 1.63]) but not in women, and sarcopenia was associated with 1.66-times increased osteoporosis risk in women (HR: 1.66 [95% CI: 1.33 to 2.08]) but not in men compared with people without sarcopenia or pre-sarcopenia. A similar magnitude of associations was found in osteoporosis without pathological fractures but weaker for those with pathological fractures. Within the individual components, low muscle mass (HR_{women}: 1.36 [95% CI: 1.22 to 1.51] and HR_{men}: 3.07 [95% CI: 1.68 to 5.59]), followed by slow gait speed (HR_{women}: 1.30 [95% CI: 1.17 to 1.45] and HR_{men}: 1.70 [95% CI: 1.43 to 2.02]), were associated with a higher risk of incident osteoporosis in both sexes. Low grip strength was associated with a higher risk of incident osteoporosis in men (HR: 1.38 [95% CI: 1.15 to 1.65]), but not in women. No significant interaction between the exposures and incident osteoporosis by age groups were identified.

Conclusions Our findings demonstrated that pre-sarcopenic men and sarcopenic women had a higher risk of developing osteoporosis even after adjustment for a large range of potential confounders. Considering that sarcopenia could be prevented, health interventions to improve physical capability may delay or prevent the onset of osteoporosis.

Keywords Sarcopenia; Osteoporosis; Muscle strength; Physical capability

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**Correspondence to: Dr Carlos Celis-Morales, BHF Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow G12 8TA, UK. Tel: + 44 141 3304201, Email:* carlos.celis@glasgow.ac.uk
†Contributed equally to this work and is joint senior author.

Introduction

Osteoporosis is the result of changes in bone turnover that reduces bone mineral density (BMD), increase bone fragility, and predispose to fragility fractures along with a higher burden of morbidity and mortality.[1] Clinically, osteoporosis is identified as a BMD more than 2.5 standard deviations (SD) below the mean value in younger and healthy individuals (a T-score of <-2.5 SD).[2,3] According to the International Osteoporosis Foundation, in 2017, approximately 2.8 million people older than 50 years had osteoporosis in the United Kingdom, while fragility fractures, associated with osteoporosis, are the fourth most common chronic disease after ischaemic heart disease, dementia, and lung cancer.[4] Moreover, the economic burden and healthcare costs linked to osteoporosis are also high. In 2017, the economic cost of the disease in the United Kingdom was £4.5 billion; however, this is projected to rise to £5.9 billion by 2030.[4] Therefore, it is important to ascertain risk factors for osteoporosis that help us identify high-risk individuals and develop interventions aimed at prevention or early treatment, in order to reduce the personal and economic burden of osteoporosis.

Although several risk factors have been linked to a higher risk of osteoporosis, the evidence has not been unequivocal.[1,5,6] Some of the well-recognized risk factors for osteoporosis include older age, white ethnic background, post-menopause in women, weight loss, smoking, excessive alcohol intake, vitamin D deficiency (lack of sunlight exposure), inadequate intake of calcium (lower than 1000 mg/day), low protein intake (lower than 0.8 g/kg/body weight) as well as lack of physical activity. Muscle weakness has also been associated with a higher risk of osteoporosis independently of physical activity.[5,6] In keeping with this finding, the age-related decline in muscle quantity and quality, known as sarcopenia, also affects mobility, bone mass, and bone microarchitecture. In fact, existing evidence has suggested that sarcopenia may be an independent predictor of low BMD and fragility fractures, that is, osteoporosis.[7–12]

Previous studies have reported that sarcopenia and osteoporosis often co-occur.[7,8,10–12] A recent meta-analysis identified that the prevalence of osteoporosis and sarcopenia in white European aged 65 years or older varied between 5.0% and 37.0%.[13] Unfortunately, the cross-sectional nature of most existing evidence has limitations and does not allow further understanding of the association between sarcopenia and osteoporosis. In terms of prospective evidence, the majority of these studies have investigated the association between individual physical capability markers and sarcopenia with fracture risk[14–22] and have been conducted on smaller samples ($n < 5000$) or focused mainly on older adults. Also, to our knowledge, there are no studies which have investigated the prospective association between sarcopenia and incident osteoporosis *per se*. Therefore, this study aimed to investigate the association between sarcopenia categories—along with its individual components—and incident osteoporosis in both middle-aged and older men and women, using data from UK Biobank, a large prospective cohort study.

Methods

Over 500,000 participants (5.5% response rate), aged 37 to 73 years, were recruited from the general population between 2006 and 2010 to be part of UK Biobank.[23] In brief, participants attended their closest assessment centre across Scotland, England, and Wales[24,25] where they completed a touch-screen questionnaire, had physical measurements taken, and provided blood, urine, and saliva sample at baseline. More information about the UK Biobank protocol can be found online (http://www.ukbiobank.ac.uk).

Incident osteoporosis

Incident osteoporosis cases were ascertained through linkage of primary care records. Diagnosis of osteoporosis was primarily based on dual-energy X-ray absorptiometry (DXA) scan results. However, women >75 years that experienced a fragility fracture may be diagnosed with osteoporosis prior to a DXA scan. Currently, this information was available only for 45% of the UK Biobank cohort (~230,000 participants) until May 2017 for Scotland, September 2017 for Wales, and August 2017 for England. The detailed linkage procedures relating to primary care records are available at http://biobank.ndph.ox.ac.uk/showcase/showcase/docs/primary_care_data.pdf. Therefore, the analyses of incident osteoporosis cases were restricted to the 228,481 participants with linkage to primary care records. Follow-up was censored at the primary care data end-date for the relevant country or the date of incident osteoporosis. Osteoporosis was defined as M80 (osteoporosis with pathological fracture) M81 (osteoporosis without pathological fracture) or M82 (osteoporosis in diseases classified elsewhere) using the International Classification of Diseases, 10th revision (ICD-10).

Sarcopenia and its components

Muscle mass index was derived from skeletal muscle mass (kg) divided by height (m) squared using the total body composition measured via bioimpedance (BIA, Tanita BC418MA, Tokyo, Japan) by trained nurses. To estimate skeletal muscle mass, the Janssen equation was utilized.[26] Following the European Working Sarcopenia in Older People 2019 (EWGSOP2) recommendations, the cut-off points used were <7.0 kg/m^2 in men and <5.5 kg/m^2 in women. Grip strength was measured using a Jamar J00105 hydraulic hand dynamometer. The mean of the right and left values was derived

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and expressed in absolute units (kg). The cut-off points applied to define low grip strength were <27 kg in men and <16 kg in women.[27] Self-reported walking pace was used as a proxy of gait speed and categorized as slow, average or brisk. A previous study determined that self-reported walking pace is a good marker of walking speed.[28] To derive a proxy for gait speed, this was then dichotomized into slow or normal (average or brisk pace).

Using these three physical capability markers, sarcopenia was classified in accordance with the EWGSOP2 statement as pre-sarcopenia, defined as low grip strength only (other physical capability markers in the normal range); sarcopenia, defined as low grip strength plus low muscle mass[27]; and severe sarcopenia, defined as the combination of sarcopenia and slow gait speed. However, because of the low number of UK Biobank participants with severe sarcopenia (n = 87), sarcopenia and severe sarcopenia were pooled together (hereafter referred to as sarcopenia). We followed this approach to avoid unreliable and unpowered hazard ratios (HR) estimates. The pre-sarcopenia and sarcopenia groups were mutually exclusive. For this study, only white European participants were included because of the ethnic differences in the reference values for sarcopenia.[27]

Covariates

Age at baseline was calculated from dates of birth and baseline assessment. Area-based socioeconomic deprivation was derived from postcode of residence, using the Townsend score.[29] Self-reported smoking status was categorized as never, former or current smoker. Physical activity was self-reported using the International Physical Activity Questionnaire short form[30] and total physical activity was computed as the sum of walking, moderate and vigorous activity, measured as metabolic equivalents (MET-hours/week). Prevalent morbidity was ascertained during a nurse-led interview at baseline. We calculated morbidity count based on 43 long-term conditions originally developed for a large epidemiological study in Scotland and subsequently adapted for UK Biobank.[31] Body composition was measured using BIA by trained nurses. Frequency of alcohol intake was self-reported at baseline and categorized as daily/almost daily, three to four times a week, once/twice a week, one to three times a month, special occasions only and never. Corticosteroid and H2 blockers use, as well as menopause and hypogonadism, were self-reported at baseline. History of fall and fractures were self-reported at baseline using these two questions: 'In the last year, have you had any falls?' and 'have you fractured/broken any bones in the last five years?' Vitamin D levels were assessed by 25-hydroxyvitamin D (25(OH)D) concentration in serum. Red and processed meat intake were collected through the touch-screen questionnaire at baseline. Finally, calcium and protein intake were estimated via the Oxford WebQ, a web-based 24-h recall questionnaire.[32] For the 71,673 participants who completed more than one the average dietary of the 24-h recall, this average intake was used. Further details of these measurements can be found in the UK Biobank online protocol (http://www.ukbiobank.ac.uk).

Ethical approval

UK Biobank was given favourable opinion by the North West Multi-Centre Research Ethics Committee (Ref: 11/NW/0382). The study protocol is available online (http://www.ukbiobank.ac.uk/). This work was conducted under the UK Biobank application number 7155.

Statistical analyses

Descriptive characteristics are presented as means with standard deviations (SD) for quantitative variables, and as frequencies and percentages for categorical variables by sex.

Associations between categories of sarcopenia (pre-sarcopenia and sarcopenia) and incident osteoporosis were investigated using Cox-proportional hazard models stratified by sex. Non-sarcopenic individuals (i.e. with the three physical capability markers in the normal range) were used as the reference group. The results are reported as HR and their 95% confidence intervals (95% CIs). The proportional hazard assumptions were checked using Schoenfeld residuals. Associations between the three individual physical capability markers (low grip strength, low muscle mass and slow gait speed) and incident osteoporosis were investigated using the same analysis. For each component, the normal range of the physical capability maker defined by the EWGSOP2 was used as the reference group.[27] Participants who self-reported osteoporosis at baseline were excluded from all analyses (n = 3472). Only participants with complete data available for the three physical capability markers used to define later categories of sarcopenia, the covariates included in the analyses, and incident osteoporosis were included. Follow-up time was used as the time-dependent variable.

We ran five models including an increasing number of covariates: model 1 (minimally adjusted) included socio-demographic covariates (age and deprivation); model 2 additionally included lifestyle and health-related factors: smoking, physical activity, alcohol intake and consumption of red and processed meat, body fat, and morbidity count at baseline (based on 43 diseases and coded as 1, 2, 3, 4 and ≥5). Model 3, as model 2, but additionally adjusted for serum vitamin D levels, use of corticosteroids and H2 blockers, falls, fractures over the previous 5 years, and menopause and hypogonadism in women and men, respectively. These covariates were chosen as they are potentially

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causal for sarcopenia and osteoporosis. Two sensitivity analyses were also performed: model 4, as per model 3, but using a 2-year landmark period which excluded participants who experienced events within the first 2 years of follow-up (1323 women and 290 men) to minimize potential reverse causation; and model 5, as per model 3, but further adjusted for calcium and protein intake (as these variables were available in 71,673 participants only). Additionally, the association of categories of sarcopenia with subtypes of osteoporosis outcomes (split out by pathological fractures and osteoporosis without pathological fractures [or classified elsewhere]) was also investigated.

The sex-specific cumulative crude hazard rate of incident osteoporosis and categories of sarcopenia was estimated using the Nelson–Aalen estimator. Finally, to investigate whether the associations between categories of sarcopenia and incident osteoporosis differed by age, the models were re-run stratified by the following age categories: (i) approximately when menopause or hypogonadism start (≥45 and <45 years as well as ≥55 and <55 years), (ii) using different definitions for aging (≥60 and <60 years as well as ≥65 and <65 years).

Stata 16 statistical software (StataCorp LP) was used to perform all analyses.

Results

After removing people who withdrew during the follow-up, 228,477 of the 502,488 UK Biobank participants had data available for incident osteoporosis. Excluding people with missing data for one or more physical capability marker (n = 2080), osteoporosis at baseline (n = 3472), non-white ethnicity (n = 10,832) or incomplete covariate data (n = 43,411), 168,682 participants (48.8% women) had data available on all essential variables (*Figure* 1). Of these, 154,429 could be classified as non-sarcopenia, pre-sarcopenia, or sarcopenia (Supporting Information, *Figure* S1). After a median follow-up of 7.4 years (interquartile range 6.7 to 8.2 years), 6296 (3.7%) participants were diagnosed with osteoporosis.

The baseline characteristics of participants by sarcopenia categories and sex are shown in *Table* 1. Briefly, 5950 (8.0%) of the 74,293 women and 4075 (5.1%) of the 80,136 men were pre-sarcopenic or sarcopenic. Overall, compared with non-sarcopenic individuals, both men and women with pre-sarcopenia or sarcopenia were older, more likely to currently smoke, use H2 blockers and/or corticosteroids, and report never drinking alcohol. They had lower levels of physical activity and reported a lower intake of protein and calcium. They were also more likely to have more than one morbidity, and to have had fractures in the last 5 years and falls in the last year. Lastly, pre-sarcopenic and sarcopenic individuals were more likely to be postmenopausal (women) and report hypogonadism (men) compared with non-sarcopenic women and men, respectively (*Table* 1). The baseline characteristics by individual physical capability marker by sex are shown in *Tables* S1 to S3.

Sex-specific associations between sarcopenia categories and incident osteoporosis are shown in *Figure* 2 and *Table* S4. In the minimally adjusted model (model 1), a higher risk of incident osteoporosis was identified in sarcopenic

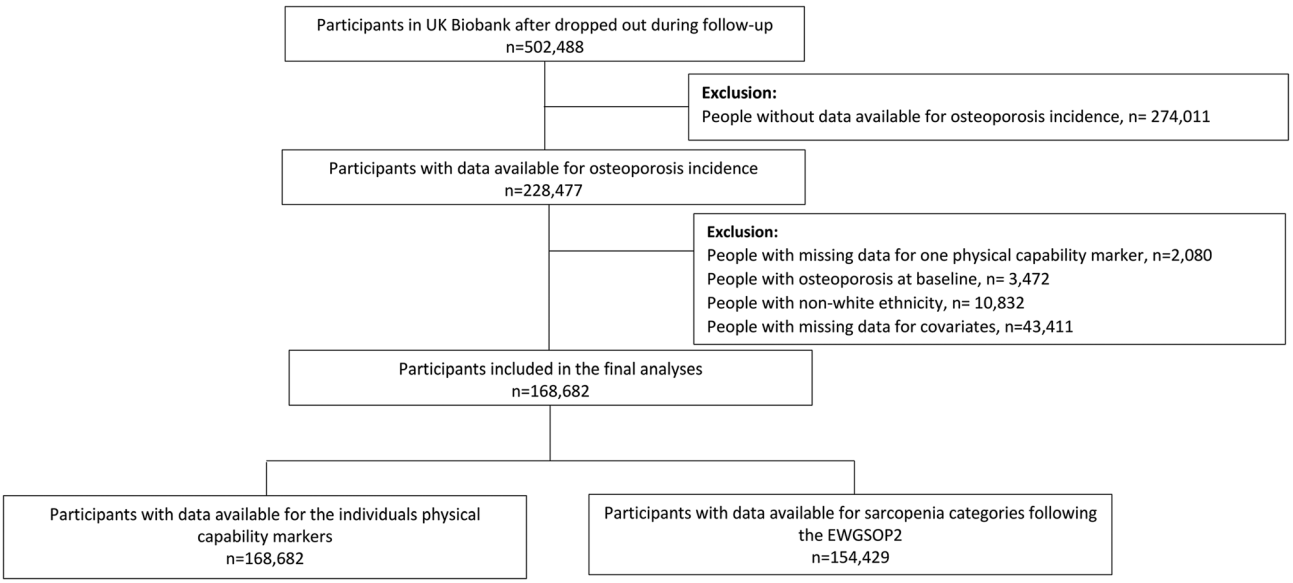

Figure 1 Flow diagram participants included in the study. EWGSOP2, European working sarcopenia in older people 2019.

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Table 1 Baseline characteristics by categories of sarcopenia and sex

	Total	Women			Men		
		Non-sarcopenic	Pre-sarcopenia*	Sarcopenia*	Non-sarcopenic	Pre-sarcopenia*	Sarcopenia*
Socio-demographics							
Total, *n* (%)	154,429 (100)	68,343 (92.0)	5430 (7.3)	520 (0.7)	76,061 (94.9)	4036 (5.0)	39 (0.1)
Age (years), mean (SD)	56.2 (8.1)	55.4 (8.1)	59.9 (7.0)	62.5 (5.4)	56.5 (8.1)	59.9 (7.4)	60.9 (7.2)
Deprivation, *n* (%)							
Lower	54,620 (35.4)	24,234 (35.5)	1590 (29.3)	153 (29.4)	27,539 (36.2)	1094 (27.1)	10 (25.6)
Middle	53,924 (34.9)	24,019 (35.1)	1968 (36.2)	210 (40.4)	26,377 (34.7)	1341 (33.2)	9 (23.1)
Higher	45,885 (29.7)	20,090 (29.4)	1872 (34.5)	157 (30.2)	22,145 (29.1)	1601 (39.7)	20 (51.3)
Lifestyle							
Body fat (kg), mean (SD)	24.1 (8.8)	26.2 (9.4)	26.9 (9.3)	22.4 (6.4)	22.0 (7.8)	22.5 (8.1)	19.2 (8.4)
Total PA (MET/h/week), mean (SD)	3067.3 (3345.0)	2751.3 (2839.4)	2707.0 (2852.2)	2562.4 (2741.2)	3378.1 (3732.8)	2998.0 (3503.0)	1938.4 (1675.7)
Total sedentary behaviour (h/day), mean (SD)	5.0 (2.2)	4.6 (1.9)	4.7 (2.0)	4.6 (1.9)	5.4 (2.4)	5.4 (2.5)	4.7 (2.9)
Red meat (portion.week^{-1}), mean (SD)	2.1 (1.4)	2.0 (1.3)	2.0 (1.3)	1.9 (1.3)	2.2 (1.4)	2.3 (1.6)	2.2 (1.6)
Processed meat intake (portion.week^{-1}), mean (SD)	1.9 (1.1)	1.6 (1.0)	1.6 (1.0)	1.7 (1.0)	2.2 (1.0)	2.2 (1.1)	2.0 (1.2)
Protein (g/day), mean (SD)	83.3 (25.8)	78.7 (23.1)	78.1 (23.8)	74.2 (22.7)	87.8 (27.5)	85.2 (26.7)	81.6 (22.4)
Calcium (mg/day), mean (SD)	995.4 (389.4)	959.5 (370.3)	960.8 (390.2)	877.3 (356.2)	1031.2 (403.9)	998.7 (373.5)	960.6 (292.7)
Alcohol frequency intake, *n* (%)							
Daily or almost daily	3868 (21.3)	11,403 (16.7)	805 (14.8)	91 (17.5)	19,560 (25.7)	994 (24.6)	1298 (20.9)
3–4 times a week	38,929 (25.2)	15,478 (22.7)	974 (17.9)	85 (16.4)	21,415 (28.2)	970 (24.0)	1177 (18.9)
Once or twice a week	42,235 (27.4)	19,007 (27.8)	1509 (27.8)	129 (24.8)	20,512 (27.0)	1072 (26.6)	1618 (26.0)
1–3 times a month	17,014 (11.0)	9212 (13.5)	655 (12.1)	64 (12.3)	6718 (8.8)	362 (9.0)	608 (9.7)
Special occasions only	14,595 (9.4)	8705 (12.7)	913 (16.8)	88 (16.9)	4565 (6.0)	322 (8.0)	782 (12.6)
Never	8788 (5.7)	4538 (6.6)	574 (10.6)	63 (12.1)	3291 (4.3)	316 (7.8)	740 (11.9)
Smoking status, *n* (%)							
Never	84,809 (54.9)	41,026 (60.0)	3177 (58.5)	295 (56.7)	38,319 (50.4)	1972 (48.9)	20 (51.3)
Previous	54,546 (35.3)	21,663 (31.7)	1832 (33.7)	176 (33.9)	29,264 (38.5)	1600 (39.6)	11 (28.2)
Current	15,074 (9.8)	5654 (8.3)	421 (7.8)	49 (9.4)	8478 (11.1)	464 (11.5)	8 (20.5)
Health status							
Multimorbidity, *n* (%)							
0	57,877 (37.5)	27,058 (39.6)	1348 (24.8)	111 (21.4)	28,336 (37.3)	1012 (25.1)	12 (30.8)
≥1	96,552 (62.5)	41,285 (60.4)	4082 (72.2)	409 (78.6)	47,725 (62.7)	3024 (74.9)	27 (69.2)
Vitamin D (nmol/L), mean (SD)	49.2 (20.8)	48.8 (20.6)	49.3 (20.4)	50.4 (22.0)	49.6 (21.0)	48.7 (20.8)	40.6 (25.7)
Using H2 blockers, *n* (%)	2558 (1.7)	1049 (1.5)	135 (2.5)	15 (2.9)	1265 (1.7)	93 (2.3)	1 (2.6)
Using steroid, *n* (%)	1420 (0.9)	532 (0.8)	79 (1.4)	12 (2.3)	722 (1.0)	74 (1.8)	1 (2.6)
Fractures in the last 5 years, *n* (%)	13,317 (8.7)	6059 (8.9)	645 (11.9)	70 (13.5)	6163 (8.2)	373 (9.3)	7 (18.0)
Falls in the last year, *n* (%)							
No falls	128,081 (83.0)	54,785 (80.3)	3901 (72.0)	373 (71.9)	65,813 (86.6)	3189 (79.3)	20 (63.9)
Only one fall	18,835 (12.2)	9978 (14.6)	987 (18.2)	105 (20.2)	7200 (9.5)	553 (13.7)	866 (14.0)
More than one fall	7322 (4.8)	3512 (5.1)	528 (9.8)	41 (7.9)	2952 (3.9)	282 (7.0)	1368 (22.1)
Hypogonadism, *n* (%)	356 (0.2)	-	-	-	328 (0.4)	28 (0.7)	39 (100)
Menopause, *n* (%)	51,366 (69.1)	46,110 (67.5)	4753 (87.5)	503 (96.7)	-	-	-

MET, metabolic-equivalent; *n*, number; PA, physical activity; SD, standard deviation; -, no data available.
*Sarcopenia includes those with sarcopenia or severe sarcopenia.

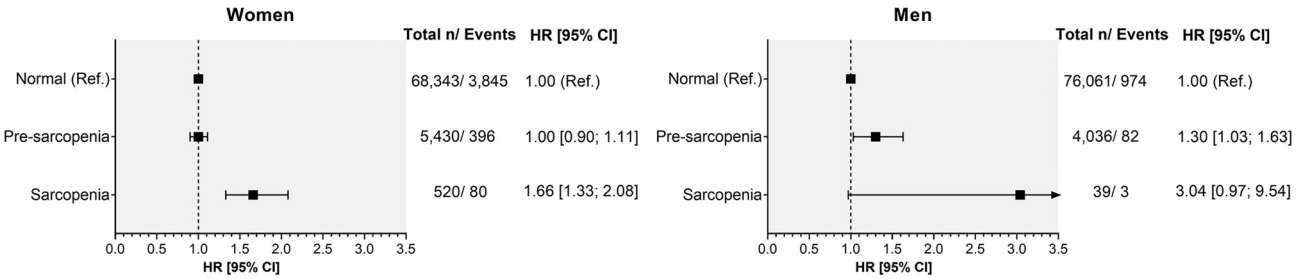

Figure 2 Association between categories of sarcopenia and osteoporosis incidence by sex. Analyses are presented as HR with their respectively CI. Non-sarcopenic participants were used as the reference group. Analyses were adjusted by socio-demographic factors (age and deprivation), morbidity count, physical activity, smoking, alcohol and red and processed meat intake, body fat, serum vitamin D levels, corticosteroids, H2 blockers, falls and fractures in the last 5 years and menopause in women and hypogonadism in men (model 3). *Sarcopenia includes those with sarcopenia or severe sarcopenia.

women compared to non-sarcopenic (HR: 2.01 [95% CI: 1.61 to 2.51]). The association was attenuated after adjustment for lifestyle factors, body composition and morbidity count (model 2) and remained significant in model 3 (HR: 1.66 [95% CI: 1.33 to 2.08]). The results were similar in the 2-year landmark analysis (model 4). However, the association were no longer present when protein and calcium intake were included as covariates (model 5). No associations were identified between pre-sarcopenic women and incident osteoporosis. Incident osteoporosis without pathological fractures showed similar patterns of associations (*Table* S5). Additionally, pre-sarcopenic women showed a higher risk of incident osteoporosis using this outcome ($HR_{model\ 3:}$ 1.15 [95% CI: 1.01 to 1.32]). Non-significant associations were identified between categories of sarcopenia and osteoporosis with pathological fractures.

The risk of osteoporosis in pre-sarcopenic and sarcopenic men was 1.40- and 4.97-times higher, respectively, in comparison to non-sarcopenic men in the minimally adjusted model (model 1). The associations were attenuated when the analysis was further adjusted for morbidity count, lifestyle and health-related factors (models 2 and 3) for sarcopenic men but remained significant for pre-sarcopenic men (HR: 1.30 [95% CI: 1.03 to 1.63]) (*Figure* 2). As per women, a similar trend was identified when a two-year landmark was included in the analysis but disappeared when protein and calcium intake were included (model 5, *Table* S4). When the subtypes of osteoporosis were used as outcomes, we observed a similar magnitude of association between pre-sarcopenic men and osteoporosis without pathological fractures. The associations with the pathological fracture incidence were non-significant (*Table* S5). On the other hand, regarding the cumulative hazard estimate, both men and women with sarcopenia had a steeper crude cumulative incidence of osteoporosis than non-sarcopenic men and women, respectively (*Figures* S2 and S3).

Of the three physical capability markers used to define categories of sarcopenia, slow gait speed and low muscle mass were independently associated with 1.30- and 1.36-times higher risk of incident osteoporosis in women and 1.70- and 3.07-times higher risk of incident osteoporosis in men, respectively (*Figure* 3, model 3). The associations remained when the analyses were further adjusted for protein and calcium intake and in the two-year landmark analysis (except for low muscle mass in men, probably due to the few numbers of cases). Low grip strength was associated with a higher risk of incident osteoporosis in men across all models ($HR_{model\ 3}$:1.38 [95% CI: 1.15 to 1.65]), but not in women. Based on model 3, low muscle mass was the physical capability marker associated with the highest risk of incident osteoporosis in both sexes.

Finally, while there were no significant interactions with age-group, the numerical magnitude of the associations between sarcopenia and incident osteoporosis was higher in the older age-group for sarcopenic women and pre-sarcopenic men compared to their counterparts (*Table* S6).

Discussion

Sarcopenia and osteoporosis are prevalent conditions that are associated with substantial health burden.[1] After adjustment for a wide range of potential confounding factors, pre-sarcopenia was associated with a higher risk of incident osteoporosis in men, but not in women, while sarcopenia was associated with a higher risk in women, but not in men. The lack of association between sarcopenic men and incident osteoporosis might be related to the low number of sarcopenic men in our study; therefore, this analysis was probably underpowered. These results were consistent for individuals without pathological fractures but not for those with osteoporosis with pathological fractures. The latter reinforces the relevance of the early assessment of sarcopenia in these individuals beyond fractures. Among the three physical capability markers used to define sarcopenia, low muscle mass was associated with the highest risk of incident osteoporosis in both sexes, followed by slow gait speed

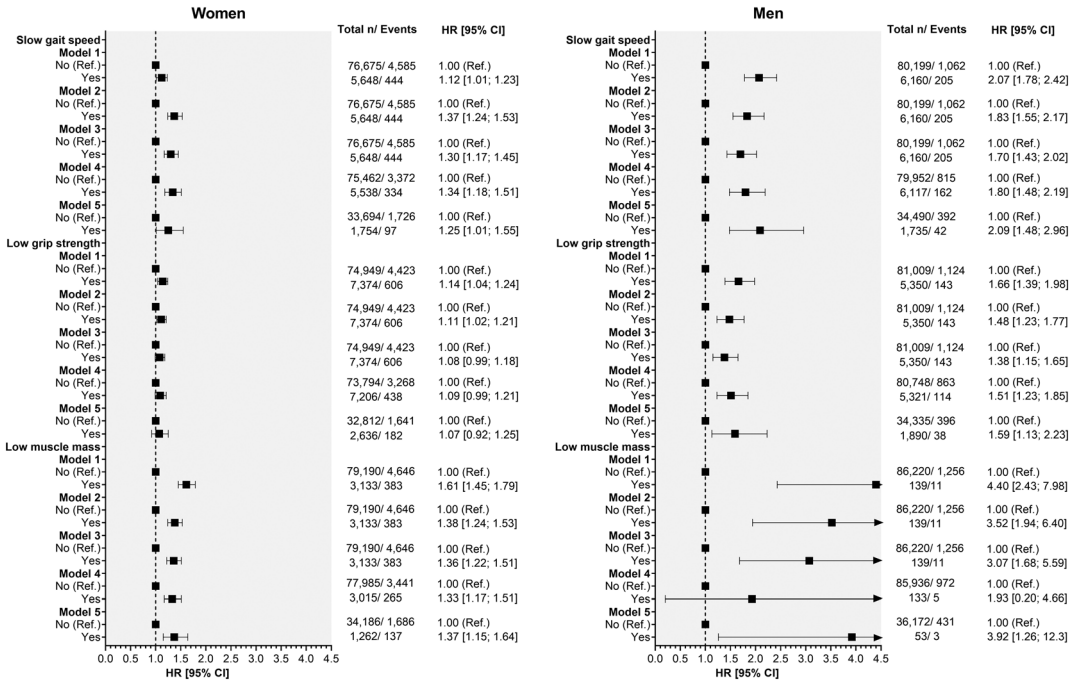

Figure 3 Associations between individual physical capability markers and incident osteoporosis by sex. Analyses are presented as HR with their respectively CI. Non-sarcopenic participants were used as the reference group. Analyses were adjusted by model 1, adjusted by socio-demographic factors (age and deprivation); model 2 as model 1, but additionally morbidity count, physical activity, smoking, body fat, alcohol and red and processed meat intake. Model 3, as model 2, but additionally adjusted by serum vitamin D levels, corticosteroids, H2 blockers, falls and fractures in the last 5 years and menopause in women and hypogonadism in men. Model 4, as per model 3, but using a 2-year landmark that excluded participants who experienced events within the first 2 years of follow-up; and model 5, as per model 3, but further adjusted for calcium and protein intake.

(in both sexes) and low grip strength (in men only). Given these findings, and considering the health and economic burden of osteoporosis in the United Kingdom,[4] preventing, diagnosing and treating sarcopenia might help prevent or delay some cases of osteoporosis and the significant health and financial burden associated with this, assuming causality. As the decrease in muscle mass starts at ~40 years,[27] and this leads to a higher risk of falls and fragility fractures, interventions improving or maintaining decent physical capability levels in middle and older ages are needed.

The association between sarcopenia and osteoporosis has been previously studied, but most evidence comes from cross-sectional studies.[7,8,10–12] To our knowledge, this is the first study reporting the longitudinal association between sarcopenia and incident osteoporosis. Previous prospective studies often used fractures as a proxy for osteoporosis, even though all fractures may not necessarily indicate osteoporosis and, as it was demonstrated in our study, pre-sarcopenic men and sarcopenic women had a higher risk of osteoporosis without pathological fractures. In terms of fracture studies, Yu et al. used the MrOs study to report that sarcopenia was an independent risk factor for fractures in men (HR: 1.87 [95% CI: 1.30 to 2.68]), but not in women (HR: 0.80 [95% CI: 0.49 to 1.31]).[19] Similarly, Scott et al. identified that sarcopenic obese community-dwelling older men had more than 3-times higher rate of self-reported fractures compared to non-sarcopenic non-obese men. Sarcopenic obese women, in contrast, had a higher risk of fracture compared with obese women (incident rate ratio: 2.82 [95% CI: 1.42 to 5.60]), but this was mediated by BMD (incident rate ratio: 1.93 [95% CI: 0.94 to 3.98]).[20] In comparison to our study, these studies used different classifications to define sarcopenia, their outcome was the risk of fracture instead of osteoporosis itself, and included only older individuals. The latter reinforces the relevance of our findings which identified an increased risk of osteoporosis in both sexes (women with sarcopenia and men with pre-sarcopenia) using the latest guidelines suggested for the EWGSOP2,[27] in both middle-aged and older adults.

In terms of the individual components used to define sarcopenia, the majority of previous studies have investigated their association with risk fractures as an outcome.[14,16,17] Only a few studies have also reported the association of these individual factors with osteoporosis or fragility fractures associated with osteoporosis.[15,33,34] Cheung et al., using a subset of 1702 participants from the prospective Hong Kong Osteoporosis study, found that grip strength was strongly associated with fragility fractures and osteoporosis at the hip.[33] Likewise, for each standard deviation lower in gait speed, there was a 2.16-times higher risk of hip fractures and 1.33-times higher risk of major osteoporotic fractures among 351 post-menopausal women who were followed up for

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10 years.[34] In Canada, after 6 years follow-up of 9622 men and women older than 40 years, Leslie et al. identified that a decrease in total body lean mass was independently associated with an increased risk of osteoporotic fractures.[15]

As a prospective study of osteoporosis, rather than a proxy, the current study fills gaps in the existing evidence base. However, several challenges remain. The lack of a single classification and definition for sarcopenia remains one of the greatest problems for research into sarcopenia, extending beyond studies of the association between sarcopenia and osteoporosis. Achieving a consensual definition would facilitate the comparison of results across studies that use a common definition and would help translation of the findings into clinical practice. Finally, future prospective studies should investigate the joint association of sarcopenia and osteoporosis, i.e., 'osteosarcopenia', on adverse health outcomes. Binkley & Buehring were the first to introduce the concept in 2009 as a subset of older adults with both osteoporosis and sarcopenia.[35] Although more studies have been carried out since that moment,[36,37] literature using prospective studies is lacking.[38]

Strength and limitations

UK Biobank provided the opportunity to test our hypothesis in a large and well characterized general population-based cohort of middle-aged and older adults. Consequently, analyses could be adjusted for multiple potential confounders. Moreover, incident osteoporosis was ascertained through linkage primary care records. However, UK Biobank is not representative of the UK population in terms of sociodemographic, lifestyle and prevalent disease. Therefore, while risk estimates can be generalized,[39] summary statistics such as the prevalence or incidence of health conditions should not.[40] Muscle mass was measured using BIA. While this method is not the gold standard, muscle mass estimated using BIA has been shown to have good agreement with DXA (r = 0.868).[41] In addition, owing to insufficient statistical power, we were unable to study severe sarcopenia as a separate category and therefore, we combined sarcopenia and severe sarcopenia. Even so, the number of participants in some sarcopenia categories, especially men, was low, which likely explains the lack of significant association for sarcopenic men. Another potential limitation is the self-reported gait speed. Although we used self-reported walking pace as a proxy of gait speed, previous studies have shown that this simple and cheap marker of physical capability has a strong predictive ability for chronic diseases and mortality, even beyond mean fracture risk.[42,43] In addition, even though our analyses adjusted for a large list of confounding factors, some of the associations identified might be due to residual or unmeasured confounding. Finally, the observational nature of the study does not allow us to infer causality from the association; therefore, future trials should investigate the potential causal link of sarcopenia and physical capability markers with osteoporosis.

In conclusion, our findings demonstrated that pre-sarcopenic men and sarcopenic women had a higher risk of incident osteoporosis even after adjustment for a large range of potential confounders. Since sarcopenia could be prevented, early public health strategies aimed at improving physical capability may help to prevent or delay some cases of osteoporosis. Randomized trials would help address this question.

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Conflict of interest

None declared.

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Author contribution

F.P.-R., J.P.P., F.K.H., and C.C.-M. contributed to the conception and design of the study, advised on all statistical aspects, and interpreted the data. F.P.-R. performed the literature search. F.P.-R. performed the analyses with support from J. P.P, F.K.H., and C.C.-M. All authors critically reviewed this and previous drafts. All authors approved the final draft for submission, with final responsibility for publication. J.P.P, F. K.H., and C.C.-M. contributed equally to this work and are joint senior authors. F.P.-R., F.K.H., J.P.P., and C.C.-M. are the guarantor.

Copyright

Transparency

The lead author, (the manuscript's guarantor), affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data availability statement

All UK Biobank information is available online on the webpage www.ukbiobank.co.uk. Data access is available through applications. This research was conducted using the application number 7155.

Online supplementary material

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

Figure S1. Diagram – Participants according to the different classification by idividuals capability markers and categories of sarcopenia by sex.
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Table S5. Associations between categories of sarcopenia with subtypes osteoporosis incidence by sex
Table S6. Associations between categories of sarcopenia and incident osteoporosis by age groups and sex.

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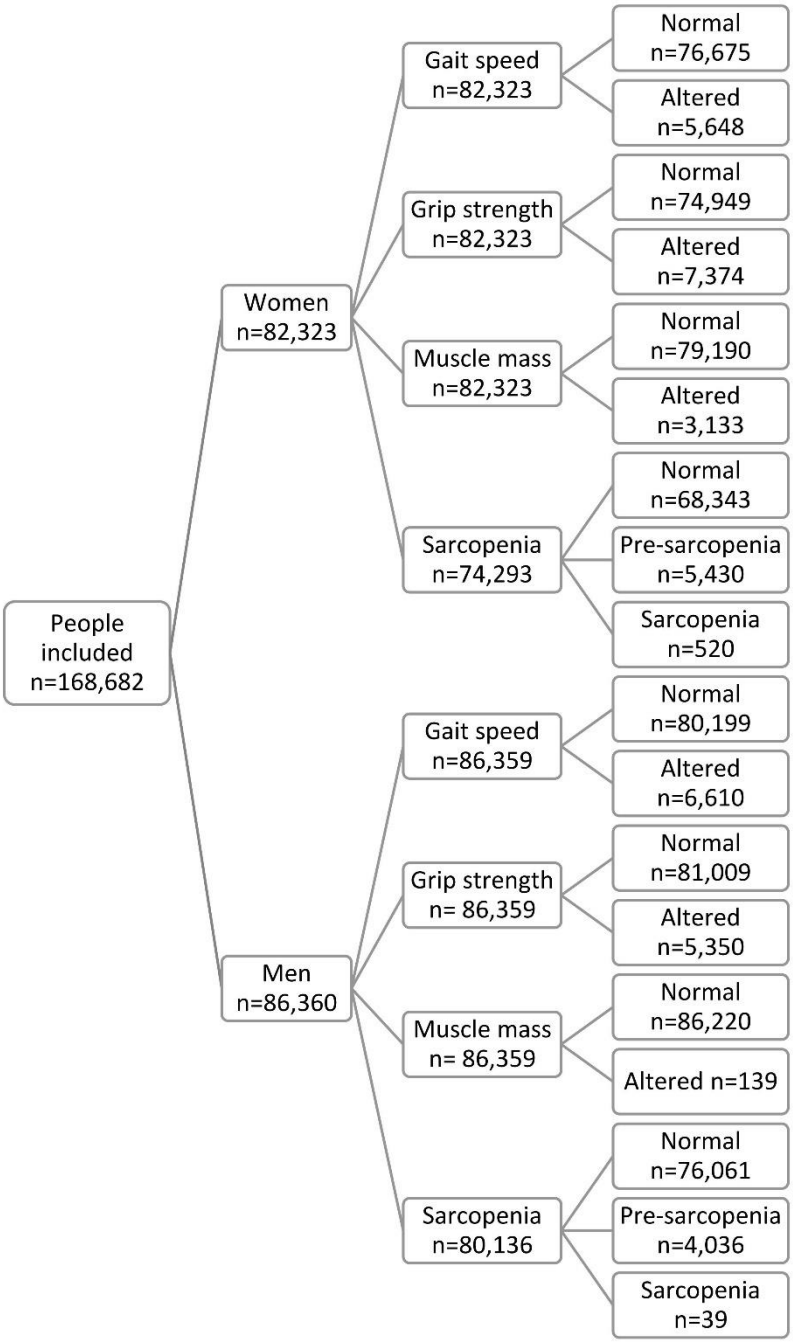
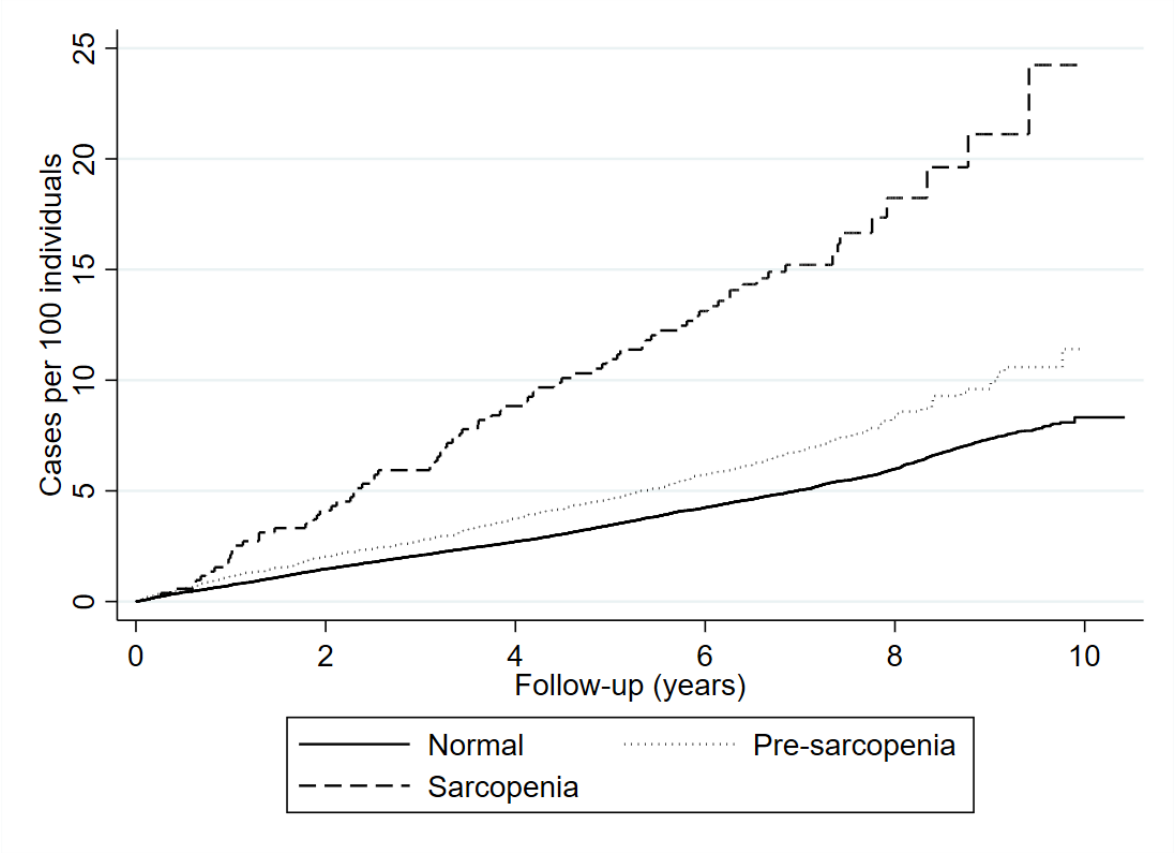
4.2.1 Appendix C



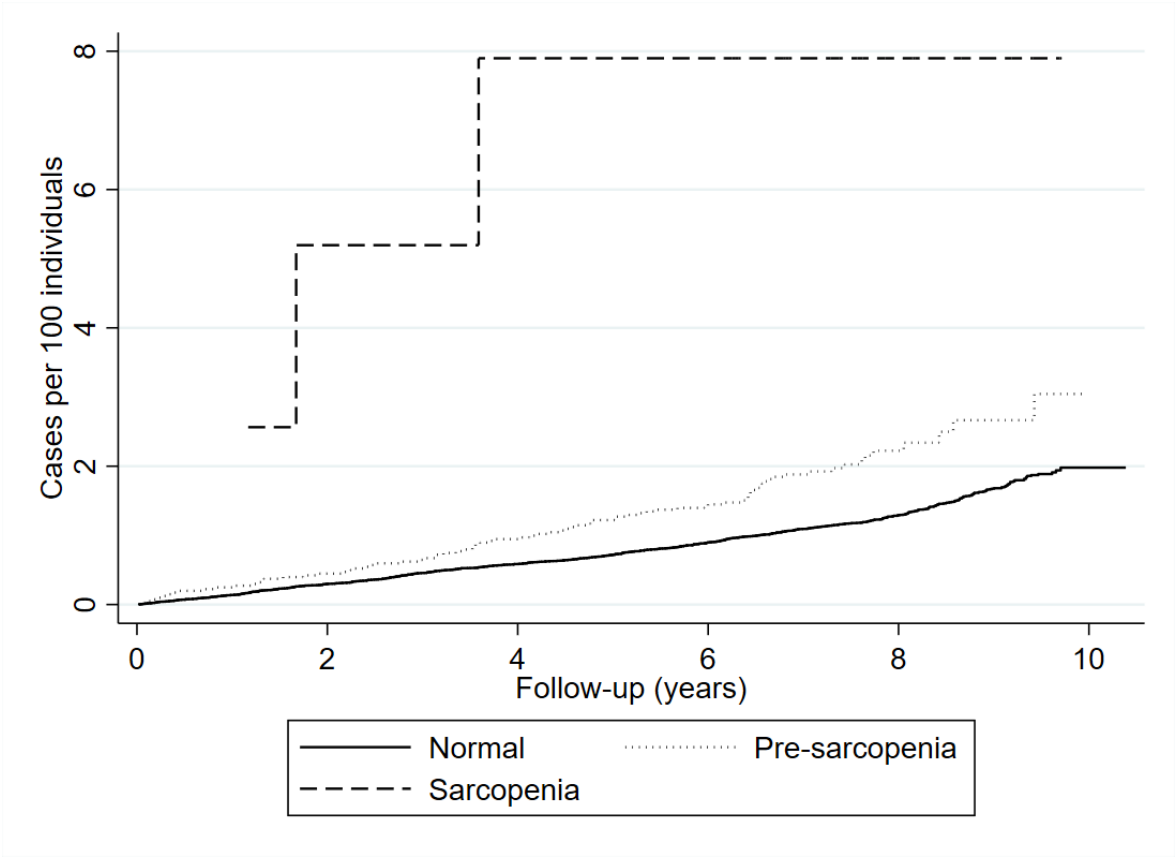
4.2.2 Figure S1. Diagram – Participants according to the different classification by idividuals capability markers and categories of sarcopenia by sex.

*Sarcopenia includes those with sarcopenia or severe sarcopenia.



4.2.3 Figure S2. Cumulative hazard plot of osteoporosis incidence by categories of sarcopenia and follow-up time in women.

Data presented as crude HR by categories of sarcopenia.



4.2.4 Figure S3. Cumulative hazard plot of osteoporosis incidence by categories of sarcopenia and follow-up time in men.

Data presented as crude HR by categories of sarcopenia.

4.2.5 Table S1. Baseline characteristics by categories of gait speed and sex

	Women		Men	
	Normal range	Slow gait speed	Normal range	Slow gait speed
Socio-demographics				
Total n, (%)	76,675 (93.1)	5,648 (6.9)	80,199 (92.9)	66,160 (7.1)
Age (years), mean (SD)	55.9 (8.1)	58.6 (7.5)	56.7 (8.1)	60.1 (6.9)
Deprivation, n (%)				
Lower	26,890 (35.1)	1,344 (23.8)	28,668 (35.8)	1,359 (22.1)
Middle	27,031 (35.2)	1,777 (31.5)	27,742 (34.6)	1,715 (27.8)
Higher	22,754 (29.7)	2,527 (44.7)	23,789 (29.6)	3,086 (50.1)
Lifestyle				
Body fat (kg), mean (SD)	26.1 (9.3)	36.3 (13.5)	22.0 (7.8)	28.2 (10.9)
Total PA (MET/h/week), mean (SD)	2,745.2 (2,835.3)	1,882.7 (2,261.7)	3,358.2 (3,721.4)	2,301.5 (2,845.5)
Total Sedentary behaviour (h/day), mean (SD)	4.6 (1.9)	5.4 (2.5)	5.4 (2.4)	6.2 (2.9)
Red meat (portion.week-1), mean (SD)	2.0 (1.3)	2.1 (1.4)	2.2 (1.5)	2.4 (1.7)
Processed meat intake (portion.week-1), mean (SD)	1.6 (1.0)	1.8 (1.1)	2.2 (1.0)	2.4 (1.1)
Protein (g/day), mean (SD)	78.6 (23.1)	79.1 (27.2)	87.7 (27.4)	85.9 (32.3)
Calcium (mg/day), mean (SD)	958.5 (371.2)	953.5 (432.6)	1,029.8 (402.8)	1,025.6 (468.2)
Alcohol frequency intake, n (%)				
Daily or almost daily	12,780 (16.7)	616 (10.9)	20,590 (25.7)	1,277 (20.7)
3-4 times a week	17,079 (22.3)	699 (12.4)	22,411 (28.0)	1,158 (18.8)
Once or twice a week	21,237 (27.7)	1,260 (22.3)	21,605 (26.9)	1,603 (26.0)
1-3 times a month	10,231 (13.3)	795 (14.0)	7,087 (8.8)	604 (9.8)
Special occasions only	9,997 (13.0)	1,314 (23.3)	4,890 (6.1)	781 (12.7)
Never	5,351 (7.0)	964 (17.1)	3,616 (4.5)	737 (12.0)
Smoking status n (%)				
Never	45,981 (60.0)	2,800 (49.6)	40,337 (50.3)	1,948 (31.6)
Previous	24,391 (31.8)	1,974 (35.0)	30,895 (38.5)	2,691 (48.1)
Current	6,303 (8.2)	874 (15.4)	8,967 (11.2)	1,251 (20.3)
Health status				
Multimorbidity, n (%)				
0	29,313 (38.2)	642 (11.4)	29,378 (36.6)	627 (10.2)
≥1	47,362 (61.8)	5,006 (88.6)	50,821 (63.4)	5,533 (89.8)
Vitamin D (nmol/l), mean (SD)	48.9 (20.6)	41.9 (20.0)	49.5 (21.0)	44.1 (21.1)
Using H2 blockers, n (%)	1,242 (1.6)	204 (3.6)	1,359 (1.7)	251 (4.1)
Using steroid, n (%)	647 (0.8)	196 (3.5)	798 (1.0)	186 (3.0)
Fractures in the last five years, n (%)	7,017 (9.2)	736 (13.1)	6,551 (8.2)	658 (10.8)
Falls in the last year, n (%)				
No falls	60,931 (79.6)	3,361 (59.7)	69,080 (86.2)	3,897 (63.6)
Only one fall	11,476 (15.0)	1,075 (19.1)	7,769 (9.7)	863 (14.1)
More than one fall	4,184 (5.4)	1,190 (21.2)	3,242 (4.1)	1,367 (22.3)
Hypogonadism, n (%)	-	-	356 (0.4)	41 (0.7)
Menopause, n (%)	53,575 (69.9)	4,686 (83.0)	-	-

n: number; PA: physical activity; MET: metabolic-equivalent; SD: standard deviation. *Sarcopenia includes those with sarcopenia or severe sarcopenia.

4.2.6 Table S2. Baseline characteristics by categories of grip strength and sex

	Women		Men	
	Normal range	Low grip strength	Normal range	Low grip strength
Socio-demographics				
Total n, (%)	74,949 (91.0)	7,374 (9.0)	81,009 (93.8)	5,350 (6.2)
Age (years), mean (SD)	55.7 (8.1)	60.0 (6.9)	56.7 (8.1)	60.2 (7.2)
Deprivation, n (%)				
Lower	26,208 (35.0)	2,026 (27.5)	28,709 (35.4)	1,318 (24.6)
Middle	26,204 (35.0)	2,604 (35.3)	27,793 (34.3)	1,664 (31.1)
Higher	22,537 (30.0)	2,744 (37.2)	24,507 (30.3)	2,368 (44.3)
Lifestyle				
Body fat (kg), mean (SD)	26.7 (9.9)	28.2 (10.6)	22.4 (8.2)	23.6 (9.0)
Total PA (MET/h/week), mean (SD)	2,713.6 (2,817.8)	2,584.0 (2,794.3)	3,331.3 (3,705.2)	2,813.1 (3,345.0)
Total Sedentary behaviour (h/day), mean (SD)	4.6 (2.0)	4.8 (2.1)	5.6 (2.4)	5.6 (2.6)
Red meat (portion.week-1), mean (SD)	2.0 (1.3)	2.0 (1.3)	2.3 (1.5)	2.3 (1.6)
Processed meat intake (portion.week-1), mean (SD)	1.6 (1.0)	1.7 (1.0)	2.2 (1.0)	2.3 (1.1)
Protein (g/day), mean (SD)	78.7 (23.2)	77.7 (23.9)	87.8 (27.7)	84.9 (27.5)
Calcium (mg/day), mean (SD)	958 (373.1)	949.6 (390.7)	1,031.0 (406.2)	1,004.7 (406.4)
Alcohol frequency intake, n (%)				
Daily or almost daily	12,386 (16.5)	1,010 (13.7)	20,625 (25.5)	1,242 (23.2)
3-4 times a week	16,582 (22.1)	1,196 (16.2)	22,379 (27.6)	1,190 (22.2)
Once or twice a week	20,550 (27.4)	1,947 (26.5)	21,800 (26.9)	1,408 (26.3)
1-3 times a month	10,112 (13.5)	914 (12.4)	7,206 (8.9)	485 (9.1)
Special occasions only	9,951 (12.3)	1,360 (18.4)	5,168 (6.4)	503 (9.4)
Never	5,368 (7.2)	947 (12.8)	3,831 (4.7)	522 (9.8)
Smoking status n (%)				
Never	44,620 (59.6)	4,161 (56.5)	39,896 (49.3)	2,389 (44.7)
Previous	23,855 (31.8)	2,510 (34.0)	31,624 (39.0)	2,232 (41.7)
Current	6,474 (8.6)	703 (9.5)	9,489 (11.7)	729 (13.6)
Health status				
Multimorbidity, n (%)				
0	28,411 (37.9)	1,544 (20.9)	28,909 (35.7)	1,096 (20.5)
≥1	46,538 (62.1)	5,830 (79.1)	52,100 (64.3)	4,254 (79.5)
Vitamin D (nmol/l), mean (SD)	48.4 (20.6)	48.2 (20.7)	49.2 (21.1)	47.3 (21.1)
Using H2 blockers, n (%)	1,240 (1.6)	206 (2.8)	1,450 (1.8)	160 (3.0)
Using steroid, n (%)	682 (0.9)	161 (2.2)	852 (1.0)	132 (2.5)
Fractures in the last five years, n (%)	6,830 (9.1)	923 (12.6)	6,669 (8.3)	540 (10.2)
Falls in the last year, n (%)				
No falls	59,260 (79.2)	5,032 (68.4)	69,125 (85.5)	3,852 (72.2)
Only one fall	11,206 (15.0)	1,345 (18.3)	7,896 (9.7)	762 (14.3)
More than one fall	4,397 (5.8)	977 (13.3)	3,890 (4.8)	719 (13.5)
Hypogonadism, n (%)	-	-	362 (0.4)	35 (0.6)
Menopause, n (%)	51,760 (69.1)	6,501 (88.2)	-	-

n: number; PA: physical activity; MET: metabolic-equivalent; SD: standard deviation. *Sarcopenia includes those with sarcopenia or severe sarcopenia.

4.2.7 Table S3. Baseline characteristics by categories of muscle mass and sex

	Women		Men	
	Normal range	Low muscle mass	Normal range	Low muscle mass
Socio-demographics				
Total n, (%)	79,190 (96.2)	3,133 (3.8)	86,220 (99.8)	139 (0.2)
Age (years), mean (SD)	55.9 (8.1)	61.4 (6.0)	56.9 (8.1)	60.6 (6.8)
Deprivation, n (%)				
Lower	27,103 (34.2)	1,131 (36.1)	29,988 (34.8)	39 (28.1)
Middle	27,685 (35.0)	1,123 (35.8)	29,422 (34.1)	35 (25.2)
Higher	24,402 (30.8)	879 (28.1)	26,810 (31.1)	65 (46.8)
Lifestyle				
Body fat (kg), mean (SD)	27.0 (10.1)	22.4 (6.6)	22.5 (8.2)	18.3 (7.4)
Total PA (MET/h/week), mean (SD)	2,706.2 (2,821.2)	2,617.7 (2.677.9)	3,303.4 (3,689.2)	2,287.0 (2,087.0)
Total Sedentary behaviour (h/day), mean (SD)	4.6 (2.0)	4.6 (1.9)	5.5 (2.4)	5.5 (2.8)
Red meat (portion.week-1), mean (SD)	2.0 (1.3)	2.0 (1.3)	2.3 (1.5)	2.2 (1.6)
Processed meat intake (portion.week-1), mean (SD)	1.6 (1.0)	1.6 (1.0)	2.2 (1.0)	2.2 (1.1)
Protein (g/day), mean (SD)	78.7 (23.4)	75.4 (21.1)	87.6 (27.7)	86.5 (31.7)
Calcium (mg/day), mean (SD)	959.5 (375.0	922.2 (356.1)	1,029.5 (406.0)	1,067.3 (512.4)
Alcohol frequency intake, n (%)				
Daily or almost daily	12,785 (16.1)	611 (19.5)	21,816 (25.3)	51 (36.7)
3-4 times a week	17,121 (21.6)	657 (21.0)	23,539 (27.3)	30 (21.6)
Once or twice a week	21,714 (27.5)	784 (25.0)	23,179 (26.9)	29 (20.9)
1-3 times a month	10,638 (13.4)	388 (12.4)	7,682 (8.9)	9 (6.5)
Special occasions only	10,896 (13.8)	415 (13.2)	5,663 (6.6)	8 (5.7)
Never	6,036 (7.6)	279 (8.9)	4,341 (5.0)	12 (8.6)
Smoking status n (%)				
Never	46,891 (59.2)	1,890 (60.3)	42,231 (49.0)	54 (38.9)
Previous	25,398 (32.1)	967 (30.9)	33,814 (39.2)	42 (30.2)
Current	6,901 (8.7)	276 (8.8)	10,175 (11.8)	43 (30.9)
Health status				
Multimorbidity, n (%)				
0	29,023 (36.6)	932 (29.8)	29,967 (34.8)	38 (27.3)
≥1	50,167 (63.4)	2,201 (70.2)	56,253 (65.2)	101 (72.7)
Vitamin D (nmol/l), mean (SD)	48.3 (20.6)	49.8 (21.0)	49.1 (21.1)	41.2 (23.5)
Using H2 blockers, n (%)	1,378 (1.7)	68 (2.2)	1,608 (1.9)	2 (1.4)
Using steroid, n (%)	792 (1.0)	51 (1.6)	981 (1.1)	3 (2.2)
Fractures in the last five years, n (%)	7,400 (9.4)	353 (11.3)	7,187 (8.4)	22 (15.8)
Falls in the last year, n (%)				
No falls	61,905 (78.3)	2,387 (76.3)	72,877 (84.7)	100 (71.9)
Only one fall	11,985 (15.2)	566 (18.1)	8,610 (10.0)	21 (15.1)
More than one fall	5,197 (6.5)	177 (5.6)	4,591 (5.3)	18 (13.0)
Hypogonadism, n (%)	-	-	397 (0.5)	0
Menopause, n (%)	55,327 (69.9)	2,935 (93.7)	-	-

n: number; PA: physical activity; MET: metabolic-equivalent; SD: standard deviation. *Sarcopenia includes those with sarcopenia or severe sarcopenia.

4.2.8 Table S4. Associations between categories of sarcopenia with incident osteoporosis by sex

Women							
	Total n	Events	Normal	Pre-sarcopenia (low grip)		Sarcopenia	
				HR (95% CI)	p-value	HR (95% CI)	p-value
Model 1	74,293	4,321	1.00 (Ref.)	1.04 (0.94; 1.16)	0.420	2.01 (1.61; 2.51)	<0.001
Model 2	74,293	4,321	1.00 (Ref.)	1.02 (0.92; 1.13)	0.717	1.70 (1.36; 2.12)	<0.001
Model 3	74,293	4,321	1.00 (Ref.)	1.00 (0.90; 1.11)	0.956	1.66 (1.33; 2.08)	<0.001
Model 4	73,166	3,195	1.00 (Ref.)	1.02 (0.90; 1.15)	0.764	1.79 (1.38; 2.33)	<0.001
Model 5	32,686	1,618	1.00 (Ref.)	1.01 (0.85; 1.21)	0.889	1.48 (0.96; 2.25)	0.072
Men							
	Total n	Events	Normal	Pre-sarcopenia (low grip)		Sarcopenia	
				HR (95% CI)	p-value	HR (95% CI)	p-value
Model 1	80,136	1,059	1.00 (Ref.)	1.40 (1.12; 1.76)	0.004	4.97 (1.60; 15.4)	0.006
Model 2	80,136	1,059	1.00 (Ref.)	1.34 (1.07; 1.68)	0.012	3.65 (1.17; 11.4)	0.026
Model 3	80,136	1,059	1.00 (Ref.)	1.30 (1.03; 1.63)	0.025	3.04 (0.97; 9.54)	0.057
Model 4	79,890	813	1.00 (Ref.)	1.37 (1.06; 1.78)	0.016	1.53 (0.21; 11.0)	0.671
Model 5	34,462	392	1.00 (Ref.)	1.37 (0.92; 2.05)	0.120	6.95 (0.97; 49.8)	0.054

Analyses are presented as HR with their respectively CI. Non-sarcopenic participants were used as the reference group. Analyses were adjusted by: model 1, adjusted by socio-demographic factors (age and deprivation); model 2 as model 1, but additionally morbidity count, physical activity, smoking, alcohol and red and processed meat intake. Model 3, as model 2, but additionally adjusted by corticosteroids, H2 blockers, falls and fractures in the last five years and menopause in women and hypogonadism in men. Model 4, as per model 3, but using a 2-year landmark that excluded participants who experienced events within the first two years of follow-up; and model 5, as per model 3, but further adjusted for calcium and protein intake.

4.2.9 Table S5. Associations between categories of sarcopenia with subtypes osteoporosis incidence by sex

Women							
	Total n	Events	Normal	Pre-sarcopenia (low grip)		Sarcopenia	
				HR (95% CI)	p-value	HR (95% CI)	p-value
Pathological fracture							
Model 1	74,293	2,852	1.00 (Ref.)	0.88 (0.77; 1.02)	0.083	1.51 (1.10; 2.07)	0.011
Model 2	74,293	817	1.00 (Ref.)	0.87 (0.76; 1.01)	0.062	1.36 (0.99; 1.87)	0.057
Model 3	74,293	817	1.00 (Ref.)	0.86 (0.75; 0.99)	0.042	1.35 (0.98; 1.86)	0.064
Model 4	73,166	2,175	1.00 (Ref.)	0.89 (0.76; 1.05)	0.159	1.36 (0.93; 1.98)	0.109
Model 5	32,686	945	1.00 (Ref.)	0.88 (0.68; 1.14)	0.331	1.29 (0.69; 2.42)	0.425
Without pathological fracture							
Model 1	74,293	2,404	1.00 (Ref.)	1.15 (1.00; 1.31)	0.042	2.52 (1.95; 3.27)	<0.001
Model 2	74,293	2,404	1.00 (Ref.)	1.10 (0.96; 1.26)	0.164	1.93 (1.49; 2.50)	<0.001
Model 3	74,293	2,404	1.00 (Ref.)	1.08 (0.94; 1.23)	0.281	1.86 (1.43; 2.41)	<0.001
Model 4	73,628	1,739	1.00 (Ref.)	1.10 (0.94; 1.28)	0.255	2.02 (1.50; 2.74)	<0.001
Model 5	32,686	975	1.00 (Ref.)	1.02 (0.82; 1.28)	0.831	1.51 (0.92; 2.49)	0.103
Classified elsewhere							
Model 1	74,293	1,473	1.00 (Ref.)	1.32 (1.12; 1.54)	0.001	2.73 (2.00; 3.73)	<0.001
Model 2	74,293	1,473	1.00 (Ref.)	1.25 (1.06; 1.47)	0.006	2.06 (1.50; 2.82)	<0.001
Model 3	74,293	1,473	1.00 (Ref.)	1.22 (1.04; 1.44)	0.013	1.98 (1.44; 2.70)	<0.001
Model 4	73,845	1,025	1.00 (Ref.)	1.25 (1.03; 1.51)	0.024	2.28 (1.59; 3.29)	<0.001
Model 5	32,686	675	1.00 (Ref.)	1.13 (0.88; 1.45)	0.352	1.62 (0.91; 2.88)	0.100
Men							
	Total n	Events	Normal	Pre-sarcopenia (low grip)		Sarcopenia	
				HR (95% CI)	p-value	HR (95% CI)	p-value
Pathological fracture							
Model 1	80,136	817	1.00 (Ref.)	1.38 (1.06; 1.80)	0.018	6.69 (2.15; 20.8)	0.001
Model 2	80,136	817	1.00 (Ref.)	1.32 (1.01; 1.72)	0.042	5.41 (1.73; 16.9)	0.004
Model 3	80,136	817	1.00 (Ref.)	1.28 (0.98; 1.67)	0.071	4.54 (1.44; 14.3)	0.010
Model 4	79,890	634	1.00 (Ref.)	1.28 (0.94; 1.74)	0.116	2.22 (0.31; 15.9)	0.429
Model 5	34,462	290	1.00 (Ref.)	1.29 (0.79; 2.12)	0.308	8.74 (1.22; 62.8)	0.031
Without pathological fracture							
Model 1	80,136	401	1.00 (Ref.)	1.64 (1.18; 2.30)	0.003	7.84 (1.95; 31.6)	0.004
Model 2	80,136	401	1.00 (Ref.)	1.56 (1.12; 2.19)	0.009	4.30 (1.05; 17.6)	0.042
Model 3	80,136	401	1.00 (Ref.)	1.49 (1.06; 2.08)	0.020	3.31 (0.80; 13.7)	0.098
Model 4	80,045	310	1.00 (Ref.)	1.60 (1.10; 2.34)	0.014	2.55 (0.35; 18.6)	0.357
Model 5	34,462	151	1.00 (Ref.)	1.46 (0.80; 2.65)	0.212	15.8 (2.12; 118.0)	0.007
Classified elsewhere							
Model 1	80,136	247	1.00 (Ref.)	1.43 (0.92; 2.22)	0.115	5.91 (0.83; 42.3)	0.077
Model 2	80,136	247	1.00 (Ref.)	1.34 (0.86; 2.09)	0.194	3.05 (0.42; 22.3)	0.271
Model 3	80,136	247	1.00 (Ref.)	1.29 (0.83; 2.02)	0.259	2.54 (0.34; 18.8)	0.360
Model 4	80,073	184	1.00 (Ref.)	1.58 (0.97; 2.58)	0.064	4.15 (0.56; 31.0)	0.165
Model 5	34,462	105	1.00 (Ref.)	1.05 (0.76; 3.00)	0.245	-	-

Non-sarcopenic participants were used as the reference group. Analyses were adjusted by: model 1, adjusted by socio-demographic factors; model 2 as model 1, but additionally morbidity count, physical activity, smoking, alcohol and red and processed meat intake. Model 3, as model 2, but additionally adjusted by corticosteroids, H2 blockers, falls and fractures in the last five years and menopause in women and hypogonadism in men. Model 4, as per model 3, but using a 2-year landmark that excluded participants who experienced events within the first two years of follow-up; and model 5, as per model 3, but further adjusted for calcium and protein intake.

4.2.10 Table S6. Associations between categories of sarcopenia and incident osteoporosis by age groups and sex

	Total n	death-events	Normal	Pre-sarcopenia (low grip)		Sarcopenia *	
			HR (95%CI)	HR (95% CI)	p-value	HR (95% CI)	p-value
≥ and < 45 years							
Women							
≥45 years	65,436	4,203	1.00 (Ref.)	1.06 (0.96; 1.18)	0.259	1.87 (1.50; 2.34)	<0.001
< 45 years	8,857	118	1.00 (Ref.)	2.09 (0.91; 4.83)	0.084	-	-
p-interaction					0.093		-
Men							
≥45 years	71,871	1,003	1.00 (Ref.)	1.27 (1.01; 1.61)	0.039	3.06 (0.97; 9.62)	0.056
< 45 years	8,265	56	1.00 (Ref.)	2.26 (0.69; 7.41)	0.179	-	-
p-interaction					0.433		
≥ and < 55 years							
Women							
≥55 years	43,134	3,408	1.00 (Ref.)	1.05 (0.94; 1.18)	0.352	1.72 (1.36; 2.17)	<0.001
< 55 years	31,159	913	1.00 (Ref.)	0.96 (0.69; 1.33)	0.804	2.64 (1.22; 5.69)	0.013
p-interaction					0.758		0.161
Men							
≥ 55 years	49,917	800	1.00 (Ref.)	1.30 (1.01; 1.66)	0.041	3.34 (1.06; 10.5)	0.040
< 55 years	30,219	259	1.00 (Ref.)	1.37 (0.77; 2.46)	0.286	-	-
p-interaction					0.850		-
≥ and < 60 years							
Women							
≥60 years	29,351	2,479	1.00 (Ref.)	0.98 (0.86; 1.11)	0.702	1.75 (1.36; 2.24)	<0.001
< 60 years	44,942	1,842	1.00 (Ref.)	1.17 (0.97; 1.42)	0.102	1.67 (0.98; 2.84)	0.058
p-interaction					0.098		0.908
Men							
≥60 years	35,654	609	1.00 (Ref.)	1.29 (0.98; 1.70)	0.064	2.32 (0.57; 9.47)	0.243
< 60 years	44,482	450	1.00 (Ref.)	1.30 (0.85; 1.99)	0.223	5.27 (0.73; 37.8)	0.098
p-interaction					0.846		0.477
≥ and < 65 years							
Women							
≥65 years	11,861	1,101	1.00 (Ref.)	0.97 (0.81; 1.16)	0.746	1.68 (1.21; 2.33)	0.002
< 65 years	62,432	3,220	1.00 (Ref.)	1.08 (0.95; 1.23)	0.255	1.84 (1.35; 2.49)	<0.001
p-interaction					0.222		0.546
Men							
≥65 years	16,074	306	1.00 (Ref.)	1.34 (0.94; 1.89)	0.103	1.99 (0.27; 14.6)	0.499
< 65 years	64,062	753	1.00 (Ref.)	1.26 (0.93; 1.71)	0.140	3.65 (0.90; 14.8)	0.071
p-interaction					0.930		0.700

Analyses are presented as HR with their respectively CI. Non-sarcopenic participants were used as the reference group. Analyses were adjusted by deprivation, morbidity count, physical activity, smoking, alcohol and red and processed meat intake, corticosteroids, H2 blockers, falls and fractures in the last five years and menopause in women and hypogonadism in men.

4.3 The joint association of sarcopenia and frailty with incidence and mortality health outcomes: A prospective study (Paper 4)

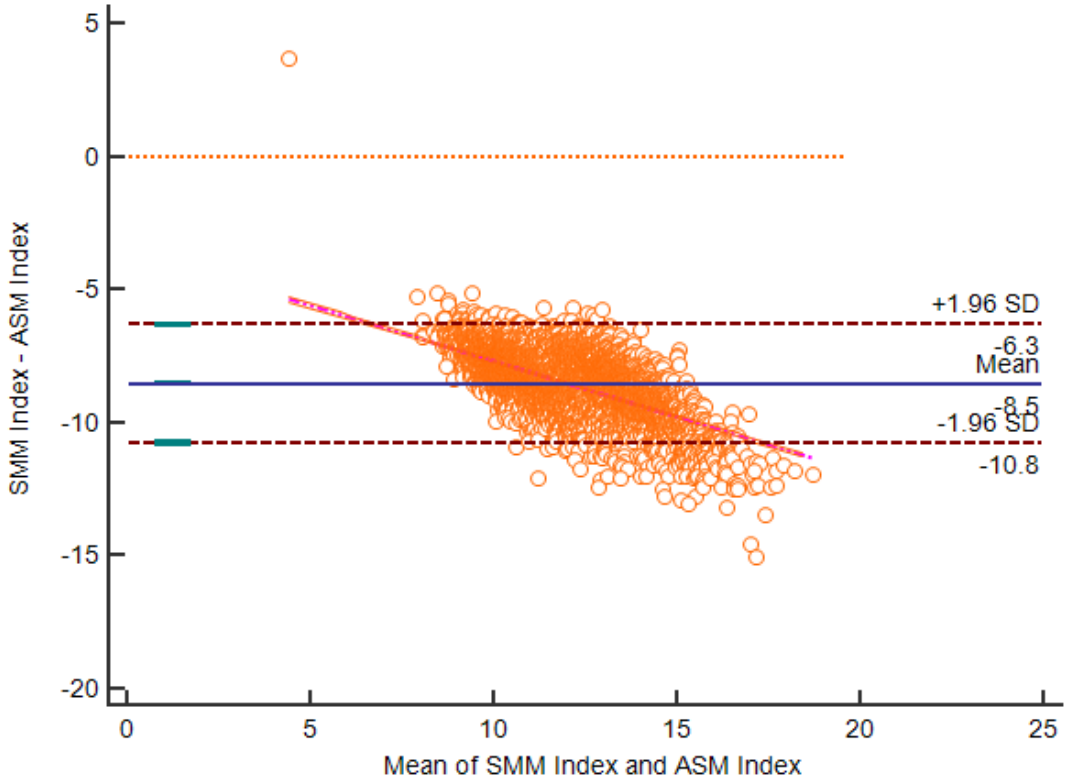
Petermann-Rocha, F., Gray, S.R., Pell, J.P., Ho, F.K. and Celis-Morales, C. (2021) The joint association of sarcopenia and frailty with incidence and mortality health outcomes: a prospective study. *Clinical Nutrition*, 40(4), pp. 2427-2434. (doi: 10.1016/j.clnu.2020.10.044)

4.3.1 Appendix D

4.3.2 Supplementary methods

Frailty measures

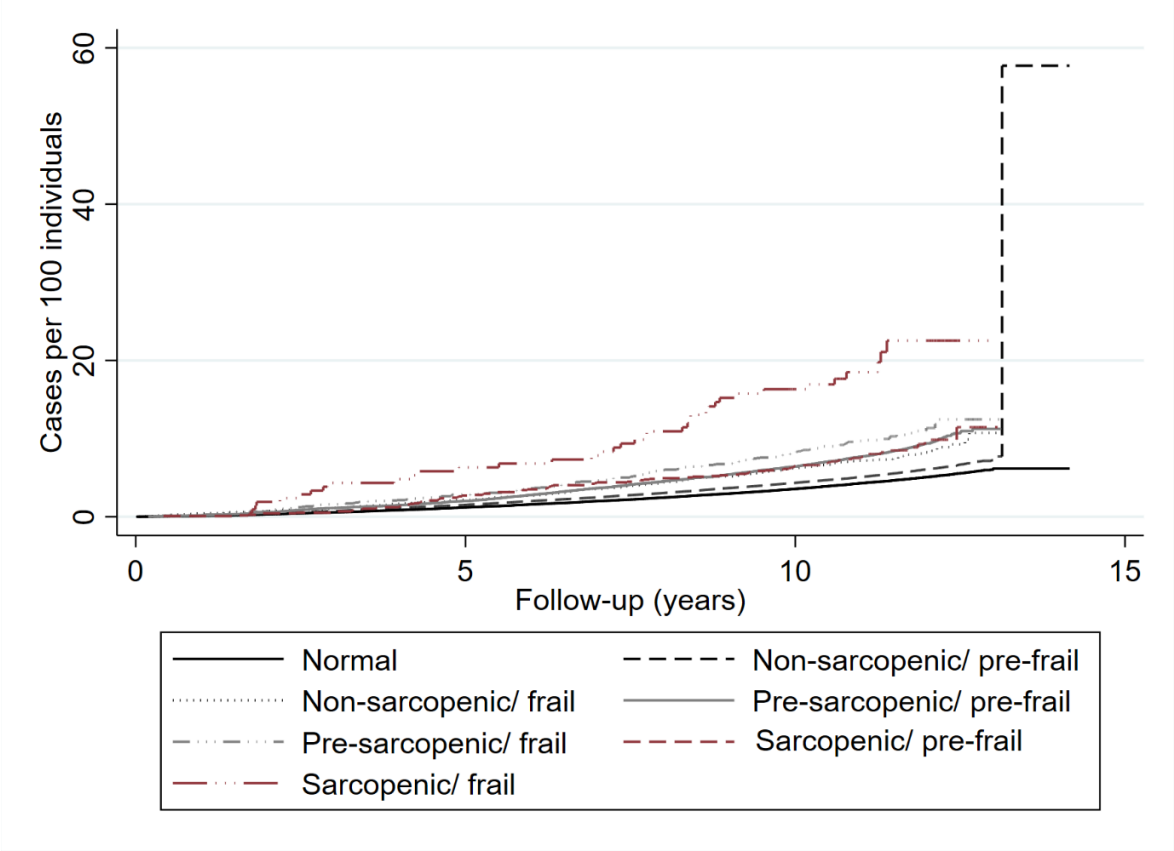
Weight loss was derived from self-report of weight loss in the previous year, dichotomised into yes or no (same weight or gained weight). Exhaustion was derived from the self-report of tiredness in the last two weeks categorised as: not at all; several days; more than half the days; nearly every day. Those participants who reported tiredness more than half the days or nearly every day were identified as meeting the Fried criterion for exhaustion (Fried et al., 2001b). Physical activity was based on self-report, collected using the International Physical Activity Questionnaire (IPAQ) short form (Guo et al., 2015). Total physical activity was computed as the sum of walking, moderate and vigorous activity, measured as metabolic equivalents (MET-hours/week). To derive a proxy for the Fried frailty criteria, this variable was categorised into age-sex-specific quintiles where the lowest quintile (20%) was classified as meeting the physical inactivity criterion for frailty. Walking speed was categorised as slow, average or brisk. To derive a proxy for gait speed, this was then dichotomised into slow or normal (average or brisk pace). Grip strength was measured using a Jamar J00105 hydraulic hand dynamometer. Isometric grip force was assessed from a single 3-second maximal grip effort, separately in the right and left arms, with the participant seated upright with their elbow by their side and flexed at 90º so that their forearm was facing forwards and resting on an armrest. The average of the right and left values were expressed in absolute units (kg) and used in subsequent analyses.



4.3.3 Supplementary Figure 1. Mean difference between BIA (SMM Index) and DXA (ASM Index)

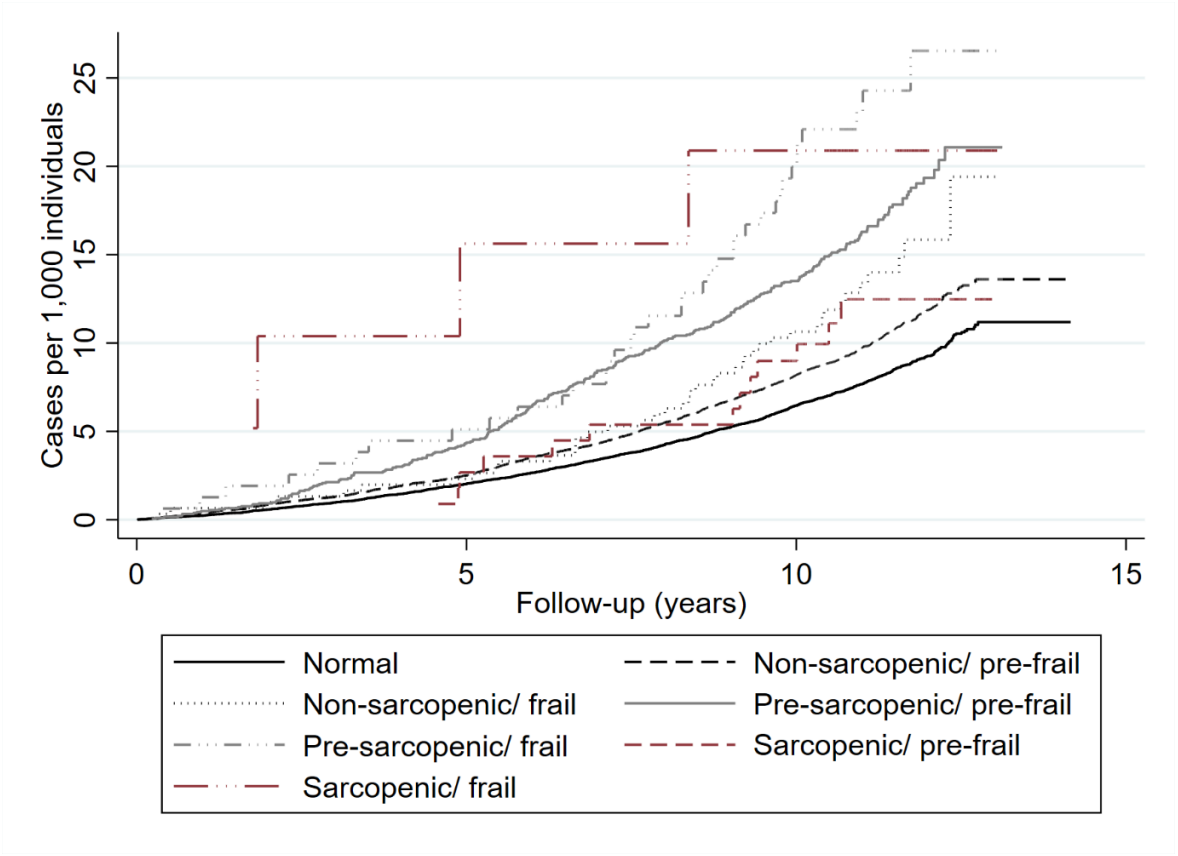
Data presented the agreement between two continues variables (ASM and SMM) using the Bland-Altman plot. Muscle mass measured using BIA showed a strong correlation with DXA (r=0.868, p<0.001) and was in a good agreement using a Bland-Altman plot.

SMM: skeletal muscle mass; ASM: appendicular skeletal muscle mass; BIA: bioimpedance; DXA: dual-energy X-ray absorptiometry.



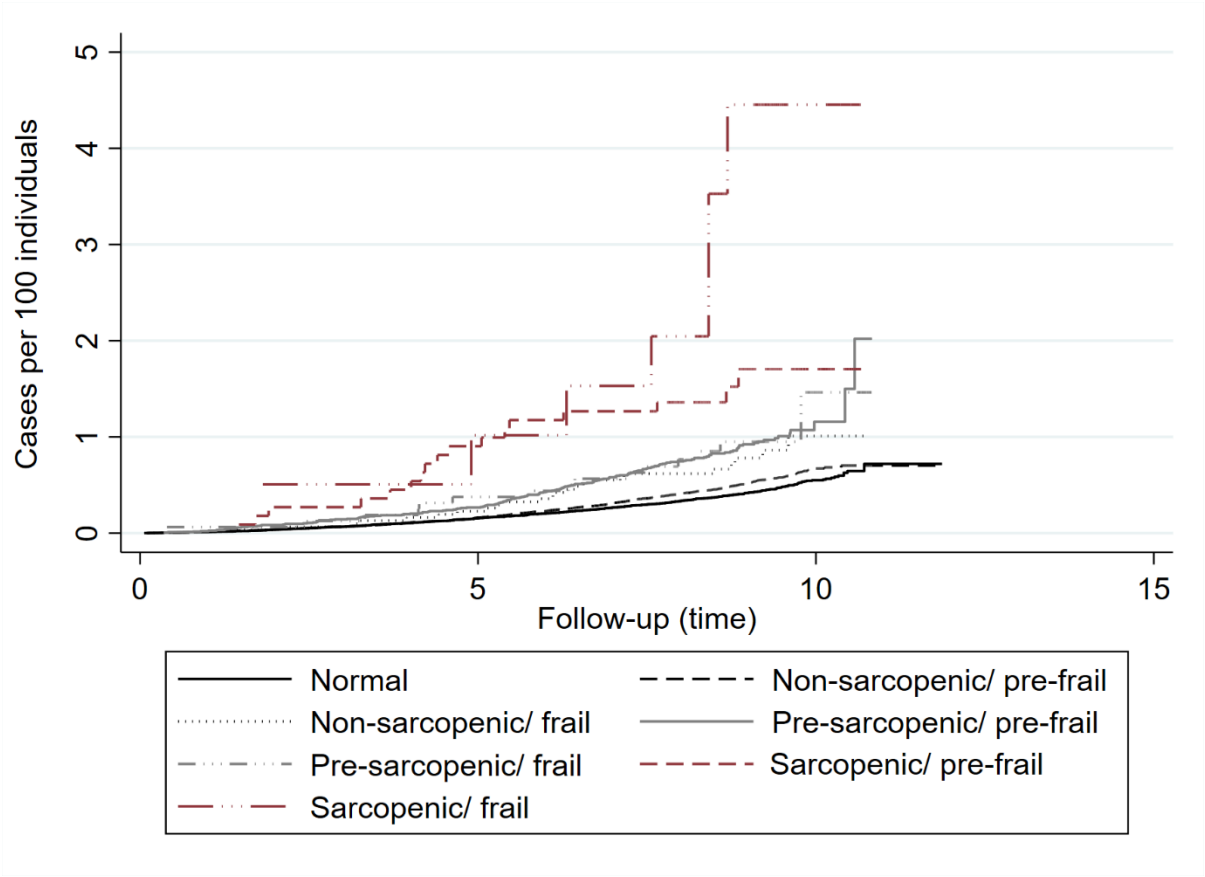
4.3.4 Supplementary Figure 2. Cumulative hazard plot of all-cause mortality by sarcopenia and frailty categories and follow-up time.

Data presented as crude HR by the sarcopenia and frailty categories.



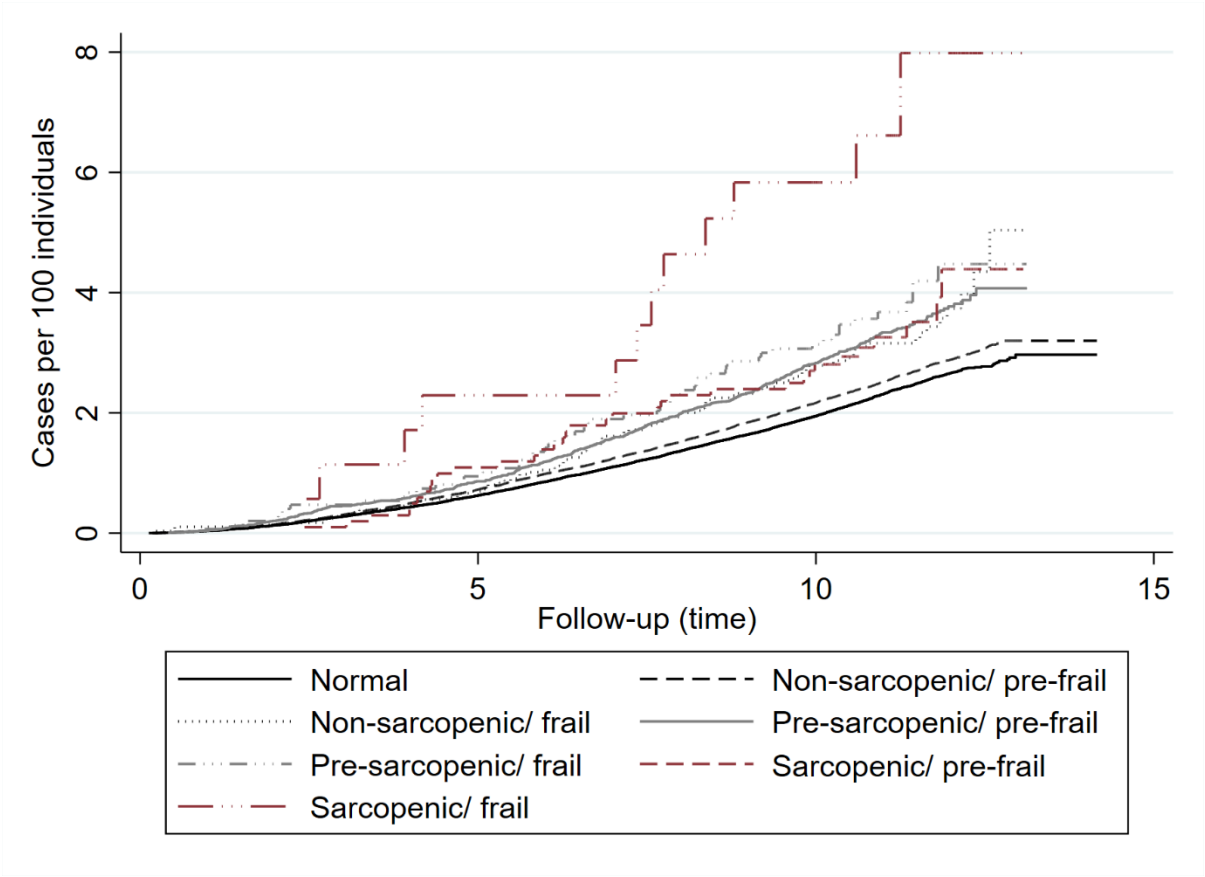
4.3.5 Supplementary Figure 3. Cumulative hazard plot of CVD mortality by sarcopenia and frailty categories and follow-up time.

Data presented as crude HR by the sarcopenia and frailty categories. All analyses were performed excluding participants with CVD at baseline.



4.3.6 Supplementary Figure 4. Cumulative hazard plot of respiratory mortality by sarcopenia and frailty categories and follow-up time.

Data presented as crude HR by the sarcopenia and frailty categories. All analyses were performed excluding participants with respiratory diseases at baseline.



4.3.7 Supplementary Figure 5. Cumulative hazard plot of cancer mortality by sarcopenia and frailty categories and follow-up time.

Data presented as crude HR by the sarcopenia and frailty categories. All analyses were performed excluding participants with cancer at baseline.

	Total n	death-events	Normal	Non-sarcopenic/ pre-frail		Non-sarcopenic/ frail		Pre-sarcopenic/ pre-frail		Pre-sarcopenic/ frail		Sarcopenic/ pre-frail*		Sarcopenic/ frail*	
			HR (95%CI)	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
CVD Incidence															
Model 1	307,971	29,136	1.00 (Ref.)	1.20 (1.17; 1.23)	<0.001	1.55 (1.40; 1.71)	<0.001	1.62 (1.55; 1.69)	<0.001	1.88 (1.66; 2.14)	<0.001	1.65 (1.40; 1.94)	<0.001	2.68 (1.95; 3.66)	<0.001
Model 2	307,971	29,136	1.00 (Ref.)	1.24 (1.21; 1.27)	<0.001	1.73 (1.56; 1.91)	<0.001	1.35 (1.29; 1.41)	<0.001	1.83 (1.61; 2.09)	<0.001	1.51 (1.28; 1.78)	<0.001	2.55 (1.86; 3.50)	<0.001
Model 3	307,971	29,136	1.00 (Ref.)	1.10 (1.07; 1.13)	<0.001	1.21 (1.09; 1.34)	<0.001	1.20 (1.14; 1.25)	<0.001	1.31 (1.15; 1.49)	<0.001	1.45 (1.24; 1.71)	<0.001	1.68 (1.22; 2.30)	0.001
Respiratory Incidence															
Model 1	313,333	48,643	1.00 (Ref.)	1.18 (1.16; 1.21)	<0.001	1.76 (1.64; 1.90)	<0.001	1.60 (1.55; 1.66)	<0.001	2.05 (1.86; 2.26)	<0.001	1.74 (1.54; 1.97)	<0.001	3.06 (2.43; 3.87)	<0.001
Model 2	313,333	48,643	1.00 (Ref.)	1.19 (1.16; 1.21)	<0.001	1.78 (1.65; 1.91)	<0.001	1.37 (1.33; 1.42)	<0.001	1.88 (1.70; 2.07)	<0.001	1.45 (1.28; 1.64)	<0.001	2.66 (2.11; 3.36)	<0.001
Model 3	313,333	48,643	1.00 (Ref.)	1.05 (1.03; 1.07)	<0.001	1.26 (1.17; 1.36)	<0.001	1.20 (1.16; 1.24)	<0.001	1.36 (1.23; 1.50)	<0.001	1.36 (1.20; 1.54)	<0.001	1.77 (1.40; 2.24)	<0.001
COPD Incidence															
Model 1	313,334	9,020	1.00 (Ref.)	1.28 (1.22; 1.34)	<0.001	1.99 (1.68; 2.35)	<0.001	2.01 (1.87; 2.16)	<0.001	2.56 (2.08; 3.13)	<0.001	3.08 (2.46; 3.84)	<0.001	5.74 (3.87; 8.51)	<0.001
Model 2	313,334	9,020	1.00 (Ref.)	1.25 (1.20; 1.31)	<0.001	1.90 (1.61; 2.25)	<0.001	1.46 (1.35; 1.57)	<0.001	2.01 (1.64; 2.46)	<0.001	2.10 (1.68; 2.63)	<0.001	4.07 (2.75; 6.04)	<0.001
Model 3	313,334	9,020	1.00 (Ref.)	1.05 (1.01; 1.10)	0.023	1.14 (0.96; 1.35)	0.120	1.21 (1.12; 1.30)	<0.001	1.17 (0.95; 1.44)	0.137	1.76 (1.40; 2.20)	<0.001	1.63 (1.10; 2.43)	0.015
Cancer Incidence															
Model 1	292,782	37,526	1.00 (Ref.)	1.02 (0.99; 1.04)	0.113	1.03 (0.92; 1.14)	0.622	1.24 (1.19; 1.29)	<0.001	1.27 (1.11; 1.44)	<0.001	1.13 (0.96; 1.34)	0.142	1.48 (1.04; 2.10)	0.030
Model 2	292,782	37,526	1.00 (Ref.)	1.03 (1.01; 1.05)	0.007	1.07 (0.96; 1.18)	0.207	1.00 (0.96; 1.05)	0.854	1.16 (1.02; 1.38)	0.022	0.85 (0.72; 1.01)	0.059	1.20 (0.85; 1.72)	0.298

Model 3	292,782	37,526	1.00 (Ref.)	1.00 (0.98; 1.03)	0.705	1.00 (0.90; 1.11)	0.968	0.99 (0.95; 1.03)	0.507	1.10 (0.97; 1.26)	0.143	0.86 (0.73; 1.02)	0.078	1.15 (0.81; 1.64)	0.429

4.3.8 Supplementary Table 1. The joint association of frailty and sarcopenia with cause-specific incidence

Data presented as adjusted hazard ratio (HR) and its 95% confidence interval (95% CI) by combined categories of sarcopenia and frailty. People without sarcopenia or frailty were used as the reference group (label as normal in the table). All analyses were conducted excluding people with cancer (n=24,197), CVD (n=9,009) and respiratory disease (n=3,646) at baseline when these were included in the outcome. We ran three models for each outcome, including an increasing number of covariates: model 1 not adjusted. Model 2, was adjusted for socio-demographic covariates (age, sex and deprivation). Model 3, as per model 2, but additionally included prevalent diseases (hypertension, diabetes, depression, major illness, as well as CVD, respiratory diseases and cancer when these were not the outcome), lifestyle factors (smoking, sleep duration, total discretionary sedentary time, alcohol, red meat and processed meat intake) and waist circumference at baseline. *Sarcopenic people include those with sarcopenia or severe sarcopenia.

	Total n	death-events	Normal	Non-sarcopenic/ pre-frail		Non-sarcopenic/ frail		Pre-sarcopenic/ pre-frail		Pre-sarcopenic/ frail		Sarcopenic/ pre-frail*		Sarcopenic/ frail*	
			HR (95%CI)	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
CVD Incidence															
Model 1	304,088	25,253	1.00 (Ref.)	1.19 (1.16; 1.22)	<0.001	1.53 (1.37; 1.70)	<0.001	1.59 (1.52; 1.67)	<0.001	1.84 (1.60; 2.12)	<0.001	1.62 (1.36; 1.92)	<0.001	2.56 (1.81; 3.62)	<0.001
Model 2	304,088	25,253	1.00 (Ref.)	1.23 (1.20; 1.26)	<0.001	1.71 (1.53; 1.90)	<0.001	1.32 (1.26; 1.39)	<0.001	1.80 (1.56; 2.07)	<0.001	1.47 (1.23; 1.75)	<0.001	2.42 (1.71; 3.43)	<0.001
Model 3	304,088	25,253	1.00 (Ref.)	1.10 (1.07; 1.13)	<0.001	1.22 (1.09; 1.36)	0.001	1.18 (1.13; 1.24)	<0.001	1.31 (1.14; 1.50)	<0.001	1.43 (1.20; 1.70)	<0.001	1.63 (1.15; 2.31)	0.006
Respiratory Incidence															
Model 1	306,876	42,186	1.00 (Ref.)	1.17 (1.15; 1.20)	<0.001	1.73 (1.59; 1.88)	<0.001	1.60 (1.55; 1.66)	<0.001	2.01 (1.81; 2.23)	<0.001	1.66 (1.45; 1.90)	<0.001	2.89 (2.22; 3.74)	<0.001
Model 2	306,876	42,186	1.00 (Ref.)	1.17 (1.15; 1.20)	<0.001	1.74 (1.61; 1.89)	<0.001	1.36(1.31; 1.41)	<0.001	1.84 (1.65; 2.04)	<0.001	1.37 (1.19; 1.58)	<0.001	2.50 (1.92; 3.24)	<0.001
Model 3	306,876	42,186	1.00 (Ref.)	1.04 (1.02; 1.07)	<0.001	1.25 (1.15; 1.36)	<0.001	1.20 (1.16; 1.25)	<0.001	1.35 (1.21; 1.50)	<0.001	1.29 (1.13; 1.48)	<0.001	1.71 (1.32; 2.22)	<0.001
COPD Incidence															
Model 1	312,962	8,378	1.00 (Ref.)	1.26 (1.21; 1.32)	<0.001	1.98 (1.67; 2.36)	<0.001	1.99 (1.84; 2.14)	<0.001	2.39 (1.92; 2.98)	<0.001	3.05 (2.42; 3.84)	<0.001	4.94 (3.18; 7.67)	<0.001
Model 2	312,962	8,378	1.00 (Ref.)	1.24 (1.18; 1.30)	<0.001	1.89 (1.60; 2.25)	<0.001	1.44 (1.33; 1.55)	<0.001	1.88 (1.51; 2.33)	<0.001	2.06 (1.64; 2.61)	<0.001	3.49 (2.25; 5.42)	<0.001
Model 3	312,962	8,378	1.00 (Ref.)	1.05 (1.00; 1.10)	0.049	1.16 (0.97; 1.38)	0.103	1.20 (1.11; 1.30)	<0.001	1.11 (0.89; 1.38)	0.346	1.74 (1.38; 2.20)	<0.001	1.44 (0.92; 2.24)	0.107
Cancer Incidence															

Model 1	287,842	32,586	1.00 (Ref.)	1.01 (0.98; 1.03)	0.494	1.06 (0.95; 1.18)	0.320	1.24 (1.18; 1.29)	<0.001	1.25 (1.08; 1.44)	0.002	1.10 (0.92; 1.32)	0.307	1.54 (1.06; 2.23)	0.022
Model 2	287,842	32,586	1.00 (Ref.)	1.02 (0.99; 1.04)	0.069	1.10 (0.99; 123)	0.074	1.01 (0.96; 1.05)	0.703	1.16 (1.00; 1.33)	0.043	0.84 (0.70; 1.01)	0.060	1.28 (0.88; 1.85)	0.193
Model 3	287,842	32,586	1.00 (Ref.)	1.00 (0.97; 1.02)	0.697	1.03 (0.92; 1.15)	0.587	0.99 (0.95; 1.04)	0.703	1.10 (0.95; 1.26)	0.202	0.85 (0.71; 1.02)	0.087	1.23 (0.85; 1.79)	0.269

4.3.9 Supplementary Table 2. The joint association of frailty and sarcopenia with cause-specific incidence using a 2-year landmark period

Data presented as adjusted hazard ratio (HR) and its 95% confidence interval (95% CI) by combined categories of sarcopenia and frailty. People without sarcopenia or frailty were used as the reference group (normal). All analyses were conducted using a 2-years landmark and excluded people with cancer (n=24,197), CVD (n=9,009) and respiratory disease (n=3,646) at baseline when these were included in the outcome. We ran three models for each outcome, including an increasing number of covariates: model 1 not adjusted. Model 2, was adjusted for socio-demographic covariates (age, sex and deprivation). Model 3, as per model 2, but additionally included prevalent diseases (hypertension, diabetes, depression, major illness, as well as CVD, respiratory diseases and cancer when these were not the outcome), lifestyle factors (smoking, sleep duration, total discretionary sedentary time, alcohol, red meat and processed meat intake) and waist circumference at baseline.
*Sarcopenic people include those with sarcopenia or severe sarcopenia.

4.3.10 Supplementary Table 3. The joint association of frailty and sarcopenia with all-cause and specific cause mortality

	Total n	death-events	Normal	Non-sarcopenic/ pre-frail		Non-sarcopenic/ frail		Pre-sarcopenic/ pre-frail		Pre-sarcopenic/ frail		Sarcopenic/ pre-frail*		Sarcopenic/ frail*	
			HR (95%CI)	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
All-cause Mortality															
Model 1	316,980	16,058	1.00 (Ref.)	1.20 (1.16; 1.24)	<0.001	1.68 (1.47; 1.92)	<0.001	1.82 (1.72; 1.93)	<0.001	2.25 (1.92; 2.64)	<0.001	1.82 (1.48; 2.25)	<0.001	4.42 (3.22; 6.09)	<0.001
Model 2	316,980	16,058	1.00 (Ref.)	1.22 (1.18; 1.26)	<0.001	1.78 (1.56; 2.02)	<0.001	1.42 (1.34; 1.50)	<0.001	2.02 (1.73; 2.37)	<0.001	1.47 (1.19; 1.81)	<0.001	3.75 (2.72; 5.16)	<0.001
Model 3	316,980	16,058	1.00 (Ref.)	1.10 (1.06; 1.14)	<0.001	1.29 (1.13; 1.48)	<0.001	1.26 (1.20; 1.34)	<0.001	1.48 (1.26; 1.73)	<0.001	1.33 (1.08; 1.64)	0.007	2.27 (1.64; 3.13)	<0.001
CVD Mortality															
Model 1	307,971	3,019	1.00 (Ref.)	1.26 (1.17; 1.36)	<0.001	1.70 (1.25; 2.32)	0.001	2.08 (1.84; 2.36)	<0.001	2.93 (2.11; 2.36)	<0.001	1.45 (0.84; 2.50)	0.186	2.58 (0.96; 6.88)	0.059
Model 2	307,971	3,019	1.00 (Ref.)	1.31 (1.21; 1.41)	<0.001	1.93 (1.42; 2.62)	<0.001	1.66 (1.47; 1.89)	<0.001	2.76 (1.99; 3.84)	<0.001	1.50 (0.87; 2.60)	0.146	2.69 (1.01; 7.20)	0.048
Model 3	307,971	3,019	1.00 (Ref.)	1.16 (1.07; 1.25)	<0.001	1.32 (0.97; 1.80)	0.080	1.47 (1.30; 1.67)	<0.001	1.89 (1.36; 2.62)	<0.001	1.44 (0.83; 2.50)	0.192	1.70 (0.63; 4.56)	0.292
Respiratory Mortality															
Model 1	312,334	2,916	1.00 (Ref.)	1.24 (1.15; 1.34)	<0.001	1.82 (1.34; 2.47)	<0.001	2.24 (1.98; 2.54)	<0.001	2.82 (2.00; 3.96)	<0.001	3.62 (2.52; 5.20)	<0.001	8.15 (4.61; 14.4)	<0.001
Model 2	312,334	2,916	1.00 (Ref.)	1.27 (1.17; 1.37)	<0.001	1.99 (1.46; 2.69)	<0.001	1.65 (1.46; 1.87)	<0.001	2.46 (1.75; 3.46)	<0.001	3.12 (2.17; 4.51)	<0.001	7.43 (4.20; 13.2)	<0.001
Model 3	312,334	2,916	1.00 (Ref.)	1.12 (1.03; 1.21)	0.006	1.33 (0.98; 1.81)	0.067	1.43 (1.26; 1.62)	<0.001	1.59 (1.13; 2.24)	0.008	2.70 (1.87; 3.90)	<0.001	3.50 (1.97; 6.23)	<0.001
Cancer Mortality															

Model 1	292,783	7,460	1.00 (Ref.)	1.09 (1.04; 1.15)	<0.001	1.40 (1.15; 1.72)	0.001	1.43 (1.31; 1.56)	<0.001	1.62 (1.24; 2.11)	<0.001	1.45 (1.03; 2.03)	0.032	2.96 (1.68; 5.22)	<0.001
Model 2	292,783	7,460	1.00 (Ref.)	1.10 (1.05; 1.16)	<0.001	1.46 (1.19; 1.79)	<0.001	1.08 (0.99; 1.18)	<0.001	1.41 (1.08; 1.84)	0.011	1.06 (0.76; 1.49)	0.727	2.35 (1.33; 4.14)	0.003
Model 3	292,783	7,460	1.00 (Ref.)	1.04 (0.99; 1.09)	0.135	1.22 (0.99; 1.50)	0.059	1.03 (0.94; 1.12)	0.562	1.20 (0.92; 1.56)	0.182	1.05 (0.75; 1.48)	0.769	1.92 (1.08; 3.38)	0.025

Data presented as adjusted hazard ratio (HR) and its 95% confidence interval (95% CI) by combined categories of sarcopenia and frailty. People without sarcopenia or frailty were used as the reference group (label as normal in the table). All analyses were conducted excluding people with cancer (n=24,197), CVD (n=9,009) and respiratory disease (n=3,646) at baseline when these were included in the outcome. We ran three models for each outcome, including an increasing number of covariates: model 1 not adjusted. Model 2, was adjusted for socio-demographic covariates (age, sex and deprivation). Model 3, as per model 2, but additionally included prevalent diseases (hypertension, diabetes, depression, major illness, as well as CVD, respiratory diseases and cancer when these were not the outcome), lifestyle factors (smoking, sleep duration, total discretionary sedentary time, alcohol, red meat and processed meat intake) and waist circumference at baseline.
*Sarcopenic people include those with sarcopenia or severe sarcopenia.

4.3.11 Supplementary Table 4. The joint association of frailty and sarcopenia with all-cause and specific cause mortality using a 2-year landmark period

	Total n	death-events	Normal	Non-sarcopenic/ pre-frail		Non-sarcopenic/ frail		Pre-sarcopenic/ pre-frail		Pre-sarcopenic/ frail		Sarcopenic/ pre-frail*		Sarcopenic/ frail*	
			HR (95%CI)	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
All-cause Mortality															
Model 1	315,813	14,891	1.00 (Ref.)	1.19 (1.15; 1.23)	<0.001	1.63 (1.42; 1.87)	<0.001	1.82 (1.72; 1.93)	<0.001	2.24 (1.90; 2.64)	<0.001	1.86 (1.50; 2.30)	<0.001	4.28 (3.06; 6.00)	<0.001
Model 2	315,813	14,891	1.00 (Ref.)	1.21 (1.17; 1.25)	<0.001	1.72 (1.50; 1.7)	<0.001	1.41 (1.33; 1.97)	<0.001	2.01 (1.33; 1.49)	<0.001	1.47 (1.19; 1.82)	<0.001	3.59 (2.56; 5.03)	<0.001
Model 3	315,813	14,891	1.00 (Ref.)	1.09 (1.06; 1.13)	<0.001	1.26 (1.10; 1.45)	0.001	1.26 (1.19; 1.34)	<0.001	1.48 (1.26; 1.75)	<0.001	1.35 (1.09; 1.68)	0.006	2.25 (1.60; 3.16)	<0.001
CVD Mortality															
Model 1	307,749	2,797	1.00 (Ref.)	1.25 (1.15; 1.35)	<0.001	1.70 (1.24; 2.34)	0.001	2.12 (1.86; 2.41)	<0.001	2.90 (2.06; 4.08)	<0.001	1.56 (0.90; 2.69)	0.112	1.39 (0.35; 5.56)	0.643
Model 2	307,749	2,797	1.00 (Ref.)	1.29 (1.19; 1.40)	<0.001	1.92 (1.40; 2.65)	<0.001	1.68 (1.48; 1.92)	<0.001	2.72 (1.94; 3.83)	<0.001	1.59 (0.92; 2.75)	0.098	1.43 (0.36; 5.72)	0.615
Model 3	307,749	2,797	1.00 (Ref.)	1.14 (1.05; 1.24)	0.002	1.31 (0.5; 1.81)	0.102	1.49 (1.30; 1.70)	<0.001	1.85 (1.31; 2.61)	<0.001	1.53 (0.88; 2.65)	0.131	0.91 (0.23; 3.66)	0.896
Respiratory Mortality															
Model 1	313,197	2,779	1.00 (Ref.)	1.25 (1.16; 1.36)	<0.001	1,74 (1.26; 2.39)	0.001	2.24 (1.97; 2.54)	<0.001	2.88 (2.04; 4.07)	<0.001	3.31 (2.24; 4.88)	<0.001	7.87 (3.35; 14.2)	<0.001
Model 2	313,197	2,779	1.00 (Ref.)	1.28 (1.18; 1.39)	<0.001	1.90 (1.38; 2.61)	<0.001	1.64 (1.44; 1.87)	<0.001	2.51 (1.77; 3.55)	<0.001	2.83 (1.91; 2.19)	<0.001	7.14 (3.93; 13.0)	<0.001
Model 3	313,197	2,779	1.00 (Ref.)	1.14 (1.05; 1.23)	0.002	1.29 (0.93; 1.78)	0.125	1.43 (1.25; 1.62)	<0.001	1.64 (1.16; 2.33)	0.005	2.47 (1.66; 3.66)	<0.001	3.48 (1.91; 6.34)	<0.001
Cancer Mortality															

Model 1	292,372	7,049	1.00 (Ref.)	1.09 (1.04; 1.15)	<0.001	1.43 (1.16; 1.76)	0.001	1.42 (1.30; 1.56)	<0.001	1.59 (1.21; 2.10)	0.001	1.53 (1.09; 2.15)	0.013	3.14 (1.78; 5.54)	
Model 2	292,372	7,049	1.00 (Ref.)	1.10 (1.05; 1.16)	<0.001	1.48 (1.20; 1.82)	<0.001	1.08 (0.98; 1.18)	0.111	1.39 (1.05; 1.82)	0.019	1.12 (0.80; 1.57)	0.511	2.48 (1.40; 4.37)	0.002
Model 3	292,372	7,049	1.00 (Ref.)	1.04 (0.99; 1.09)	0.147	1.24 (1.00; 1.53)	0.047	1.02 (0.93; 1.12)	0.640	1.18 (0.90; 1.56)	0.234	1.12 (0.79; 1.57)	0.529	2.05 (1.16; 3.62)	0.014

Data presented as adjusted hazard ratio (HR) and its 95% confidence interval (95% CI) by combined categories of sarcopenia and frailty. People without sarcopenia or frailty were used as the reference group (label as normal in the table). All analyses were conducted using a 2-years landmark and excluded people with cancer (n=24,197), CVD (n=9,009) and respiratory disease (n=3,646) at baseline when these were included in the outcome. We ran three models for each outcome, including an increasing number of covariates: model 1 not adjusted. Model 2, was adjusted for socio-demographic covariates (age, sex and deprivation). Model 3, as per model 2, but additionally included prevalent diseases (hypertension, diabetes, depression, major illness, as well as CVD, respiratory diseases and cancer when these were not the outcome), lifestyle factors (smoking, sleep duration, total discretionary sedentary time, alcohol, red meat and processed meat intake) and waist circumference at baseline. *Sarcopenic people include those with sarcopenia or severe sarcopenia.

4.3.12 Supplementary Table 5. The joint association of frailty and sarcopenia with cause-specific incidence by age groups

	Total n	death-events	Normal	Non-sarcopenic/ pre-frail		Non-sarcopenic/ frail		Pre-sarcopenic/ pre-frail		Pre-sarcopenic/ frail		Sarcopenic/ pre-frail*		Sarcopenic/ frail*	
			HR (95%CI)	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
CVD Incidence															
≥60 years	131,636	19,413	1.00 (Ref.)	1.09 (1.06; 1.13)	<0.001	1.29 (1.13; 1.46)	<0.001	1.24 (1.18; 1.30)	<0.001	1.35 (1.15; 1.57)	<0.001	1.54 (1.29; 1.83)	<0.001	1.78 (1.26; 2.52)	0.001
< 60 years	176,335	9,723	1.00 (Ref.)	1.13 (1.08; 1.18)	<0.001	1.14 (0.96; 1.36)	0.120	1.40 (1.27; 1.54)	<0.001	1.46 (1.16; 1.85)	0.001	2.21 (1.39; 3.52)	0.001	2.90 (1.38; 6.10)	0.005
p-interaction					0.048¥		0.637		0.012¥		0.378		0.218		0.285
Respiratory Incidence															
≥60 years	135,780	27,784	1.00 (Ref.)	1.06 (1.03; 1.09)	<0.001	1.28 (1.15; 1.42)	<0.001	1.25 (1.20; 1.30)	<0.001	1.45 (1.28; 1.64)	<0.001	1.46 (1.27; 1.67)	<0.001	2.10 (1.62; 2.71)	<0.001
< 60 years	177,553	20,859	1.00 (Ref.)	1,04 (1.02; 1.08)	0.003	1.25 (1.12; 1.39)	<0.001	1.27 (1.19; 1.36)	<0.001	1.33 (1.14; 1.56)	<0.001	1.72 (1.26; 2.33)	0.001	1.46 (0.83; 2.57)	0.192
p-interaction					0.485		0.463		0.099		0.887		0.124		0.485
COPD Incidence															
≥60 years	135,780	6,262	1.00 (Ref.)	1.07 (1.01; 1.13)	0.021	1.19 (0.96; 1.46)	0.107	1.27 (1.17; 1.38)	<0.001	1.15 (0.89; 1.49)	0.282	2.06 (1.63; 2.62)	<0.001	2.02 (1.32; 3.08)	0.001
< 60 years	177,554	2,758	1.00 (Ref.)	1.04 (0.96; 1.13)	0.344	1.09 (0.82;1.45)	0.550	1.49 (1.27; 1.75)	<0.001	1.45 (1.03; 2.05)	0.034	1.85 (0.92; 3.71)	0.085	1.73 (0.56; 5.41)	0.342
p-					0.693		0.853		0.008¥		0.081		0.967		0.01¥

interaction															
Cancer Incidence															
≥60 years	123,461	23,374	1.00 (Ref.)	1.00 (0.97; 1.03)	0.914	1.02 (0.89; 1.17)	0.767	1.07 (1.02; 1.12)	0.008	1.17 (0.99; 1.37)	0.054	0.97 (0.81; 1.17)	0.775	1.39 (0.94; 2.04)	0.096
< 60 years	169,321	14,152	1.00 (Ref.)	1.02 (0.98; 1.05)	0.390	0.99 (0.85; 1.17)	0.993	1.05 (0.96; 1.4)	0.287	1.18 (0.94; 1.48)	0.164	1.40 (0.92; 2.13)	0.117	1.13 (0.47; 2.73)	0.779
p-interaction					0.111		0.664		0.494		0.545		0.019¥		0.970

Data presented as adjusted hazard ratio (HR) and its 95% confidence interval (95% CI) by combined categories of sarcopenia and frailty. People without sarcopenia or frailty were used as the reference group (label as normal in the table).

All analyses were conducted excluding people with cancer (n=24,197), CVD (n=9,009) and respiratory disease (n=3,646) at baseline when these were included in the outcome. Analyses were adjusted for sex, deprivation, smoking status, sleep duration, discretionary sedentary time, waist circumference, dietary intake (alcohol, red meat and processed meat intake), systolic blood pressure, diabetes, depression, comorbidities, as well as CVD, cancer, and respiratory disease, when these were not the outcome. *: Sarcopenic people include those with sarcopenia or severe sarcopenia; ¥: Significant p-interaction.

4.3.13 Supplementary Table 6. The joint association of frailty and sarcopenia with all-cause and specific cause mortality by age groups

	Total n	death-events	Normal	Non-sarcopenic/ pre-frail		Non-sarcopenic/ frail		Pre-sarcopenic/ pre-frail		Pre-sarcopenic/ frail		Sarcopenic/ pre-frail*		Sarcopenic/ frail*	
			HR (95%CI)	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
All-cause mortality															
≥60 years	138,083	11,396	1.00 (Ref.)	1.11 (1.07; 1.16)	<0.001	1.47 (1.25; 1.72)	<0.001	1.35 (1.27; 1.44)	<0.001	1.65 (1.38; 1.98)	<0.001	1.39 (1.10; 1.75)	0.005	2.81 (2.00; 3.95)	<0.001
< 60 years	178,897	4,662	1.00 (Ref.)	1.08 (1.01; 1.15)	0.015	1.04 (0.81; 1.34)	0.760	1.42 (1.25; 1.62)	<0.001	1.34 (0.97; 1.85)	0.078	2.96 (1.81; 4.86)	<0.001	2.21 (0.83; 5.91)	0.114
p-interaction					0.543		0.188		0.049¥		0.807		0.001¥		0.940
CVD mortality															
≥60 years	131,636	2,253	1.00 (Ref.)	1.14 (1.04; 1.25)	0.004	1.59 (1.12; 2.25)	0.009	1.48 (1.28; 1.70)	<0.001	2.18 (1.52; 3.13)	<0.001	1.16 (0.60; 2.25)	0.658	1.63 (0.52; 5.08)	0.402
< 60 years	176,335	766	1.00 (Ref.)	1.23 (1.06; 1.44)	0.007	0.84 (0.41; 1.71)	0.633	2.18 (1.64; 2.91)	<0.001	1.49 (0.66; 3.36)	0.338	7.46 (2.74; 20.3)	<0.001	7.90 (1.10; 56.8)	0.040
p-interaction					0.152		0.209		0.005¥		0.597		0.003¥		0.212
Respiratory mortality															
≥60 years	135,780	2,310	1.00 (Ref.)	1.14 (1.04; 1.25)	0.005	1.54 (1.09; 2.16)	0.013	1.50 (1.31; 1.72)	<0.001	1.73 (1.18; 2.55)	0.005	3.24 (2.21; 4.75)	<0.001	5.09 (2.85; 9.07)	<0.001
< 60 years	177,554	606	1.00 (Ref.)	1.08 (0.91; 1.29)	0.366	0.90 (0.44; 1.84)	0.781	2.12 (1.56; 2.88)	<0.001	1.75 (0.82; 3.75)	0.148	3.16 (0.78; 12.8)	0.107	-	-

p-interaction					0.663		0.434		0.006¥		0.582		0.845		-
Cancer Mortality															
≥60 years	123,462	5,192	1.00 (Ref.)	1.04 (0.98; 1.11)	0.156	1.39 (1.09; 1.77)	0.007	1.10 (0.99; 1.22)	0.052	1.27 (0.93; 1.73)	0.136	1.11 (0.77; 1.62)	0.570	2.39 (1.32; 4.33)	0.004
< 60 years	169,321	2,268	1.00 (Ref.)	1.04 (0.95; 1.13)	0.409	0.95 (0.64; 1.41)	0.809	1.19 (0.97; 1.47)	0.095	1.30 (0.78; 2.18)	0.309	2.53 (1.13; 5.65)	0.024	1.43 (0.20; 10.2)	0.720
p-interaction					0.649		0.200		0.300		0.721		0.043		0.690

Data presented as adjusted hazard ratio (HR) and its 95% confidence interval (95% CI) by combined categories of sarcopenia and frailty. People without sarcopenia or frailty were used as the reference group (label as normal in the table).

All analyses were conducted excluding people with cancer (n=24,197), CVD (n=9,009) and respiratory disease (n=3,646) at baseline when these were included in the outcome. Analyses were adjusted for sex, deprivation, smoking status, sleep duration, discretionary sedentary time, waist circumference, dietary intake (alcohol, red meat and processed meat intake), systolic blood pressure, diabetes, depression, comorbidities, as well as CVD, cancer, and respiratory disease, when these were not the outcome. The association between sarcopenic/frail and respiratory morality for individuals <60 years is not shown for lack of statistical power as no individuals in this group died from this condition and the minimum number required for the analyses is five (Vittinghoff and McCulloch, 2006). *Sarcopenic people include those with sarcopenia or severe sarcopenia. ¥: Significant p-interaction.

4.4 Frailty, sarcopenia, cachexia and malnutrition as comorbid conditions and their associations with mortality: a prospective study from UK Biobank (Paper 5)

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Frailty, sarcopenia, cachexia and malnutrition as comorbid conditions and their associations with mortality: a prospective study from UK Biobank

Fanny Petermann-Rocha[1,2], Jill P. Pell[1], Carlos Celis-Morales[1,2,3,4], Frederick K. Ho[1]

[1]Institute of Health and Wellbeing, University of Glasgow, Glasgow G12 8RZ, UK
[2]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow G12 8TA, UK
[3]Centre of Exercise Physiology Research (CIFE), Universidad Mayor, Santiago 8330015, Chile
[4]Research Group in Education, Physical Activity and Health (GEEAFyS), Universidad Católica del Maule, Talca 3466706, Chile

Address correspondence to Frederick K. Ho, E-mail: frederick.ho@glasgow.ac.uk.

JPP, CC-M, and FKH contributed equally to this work and are joint senior authors.

ABSTRACT

Background Frailty, sarcopenia, cachexia and malnutrition are clinical conditions that share similar diagnostic criteria. This study aimed to investigate the clustering and mortality risk among these clinical conditions in middle- and older-aged adults.

Methods 111 983 participants from UK Biobank were included. Sarcopenia was defined according to the EWGSOP 2019 while frailty using a modified version of the Fried criteria. Cachexia was defined using the Evans *et al*. classification and malnutrition using the Global Leadership Initiative on Malnutrition. The exposure variable was categorized as: no conditions; frailty only (one condition); frailty with sarcopenia (two conditions); frailty with ≥2 other conditions (three or four conditions). Its association with all-cause mortality was investigated using Cox-proportional hazard analysis.

Results Frailty had the highest prevalence (45%) and was present in 92.1% of people with malnutrition and everyone with sarcopenia or cachexia. Compared with people with no conditions, those with frailty only and frailty with sarcopenia had higher risk of all-cause mortality. Individuals with frailty plus ≥2 other conditions had even higher risk (HR: 4.96 [95% CI: 2.73 to 9.01]).

Conclusions The four clinical conditions investigated overlapped considerably, being frailty the most common. The risk of all-cause mortality increased with the increasing number of conditions in addition to frailty.

Keywords cachexia, frailty, malnutrition, mortality, sarcopenia

Introduction

Frailty, sarcopenia, cachexia and malnutrition are common clinical conditions that can herald early stages of disability.[1] These conditions are widely recognized as predisposing to falls, fractures, hospitalization, morbidity and mortality in middle- and older-aged adults.[2–5] However, they also share similar diagnostic criteria and etiologies.[1]

Frailty is a multisystem dysregulation characterized by weakness, slowness, low levels of physical activity, exhaustion and weight loss.[6,7] Sarcopenia—defined as the age-associated loss of muscle mass and function—was classified as a disease in the International Classification of Diseases in 2016[8] and contributes to frailty as a result of weakness and slowness.[9] Malnutrition, on the other hand, is a chronic energy deficiency due to inadequate food consumption, poor assimilation of nutrients or disease-associated inflammatory mechanisms.[10] Malnutrition also contributes to loss of muscle mass and strength, which are part of the pathogenesis of both sarcopenia and frailty.[11] Finally, cachexia is a multifactorial syndrome characterized by progressive weight loss, reduction

Fanny Petermann-Rocha, PhD student
Jill P. Pell, MD
Carlos Celis-Morales, PhD
Frederick K. Ho, PhD

of muscle quantity and quality, anorexia, fatigue and increased inflammatory response[12]; features also present in frailty, sarcopenia and malnutrition (Supplementary Fig. 1).

Due to their similarities, it is likely that a significant proportion of people have multiple or even all these conditions. Moreover, since each of these clinical conditions is individually associated with worse health-related outcomes,[4,5,13,14] having more than one may have a cumulative impact on mortality. To our knowledge, only one article has investigated the prevalence and overlap among these conditions in older inpatients.[15] However, it is recognized that these conditions start earlier in life. Therefore, this study aimed to investigate the clustering and mortality risk among these clinical conditions in the middle- and older-aged adults from the UK Biobank study.

Methods

UK Biobank (www.ukbiobank.co.uk) is a large, general population cohort study. Between 2006 and 2010, UK Biobank recruited over 500 000 participants (5.5% response rate), aged 37–73 years.[16] Participants attended one of 22 assessment centres across England, Wales and Scotland[17,18] where they completed a touch-screen questionnaire, had physical measurements taken, and provided biological samples, as is described in detail elsewhere.[17,18]

Sarcopenia definition

The European Working Group on Sarcopenia in Older People 2019 (EWGSOP2) statement was used to define sarcopenia.[9] Suspected sarcopenia or pre-sarcopenia was defined as low grip strength.[9] Sarcopenia was defined as the combination of low grip strength plus low muscle mass, and severe sarcopenia was defined as sarcopenia with the addition of slow gait speed.[9] Due to the low number of UK Biobank participants with severe sarcopenia (n = 469), these two groups were pooled (hereafter called 'sarcopenia') (see Supplementary methods).

Frailty definition

An adapted version of the frailty classification derived by Fried *et al*. was used in this study. The Fried classification uses the following five criteria: weight loss, exhaustion, physical activity, walking speed and grip strength.[7] However, some of these items had to be adapted to fit the data available within UK Biobank. Weight loss, tiredness/exhaustion, gait speed and grip strength were derived following a similar approach previously published by Hanlon *et al*.[19] Physical activity, in turn, was based on self-report, collected using the International Physical Activity Questionnaire short form.[20] Participants were classified as frail if they fulfilled three or more criteria, prefrail if they fulfilled one or two criteria and robust (normal) if they did not fulfil any criteria (see Supplementary methods).

Cachexia definition and measures

Cachexia was defined according to Evans *et al*. as a body mass index (BMI) < 20 kg/m^2 and the presence of three out of five of the following weakness/fatigue components: low grip strength, low muscle mass, fatigue, anorexia and abnormal biochemistry.[12]

After excluding people with missing data for some of the components (see Supplementary methods), 454 292 participants could be assessed for cachexia in UK Biobank.

Malnutrition definition and measures

In accordance with the last guideline of the Global Leadership Initiative on Malnutrition—from the European Society for Clinical Nutrition and Metabolism[10]—malnutrition was defined as the presence of at least one phenotypic (low muscle mass or low BMI) and one etiologic (anorexia or inflammation) criteria.[10]

After excluding people with missing data for some of the components (see Supplementary methods), 142 880 were finally included as fulfilling the criteria for non-malnutrition (normal phenotypic and etiologic criteria) and malnutrition (at least one phenotypic and one etiologic criterion).

More information about the measures of sarcopenia, frailty, cachexia and malnutrition is available in Supplementary methods and Supplementary Tables 1 and 2.

All-cause mortality

The outcome in the current study was all-cause mortality. Date of death was obtained from death certificates held by the National Health Service (NHS) Information Centre (England and Wales) and the NHS Central Register Scotland (Scotland). Details of the linkage procedure can be found at http://www.ic.nhs.uk/services/medical-research-information-service. Mortality data were available until June 2020. Therefore, mortality follow-up was censored on this data or the date of death if this occurred earlier.

Covariates

Age was calculated from dates of birth and baseline assessment. Ethnicity was self-reported and categorized into: White, South Asian, Black, Chinese and mixed ethnic background. Area-based socioeconomic status (deprivation) was derived from the postcode of residence, using the Townsend score[21]

which is based on four Census variables; unemployment, non-car ownership, non-house ownership and household overcrowding. Self-reported smoking status was categorized as never, former or current smoker. Total time spent in sedentary behaviours was derived from the sum of self-reported time spent driving, using a computer and watching television. Waist circumference (WC) was used to derive central obesity, defined as ≥88 cm for women and ≥102 cm for men.[22] Hours of sleep were self-reported. Frequency of alcohol intake was self-reported at baseline via touch-screen questionnaire and categorized as daily/almost daily, 3–4 times a week, once/twice a week, 1–3 times a month, special occasions only and never. Red and processed meat were also collected through the touch-screen questionnaire at baseline. Prevalent morbidity was ascertained during a nurse-led interview at baseline. We calculated morbidity count based on 43 long-term conditions and coded as ordinal 1, 2, 3, 4 and ≥5. Further details of these measurements can be found in the UK Biobank online protocol (http://www.ukbiobank.ac.uk).

Statistical analyses

The prevalence and overlap of each clinical condition were determined both for the whole study population and stratified by sex. In addition, four categories were created according to the number of conditions that each participant had, structured around frailty as was the most prevalent condition: (i) no conditions; (ii) frailty only (one condition); (iii) frailty with sarcopenia (two conditions); (iv) frailty with ≥2 other conditions (individuals with three or four conditions).

Descriptive characteristics, broken down by the combination of these four conditions, were derived using means with standard deviations (SD) for quantitative variables and percentages for categorical variables. Associations between the combinations of these four clinical conditions with all-cause mortality were investigated using Cox-proportional hazard models. Individuals with none of the aforementioned clinical conditions were used as the reference group. The results are reported as hazard ratios (HR) and their 95% confidence intervals (95% CI). The proportional hazard assumption was checked based on Schoenfeld residuals. Because poor health may be manifested as frailty, sarcopenia, malnutrition, and cachexia and eventually causing death, such reverse causation was minimized using a 2-year landmark analysis 109 participants with events in the landmark period were excluded. The cumulative crude hazard rate for all-cause mortality was estimated using the Nelson-Aalen estimator.

The Cox proportional analyses were adjusted for confounding factors, including sociodemographic covariates (age, sex, ethnicity and deprivation), comorbidities, lifestyle factors (smoking, sleep duration, total discretionary sedentary time, alcohol, red meat and processed meat intake) and WC at baseline. These factors were chosen because of their potential influence on both the exposures and the outcome.

Only individuals with full data available for the four clinical conditions and covariates investigated in this study were included. Finally, STATA 16 statistical software (StataCorp LP) was used to perform the analyses.

Results

From the total UK Biobank population, 111 983 (53.5% women) had available data for all four clinical conditions and were, therefore, included in the final analyses (Supplementary Fig. 2). Of them, 50 438 (45.0%) had frailty (including pre-frail) 6446 (5.8%) had sarcopenia (including pre-sarcopenia), 63 (0.1%) malnutrition and 43 (0.04%) had cachexia (Table 1).

All conditions overlapped considerably. For instance, 12.8% of the individuals with frailty also had sarcopenia, and 0.1% also had either cachexia or malnutrition. All sarcopenic people had frailty, 68.2% of people with malnutrition had cachexia, 90.5% sarcopenia and 92.1% frailty, and all participants with cachexia also had sarcopenia, frailty and malnutrition (Table 2). The prevalence data and overlap by sex are shown in Table 2.

The cohort's characteristics by the number of clinical conditions are presented in Table 3. In summary, the prevalence of frailty only (39.25%) was higher than the prevalence of frailty with sarcopenia (5.7%), which in turn was higher than the combination of frailty with ≥2 other conditions (0.05%). In comparison to those with no conditions, participants with one or more clinical conditions were older, more deprived, more likely to be female, from a non-white background, and current smokers. They had lower grip strength values, body weight, height and WC. They also had a higher prevalence of comorbidities compared with those with no clinical conditions (Table 3).

The median follow-up period was 9.3 years (interquartile range: 8.6–10.0) after excluding the 2 years-landmark period for all-cause mortality. Over the follow-up, 3547 (3.2%) participants died. As is shown in Figure 1, the risk of all-cause mortality increased with the numbers of clinical conditions. After adjustment for confounding factors, and compared with people without clinical conditions, people with frailty only had 13% higher risk of all-cause mortality while those with frailty and sarcopenia had 27% higher risk. However, the risk was almost 5-fold in those with frailty and ≥2 conditions (i.e. three or four clinical conditions) in comparison to those without (HR: 4.96 [95% CI: 2.73 to 9.01]). The individual

Table 1 Numbers of participants by each clinical condition

	Sarcopenia			*Frailty*			*Cachexia*			*Malnutrition*		
	Women	*Men*	*Total*	*Women*	*Men*	*Total*	*Women*	*Men*	*Total*	*Women*	*Men*	*Total*
Normal, *n* (%)	55 994 (93.4)	49 543 (95.2)	105 537 (94.2)	31 983 (53.4)	29 562 (56.8)	61 545 (55.0)	59 904 (99.95)	52 036 (99.97)	111 940 (99.96)	59 889 (99.9)	52 031 (99.96)	111 920 (99.9)
Pre-condition, *n* (%)	3903 (6.5)	2498 (4.7)	6401 (5.7)	27 149 (45.3)	22 028 (42.3)	49 177 (43.9)	—	—	—	—	—	—
Condition, *n* (%)	36 (0.1)	9 (0.1)	45 (0.1)	801 (1.3)	460 (0.9)	1261 (1.1)	29 (0.05)	14 (0.03)	43 (0.04)	44 (0.1)	19 (0.04)	63 (0.1)
Total	**59 933**	**52 050**	**111 983**	**59 933**	**52 050**	**111 983**	**59 933**	**52 050**	**111 983**	**59 933**	**52 050**	**111 983**

Data present as absolute numbers and prevalence (%) for each clinical condition (total and by sex).

Table 2 Prevalence of comorbid clinical conditions by sex

	Total				*Women*				*Men*			
	S	*F*	*C*	*M*	*S*	*F*	*C*	*M*	*S*	*F*	*C*	*M*
Sarcopenia, *n* (%)	—	6446 (100)	43 (0.7)	57 (0.9)	—	3939 (100)	29 (0.7)	41 (1.0)	—	2507 (100)	14 (0.6)	16 (0.6)
Frailty, *n* (%)	6446 (12.8)	—	43 (0.1)	58 (0.1)	3939 (14.1)	—	29 (0.1)	42 (0.1)	2507 (11.2)	—	14 (0.1)	16 (0.1)
Cachexia, *n* (%)	43 (100)	43 (100)	—	43 (100)	29 (100)	29 (100)	—	29 (100)	14 (100)	14 (100)	—	14 (100)
Malnutrition, *n* (%)	57 (90.5)	58 (92.1)	43 (68.2)	—	41 (93.2)	42 (95.4)	29 (65.9)	—	16 (84.2)	16 (84.2)	14 (73.7)	—

Data and overlap present as absolute numbers and prevalence (%) for each clinical condition (total and by sex). Data for sarcopenia and frailty include pre-condition.
S: sarcopenia; F: frailty; C: cachexia; M: malnutrition.

Table 3 Cohort's characteristic by numbers of clinical conditions

	No conditions	*Frailty only*	*Frailty with sarcopenia*	*Frailty with ≥2 conditions*
Socio-demographics				
Total, *n* (%)	61 540 (55.0)	43 996 (39.25)	6390 (5.7)	57 (0.05)
Age (years), mean (SD)	55.7 (8.0)	55.6 (8.0)	59.4 (7.1)	61.4 (7.0)
Sex (females), *n* (%)	31 981 (52.0)	24 012 (54.6)	3899 (61.0)	41 (71.9)
Ethnicity, *n* (%)				
White	59 825 (97.2)	42 369 (96.3)	6021 (94.2)	54 (94.7)
Mixed	638 (1.0)	561 (1.3)	106 (1.7)	0
South Asian	471 (0.8)	497 (1.1)	191 (3.0)	3 (5.3)
Black	470 (0.8)	453 (1.0)	45 (0.7)	0
Chinese	136 (0.2)	116 (0.3)	27 (0.4)	0
Deprivation, *n* (%)				
Lower	23 399 (38.0)	15 885 (36.1)	2072 (32.4)	13 (22.8)
Middle	21 460 (34.9)	15 208 (34.6)	2202 (34.5)	17 (29.8)
Higher	16 681 (27.1)	12 903 (29.3)	2116 (33.1)	27 (47.4)
Obesity-related markers				
Body weight (kg), mean (SD)	74.3 (12.8)	76.1 (13.4)	71.8 (12.4)	52.6 (6.9)
Height (m), mean (SD)	1.70 (0.09)	1.69 (0.09)	1.65 (0.09)	1.64 (0.08)
Waist circumference (cm)	85.8 (11.2)	88.1 (11.6)	87.0 (11.5)	74.9 (9.0)
Central obesity, *n* (%)	10 259 (16.7)	11 323 (25.7)	1630 (25.5)	4 (7.0)
Lifestyle and health status				
Handgrip (kg), mean (SD)	33.7 (9.9)	31.1 (10.2)	16.7 (5.8)	13.4 (6.0)
Total sedentary behaviour (h.day^{-1}), mean (SD)	4.7 (2.0)	5.0 (2.1)	4.9 (2.0)	4.9 (2.8)
Smoking status, *n* (%)				
Never	35 696 (58.0)	25 156 (57.2)	3749 (58.7)	24 (42.1)
Previous	21 810 (35.4)	15 566 (35.4)	2254 (35.3)	18 (31.6)
Current	4034 (6.6)	3274 (7.4)	387 (6.0)	15 (26.3)
Alcohol frequency intake, *n* (%)				
Daily or almost daily	16 419 (26.7)	40 341 (23.5)	1460 (22.8)	14 (24.6)
3–4 times a week	17 639 (28.7)	11 457 (26.0)	1506 (23.6)	8 (14.0)
Once or twice a week	14 902 (24.2)	11 024 (25.1)	1555 (24.3)	8 (14.0)
1–3 times a month	5742 (9.3)	4808 (10.9)	644 (10.1)	5 (8.8)
Special occasions only	4193 (6.8)	3972 (9.0)	702 (11.0)	10 (17.5)
Never	2645 (4.3)	2394 (5.0)	523 (8.2)	12 (21.1)
Red meat (portion.week-1), mean (SD)	2.0 (1.4)	2.0 (1.4)	2.0 (1.4)	1.9 (1.3)
Processed meat intake (portion.week-1), mean (SD)	1.8 (1.1)	1.8 (1.1)	1.8 (1.1)	1.9 (1.2)
Sleep time (hours), mean (SD)	7.2 (0.9)	7.1 (1.0)	7.1 (1.1)	7.1 (1.6)
Multimorbidity, *n* (%)				
0	27 654 (44.9)	16 515 (37.5)	1933 (30.3)	5 (8.7)
1	20 899 (34.0)	15 071 (34.3)	2110 (33.0)	14 (24.6)
2	9145 (14.9)	7992 (18.2)	1411 (22.1)	18 (31.6)
3	2912 (4.7)	3085 (7.0)	629 (9.8)	14 (24.6)
4	725 (1.2)	946 (2.1)	204 (3.2)	5 (8.7)
≥5	205 (0.3)	387 (0.9)	103 (1.6)	1 (1.8)

Frailty only represents 43 991 people with frailty (pre-frail or frail) and five people with only malnutrition. Frailty with sarcopenia represents 6390 people with frailty (pre-frail or frail) and sarcopenia (pre-sarcopenia, sarcopenia or severe sarcopenia). Frailty with ≥2 conditions represents the combination of frailty, sarcopenia and cachexia or malnutrition.

BMI: body mass index; SD: standard deviation.

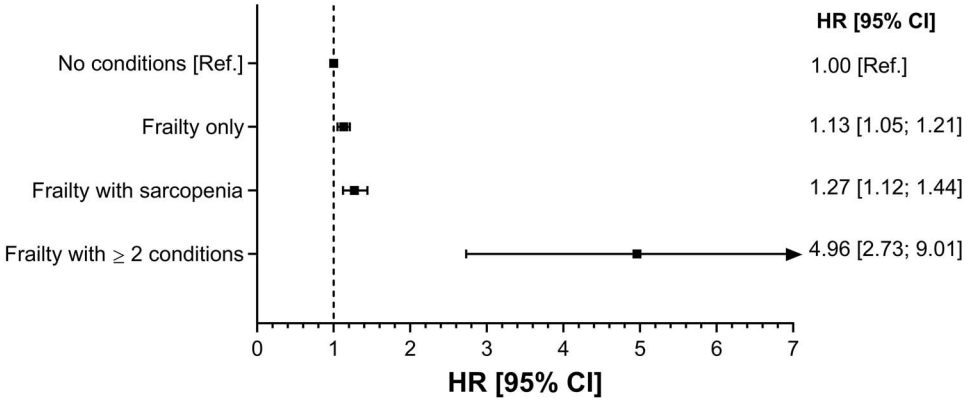

Fig. 1 Association between numbers of clinical conditions and all-cause mortality. Data presented as adjusted HR and its 95% CI by cumulative clinical conditions. People with no conditions were used as the reference group (normal). Frailty only represents 43 991 people with frailty (pre-frail or frail) and five people with only malnutrition. Frailty with sarcopenia represents 6390 people with frailty (pre-frail or frail) and sarcopenia (pre-sarcopenia, sarcopenia or severe sarcopenia). Frailty with ≥2 conditions represents the combination of frailty, sarcopenia and cachexia or malnutrition. All analyses were conducted using a 2-years landmark analysis and adjusted for age, sex, deprivation, smoking status, ethnicity, discretionary sedentary time, WC, dietary intake (alcohol, red meat and processed meat intake) and multimorbidity at baseline.

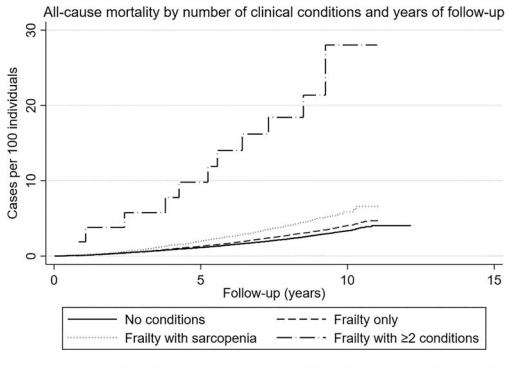

Fig. 2 Crude cumulative hazard plot of All-cause mortality by numbers of clinical conditions by follow-up. Frailty only represents 43 991 people with frailty (pre-frail or frail) and five people with only malnutrition. Frailty with sarcopenia represents 6390 people with frailty (pre-frail or frail) and sarcopenia (pre-sarcopenia, sarcopenia or severe sarcopenia). Frailty with ≥2 conditions represents the combination of frailty, sarcopenia and cachexia or malnutrition.

associations of each condition with all-cause mortality are shown in appendices (Supplementary Fig. 3).

Similar results were found when the crude cumulative mortality curves by follow-up were investigated (Fig. 2). Individuals with a higher number of clinical conditions had a sharper gradient compared with those without any condition. In particular, individuals with frailty with ≥2 other clinical conditions had the highest mortality rate during the follow-up (Fig. 2).

Discussion

Main findings of this study

Sarcopenia, frailty, malnutrition and cachexia are phenotypically similar.[1] As these conditions share underlying mechanisms for their operational definition, differentiation of participants is complicated.[1] In this study, we demonstrated significant clustering of these clinical conditions. However, frailty was the most common condition being present in 45% of the whole population studied, 92.1% of people with malnutrition and everyone diagnosed with sarcopenia or cachexia. Furthermore, we demonstrated that the risk of all-cause mortality increased with the numbers of clinical conditions present. In fact, people with three or four conditions (frailty plus at least two other conditions) had almost five-fold risk of dying. Considering the ageing population, clinical conditions are likely to become more prevalent. Nevertheless, despite the fact that these conditions are more frequent in older stages, their development could begin earlier in life as it was demonstrated with our findings. In consequence, studying these conditions sooner in life might be a good strategy to prevent further complications later.

What is already known on this topic?

The overlap between sarcopenia and frailty,[2,23] between sarcopenia, cachexia and malnutrition,[24] and among other clinical conditions have been previously reported.[25] For example, Bulut *et al*. investigated the frequency and overlap among different conditions—including frailty, sarcopenia and malnutrition– in a cohort of 2816 geriatric outpatients. They identified that 53% of the frail participants were also sarcopenic and that 48% of the population older than 80 years of age had more than four conditions.[25] However, to our knowledge, only one study has investigated the overlap and prevalence of the four clinical conditions included in this study.[15] Gingrich *et al*. demonstrated that sarcopenia was the most prevalent

syndrome among 100 German inpatients (42%), followed by frailty (33%), cachexia (32%) and malnutrition (15%).[15] They also highlighted that 63% of the participants studied had at least one condition. In our study, in turn, frailty was the most common condition, and 39.25% of the individuals included had at least one clinical condition. However, the population of Gringrich *et al*. and the population included in this study are different. In the former, participants were older, hospitalized and had medical complications.[15] In our study, participants were recruited from the general adult population and were middle-aged as well as older.

What this study adds?

Previous studies have focused on investigating the independent associations with mortality of frailty,[13] sarcopenia,[14] cachexia[26] and malnutrition.[4] Other studies have also shown that people with two conditions, such as sarcopenia and malnutrition had 4.7 [95% CI: 2.09 to 10.97]) times risk of dying compared to those without sarcopenia or malnutrition.[27] However, to our knowledge, this is the first study to explore the cumulative risk across four levels of increasing numbers of conditions in middle and older age people.

Finally, although consensus definitions have been developed for the four clinical conditions included,[7,9,10,12] the lack of universal and standardized definitions for all of them still remains as one of the main challenges and priorities. In this context, there is a need for a more comprehensive approach to a better understanding of all these conditions, how to identify them in early stages and a more in-depth study of the age-related changes in physical capability, body composition and health associated beyond the ageing progress. Furthermore, considering that these conditions share many of the parameters used for their definitions and, therefore, the overlap is highly probably among them, the creation of a unique and global definition could have a high impact in clinical practise as well as in a better diagnostic.

Limitations of this study

Using the UK Biobank study provided the opportunity to test our research question in a large general population cohort as well as the opportunity to work with information collected using validated and standardized methods. However, UK Biobank is not representative of the UK population in terms of lifestyle, ethnicity and prevalent disease.[28] Therefore, while estimates of effect sizes could be generalized, summary statistics should not be.[29] In terms of the clinical conditions studied, there were different limitations for each one. For instance, the frailty phenotype was created using similar, but not identical variables to those suggested by Fried *et al*.[7] Sarcopenia was estimated using BIA instead of dual-energy X-ray absorptiometry (DXA). DXA is the most commonly used method for deriving muscle mass, but, in UK Biobank, only 5000 participants had data available from DXA. Weight loss was not used for the definition of malnutrition nor cachexia as it was not clear if this weight loss was intentional or not. However, as both definitions recommend the use of BMI when weight loss is not documented, both syndromes were correctly derived. Furthermore, the four clinical conditions are dynamic states and are likely to have changed over time. In this context, it is likely that a proportion of those identified as without clinical conditions at baseline might have become sarcopenic, frailty, with malnutrition or cachexia during the follow-up period. Finally, although frailty, sarcopenia, cachexia and malnutrition could occur early in life, they are more prevalent in an elderly population. As the mean age of the participants in this study ranged from 55 to 61 years, the prevalence was lower than studies conducted on older populations. Therefore, the analyses should be repeated in an older study population.

Conclusion

Frailty was the most prevalent clinical condition in this study and was also present in almost all people with sarcopenia, cachexia and malnutrition. In addition, the risk of all-cause mortality increased with increasing numbers of clinical conditions and was particularly high among people with three or four conditions, who had an almost 5-fold risk of dying. Considering that our study population included middle-aged as well as elderly participants, our results may be a conservative estimate of the level of risk in the elderly. However, our results highlight the high prevalence of these clinical conditions before ageing, emphasising the relevance of early detection in middle-age adults for their high association with mortality.

Acknowledgements

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Supplementary data

Supplementary data are available at the *Journal of Public Health* online.

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Authorship statement

FP-R, FKH, JPP and CC-M contributed to the conception and design of the study, advised on all statistical aspects, and interpreted the data. FP-R performed the literature search. FP-R performed the analyses with support from FKH, JPP and CC-M. All authors critically reviewed this and previous drafts. All authors approved the final draft for submission. JPP, CC-M and FKH contributed equally to this work and are joint senior authors. FKH is the guarantor.

Data statement

All UK Biobank information is available online on the webpage www.ukbiobank. Data access are available through applications. This research was conducted using the application number 7155.

Conflict of interest

None to declare.

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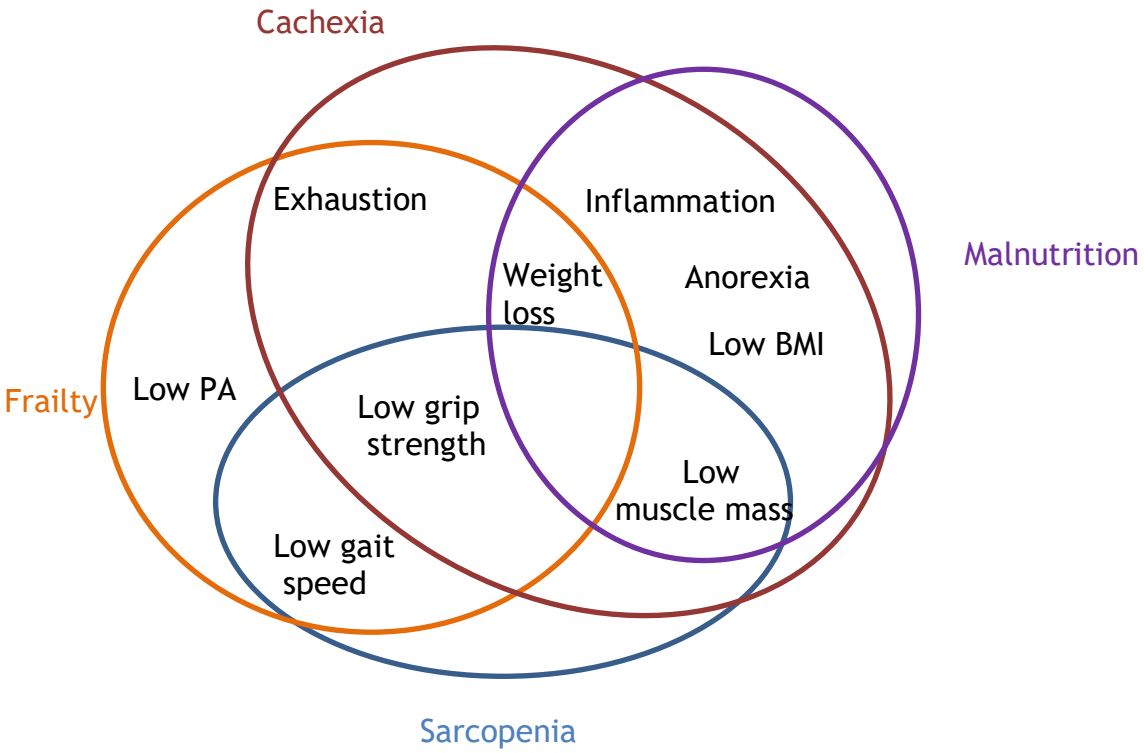
4.4.1 Appendix E



4.4.2 Supplementary Fig 1. Diagram - Overlap among frailty, sarcopenia, cachexia and malnutrition

4.4.3 Supplementary Methods

a Sarcopenia definition and measures

The European Working Group on Sarcopenia in Older People 2019 (EWGSOP2) statement was used to define sarcopenia (Cruz-Jentoft et al., 2019a). Suspected sarcopenia or pre-sarcopenia was defined as low grip strength (Cruz-Jentoft et al., 2019a). Sarcopenia was defined as the combination of low grip strength plus low muscle mass, and severe sarcopenia was defined as sarcopenia with the addition of slow gait speed (Cruz-Jentoft et al., 2019a). Due to the low number of UK Biobank participants with severe sarcopenia (n=469), these two groups were pooled (hereafter called 'sarcopenia').

Grip strength was measured using a Jamar J00105 hydraulic hand dynamometer. Isometric grip force was assessed from a single 3-second maximal grip effort, separately in the right and left arms, with the participant seated upright with their elbow by their side and flexed at 90º so that their forearm was facing forwards and resting on an armrest. The average of the right and left values was expressed in absolute units (kg) and used in subsequent analyses. Muscle mass index was derived from skeletal muscle mass (kg) divided by height (m) squared. To estimate skeletal muscle mass, the Janssen equation was utilised (Janssen et al., 2000) using the total body composition measured by bioimpedance (BIA) by trained nurses. Walking speed was categorised as slow, average or brisk. To derive a proxy for gait speed, this was then dichotomised into slow or normal (average/brisk) pace.

b Frailty definition and measures

An adapted version of the frailty classification derived by Fried et al. was used in this study. The Fried classification uses the following five criteria: weight loss, exhaustion, physical activity, walking speed and grip strength (Fried et al., 2001b). However, some of these items had to be adapted to fit the data available within UK Biobank. Participants were classified as frail if they fulfilled three or more criteria, prefrail if they fulfilled one or two criteria and robust (normal) if they did not fulfil any criteria.

Weight loss, tiredness/exhaustion, gait speed and grip strength were derived following a similar approach previously published by Hanlon et al (Hanlon et al., 2018b). Physical activity, in turn, was based on self-report, collected using the International Physical Activity Questionnaire (IPAQ) short form (Guo et al., 2015). Total physical activity was computed as the sum of walking, moderate and vigorous activity, measured as metabolic equivalents (MET-hours/week). To derive a proxy for the Fried frailty criteria, this variable was categorised into age-sex-specific quintiles where the lowest quintile (20%) was classified as meeting the physical inactivity criterion for frailty.

Participants with missing data for one or more frailty criteria were excluded from this study.

c Cachexia definition and measures

Cachexia was defined according to Evans et al. as a body mass index (BMI) <20 kg/m^2 and the presence of three out of five of the following weakness/fatigue components: low grip strength, low muscle mass, fatigue, anorexia and abnormal biochemistry (Evans et al., 2008).

Usually, a BMI <20 kg/m^2 or unintentional weight loss are used to define cachexia. However, in UK Biobank it is not clear if the variable "weight loss last year" was intentional or not. Therefore, we followed the recommendation of Evans et at. and defined cachexia using BMI<20 kg/m^2 only (Evans et al., 2008).

Low grip strength and low muscle mass were defined following the EWGSOP2 statement and cut-off points while fatigue was defined as for frailty. Anorexia was defined as limited food intake. A total caloric intake < 20 kg/kg body weight/day was used as a proxy of anorexia. This variable was only available in 210,525 participants in UK Biobank. Abnormal biochemistry was identified using the following biochemistry parameters: high C-reactive protein (CRP) (>5.0 mg/L), presence of anaemia and low serum albumin (<3.2 g/L).

As cachexia is defined as BMI <20 kg/m^2 plus three out five of weakness/fatigue components, we exclude people with missing data for three or more components (n= 2,167). In addition, those with missing data for one point when the sum of

the variables was two (n=11,074), or with missing data for two points when the sum of variables was one or two (n=17,667), were excluded. 17,303 were further excluded as presented normal BMI but altered weakness/fatigue components or vice-versa. Therefore, 454,282 participants met the criteria for cachexia in UK Biobank.

d Malnutrition definition and measures

In accordance with the last guideline of the Global Leadership Initiative on Malnutrition (GLIM) – from the European Society for Clinical Nutrition and Metabolism (ESPEN)(Cederholm et al., 2019) – malnutrition was defined as the presence of at least one phenotypic (low muscle mass or low BMI) and one etiologic (anorexia or inflammation) criteria (Cederholm et al., 2019).

Phenotypic criteria were defined as a BMI <20 kg/m^2 in people younger than 70 years and <22 kg/m^2 in people older than 70 years. Low muscle mass was defined using the cut-off points and classification from the EWGSOP2. As with cachexia, we did not use the weight loss criterion for malnutrition. We excluded people with missing data for these two conditions (n=15) as well as those with missing data for one condition when the sum of conditions was zero (n=2,919).

Etiologic criteria were defined as anorexia (using a similar approach as for cachexia) and the presence of inflammation. Inflammation was identified as CRP >5.0 mg/L or the presence of a relevant chronic disease-related: chronic obstructive pulmonary disease, inflammatory bowel disease, heart failure or Crohn's disease. We excluded people with missing data for the two criteria (n=21,216) as well as those with missing data for one condition when the sum of conditions was zero (n=240,064).

97,870 participants were further excluded as presented only the etiologic criteria or the phenotypic criteria but not both. Therefore, 142,876 were finally included as fulfilling the criteria for non-malnutrition (normal phenotypic and etiologic criteria) and malnutrition (at least one phenotypic and one etiologic criterion).

4.4.4 Supplementary Table 1. Individual components of clinical conditions

	Sarcopenia	Frailty	Cachexia	Malnutrition
Low grip strength ¥	X	X	X	
Low muscle mass¥¥	X		X	X (P)
Low gait speed	X	X		
Weight loss last year*		X	X (or)	X (P)
Low BMI** kg/m^2			X (or)	X (P)
Tired (exhaustion)		X	X	
Low PA		X		
Anorexia***			X	X (E)
Abnormal biochemistry ****			X	
Disease burden/inflammatory condition *****				X (E)

¥ For cachexia and sarcopenia was calculated using the EWGSOP2. For Frailty, following Fried 2001.

¥¥ For all the syndromes was estimated using BIA and the EWGSOP2 cut-off points.

*As in Uk Biobank the unintentional weight loss was not measured, only BMI was used both for malnutrition and cachexia.

**For cachexia, BMI was defined as <20 kg/m^2; In the malnutrition case, the BMI was <20 kg/m^2 if age was <70 years or <22 kg/m^2 if age was ≥70 years.

***poor appetite, limited food intake (Total caloric intake less than 20 kcal/kg body weight/day. Available in ~210,524 participants).

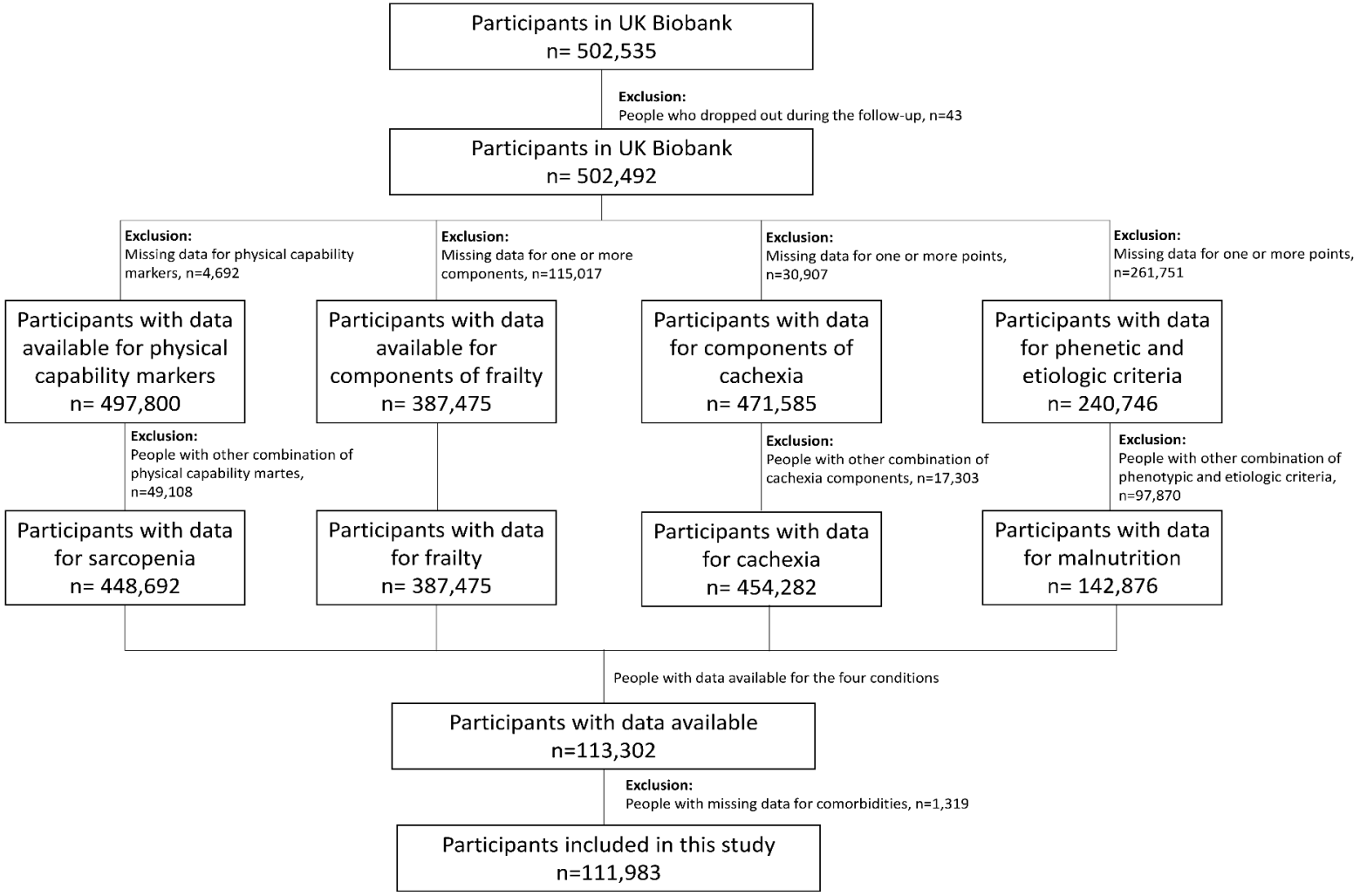
**** (albumin <3.2g/dl or CRP>5mg/L or Hb<12g/dl (anaemia)).

*****acute disease/injury or chronic disease-related. (R-reactive protein may be used as a supportive laboratory measure).

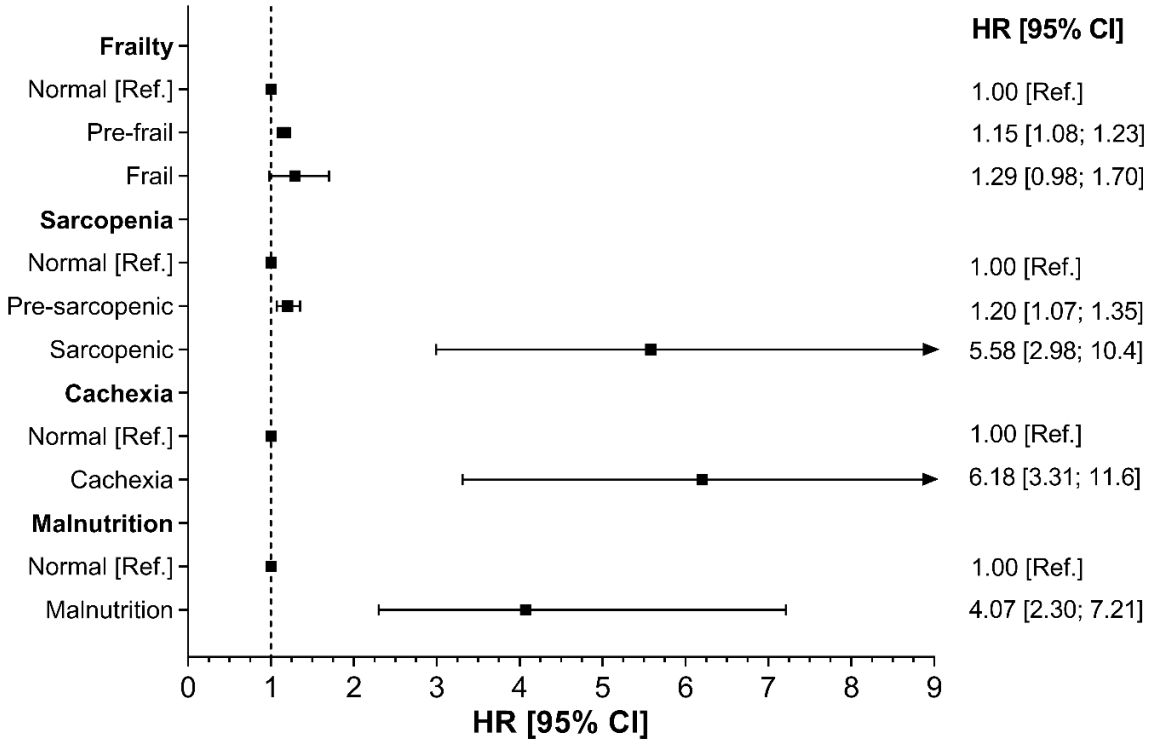
P: phenotypic criteria; E: etiologic criteria

4.4.5 Supplementary Table 2. Diagnostic definition

Sarcopenia (EWGSOP2 2019)	
Pre-sarcopenia	Low grip strength
Sarcopenia	Low grip strength plus low muscle mass.
Severe sarcopenia	Low grip strength plus low muscle mass plus low gait speed.
Frailty (Fried 2001)	
Robust	All parameters normal (0/5)
Pre-frail	1 to 2 abnormal parameters (1-2/5)
Frail	3 or more abnormal parameters (≥3/5)
Cachexia (Evans 2008)	Weight lost (or BMI<20kg/m^2) plus three out of five: Low grip strength Fatigue Anorexia Low muscle mass Abnormal biochemistry
Malnutrition (ESPEN 2019)	At least 1 phenotypic and 1 etiologic criterion
Malnutrition	Severe deficit determined based of phenotypic criteria.
Severe malnutrition	



4.4.6 Supplementary Fig 2. Diagram - Individuals included in the study.



4.4.7 Supplementary Fig 3. Association of Sarcopenia, Frailty, cachexia and malnutrition and all-cause mortality

Data presented as adjusted hazard ratio (HR) and its 95% confidence interval (95% CI) by different clinical conditions. People without the condition by each clinical syndrome were used as the reference group (normal).

All analyses were conducted using a 2-years landmark analyses and adjusted for age, sex, deprivation, smoking status, ethnicity, discretionary sedentary time, waist circumference, dietary intake (alcohol, red meat and processed meat intake), and multimorbidity at baseline.

4.5 Comparison of two different frailty measurements and risk of hospitalisation or death from COVID-19: findings from UK Biobank (Paper 6)

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RESEARCH ARTICLE Open Access

Comparison of two different frailty measurements and risk of hospitalisation or death from COVID-19: findings from UK Biobank

Fanny Petermann-Rocha[1,2†], Peter Hanlon[1†], Stuart R. Gray[2], Paul Welsh[2], Jason M. R. Gill[1], Hamish Foster[1], S. Vittal Katikireddi[1], Donald Lyall[1], Daniel F. Mackay[1], Catherine A. O'Donnell[1], Naveed Sattar[2], Barbara I. Nicholl[1†], Jill P. Pell[1†], Bhautesh D. Jani[1†], Frederick K. Ho[1†], Frances S. Mair[1†] and Carlos Celis-Morales[1,2,3,4*†]

Abstract

Background: Frailty has been associated with worse prognosis following COVID-19 infection. While several studies have reported the association between frailty and COVID-19 mortality or length of hospital stay, there have been no community-based studies on the association between frailty and risk of severe infection. Considering that different definitions have been identified to assess frailty, this study aimed to compare the association between frailty and severe COVID-19 infection in UK Biobank using two frailty classifications: the frailty phenotype and the frailty index.

Methods: A total of 383,845 UK Biobank participants recruited 2006–2010 in England (211,310 [55.1%] women, baseline age 37–73 years) were included. COVID-19 test data were provided by Public Health England (available up to 28 June 2020). An adapted version of the frailty phenotype derived by Fried et al. was used to define frailty phenotype (robust, pre-frail, or frail). A previously validated frailty index was derived from 49 self-reported questionnaire items related to health, disease and disability, and mental wellbeing (robust, mild frailty, and moderate/severe frailty). Both classifications were derived from baseline data (2006–2010). Poisson regression models with robust standard errors were used to analyse the associations between both frailty classifications and severe COVID-19 infection (resulting in hospital admission or death), adjusted for sociodemographic and lifestyle factors.

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* Correspondence: Carlos.Celis@glasgow.ac.uk
†Fanny Petermann-Rocha and Peter Hanlon are joint first authors.
†Barbara I Nicholl, Jill P Pell, Bhautesh D Jani, Frederick K Ho, Frances S Mair, and Carlos Celis-Morales are joint senior authors.
[1]Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK
[2]British Heart Foundation Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow G12 8TA, UK
Full list of author information is available at the end of the article

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Results: Of UK Biobank participants included, 802 were admitted to hospital with and/or died from COVID19 (323 deaths and 479 hospitalisations). After analyses were adjusted for sociodemographic and lifestyle factors, a higher risk of COVID-19 was observed for pre-frail (risk ratio (RR) 1.47 [95% CI 1.26; 1.71]) and frail (RR 2.66 [95% CI 2.04; 3.47]) individuals compared to those classified as robust using the frailty phenotype. Similar results were observed when the frailty index was used (RR mildly frail 1.46 [95% CI 1.26; 1.71] and RR moderate/severe frailty 2.43 [95% CI 1.91; 3.10]).

Conclusions: Frailty was associated with a higher risk of severe COVID-19 infection resulting in hospital admission or death, irrespective of how it was measured and independent of sociodemographic and lifestyle factors. Public health strategies need to consider the additional risk that COVID-19 poses in individuals with frailty, including which additional preventive measures might be required.

Keywords: COVID-19, Coronavirus, Frailty, Risk factors

Background

Since January 2020, COVID-19—the disease generated by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—has reached pandemic status due to its infectivity and fatality [1, 2]. Globally, more than 43 million people have been infected with the virus, and more than 1 million have died from it up to the end of October 2020 [3]. Age, sex, ethnicity, and the pre-existence of multiple comorbidities have been recognised as factors associated with prognosis in COVID-19 [1, 4, 5]. Frailty is also common among hospital inpatients with COVID-19 [6–8].

Frailty is a clinical state associated with older age and characterised by an increased susceptibility to decompensation in response to physiological stress [9]. While a large number of measures have been used to identify frailty, two operational definitions of frailty have dominated the scientific literature on this field: the frailty phenotype and the frailty index [10]. Using each of these definitions, frailty has been associated with higher risk of disability, morbidity, and mortality [11]. Several studies have also reported a high prevalence of frailty in people with chronic respiratory diseases [12–14], suggesting that frailty may be an independent risk factor in the development and progression of respiratory diseases [14].

One in four adults older than 85 years lives with frailty, and according to a recent systematic review and meta-analysis, one in six community-dwelling older adults might have frailty [15]. Frailty is not, however, only associated with older age. Frailty and pre-frailty are higher among those living with socioeconomic deprivation and those with multimorbidity (≥ 2 long-term conditions [LTCs]) even in middle-age [16].

During this pandemic, the clinical importance of frailty is highlighted in clinical guidelines recommending frailty assessment for all adults admitted to hospital [17, 18]. In this context, frailty assessment is recommended as part of a holistic approach to identifying patients in need of comprehensive geriatric assessment as well as identifying people with the most severe frailty to guide consideration of the appropriateness of critical care interventions. The literature around COVID-19 and frailty is rapidly evolving, and a number of hospital-based studies have demonstrated that frailty is associated with greater risk of mortality and intensive-care admission with COVID-19 [7, 8, 19–21]. Most notably, the multi-centre COVID-19 in Older People (COPE) study demonstrated that the Clinical Frailty Scale was a better predictor of in-hospital death than either age or comorbidity [19]. However, this association with in-hospital mortality has not been consistently observed across all studies to-date [7]. To our knowledge, there have been no community-based studies on the association between frailty and risk of COVID-19 infection. Therefore, this study aimed to compare the association between frailty and severe COVID-19 infection resulting in hospital admission or death in UK Biobank using two different approaches to measuring frailty: the frailty phenotype and the frailty index.

Methods

This study uses data from UK Biobank. Over 500,000 participants (5.5% response rate), aged 37 to 73 years from the general population, were recruited into UK Biobank between March 2006 and December 2010 [22]. Participants attended one of 22 assessment centres across the UK [23, 24] where they completed a touch-screen questionnaire, had physical measurements taken, and provided biological samples, as described in detail elsewhere [23, 24]. For this study, only participants from English assessment centres were included since data on COVID-19 status of UK Biobank participants were only provided from Public Health England (PHE) and no other parts of the UK. Additionally, we excluded all participants known to have died of non-COVID causes up to 16 March 2020.

Outcomes

PHE provided the COVID-19 test data, including the specimen date, location, and result (positive or negative) of the test. Data were available for the period 16 March 2020 to 28 June 2020. Records were also linked to inpatient Hospital Episode Statistics and national mortality

registers. From these, we identified individuals who tested positive during an inpatient hospital episode, in the 14 days prior to admission, or within 7 days of hospital discharge. We also identified individuals who had died with COVID-19 (ICD-10 code U70 on death certification). Participants meeting this definition were considered to have 'severe COVID-19' leading to hospitalisation or death. We compared these participants to those who were alive during the pandemic but who had not had an admission to hospital associated with COVID-19.

More information on COVID-19 in UK Biobank can be found here: http://biobank.ndph.ox.ac.uk/ukb/exinfo.cgi?src=COVID19_tests.

Exposures: the frailty phenotype and the frailty index

We undertook our analyses using two different approaches to assessing frailty: the frailty phenotype and the frailty index. Both frailty assessments were based on assessment centre data collected at baseline (2006–2010).

An adapted version of the frailty phenotype derived by Fried et al., and previously published using the UK Biobank baseline data, was used in this study [16]. The Fried phenotype uses the following five criteria: weight loss, exhaustion, physical activity, walking speed, and grip strength [25]. Some of these criteria were adapted to fit the data available within UK Biobank [16].

Weight loss was derived from self-report of weight loss in the previous year, dichotomised into yes or no (same weight or gained weight). Exhaustion was derived from the self-report of tiredness in the last 2 weeks categorised as follows: not at all, several days, more than half the days, and nearly every day. Those participants who reported tiredness more than half the days or nearly every day were identified as meeting the Fried criterion for exhaustion. Walking pace was categorised as slow, average, or brisk. To derive a proxy for gait speed, this was then dichotomised into slow or normal (average or brisk pace). Grip strength was measured using a Jamar J00105 hydraulic hand dynamometer. Isometric grip force was assessed from a single 3-s maximal grip effort, separately in the right and left arms, with the participant seated upright with their elbow by their side and flexed at 90° so that their forearm was facing forwards and resting on an armrest. The average of the right and left values were expressed in absolute units (kg) and used in subsequent analyses. Low grip strength was based on cut-offs from Fried et al.'s original description, stratified by sex and body mass index. Physical activity was self-reported and classified as follows: none (response: none or light activity with a frequency of once per week or less = 1) and physically active (medium or heavy activity, or light activity more than once per week = 0) [16].

Participants were classified as frail if they fulfilled three or more criteria, pre-frail if they fulfilled one or two criteria, and robust if they did not fulfil any criteria at baseline. The three frailty groups were mutually exclusive.

A frailty index has previously been validated using baseline data from UK Biobank [26]. The frailty index approach was developed by Rockwood and Mitnitski and is a cumulative count of 'deficits' [27, 28]. The frailty index was initially described using 70 deficits from the Canadian Study of Health Ageing [28]. However, the frailty index method was developed as a standard technique which can be adapted to the deficits available in a given dataset [29]. The adaptation of the frailty index approach to UK Biobank is described in detail elsewhere [26]. Briefly, deficits should be associated with age, associated with poor health status, and be neither universal nor too rare within the target population [29]. A frailty index is calculated for each individual by calculating the total number of deficits present in an individual and divided by the total number of possible deficits measurable to give a value between 0 and 1 (higher values indicating a greater degree of frailty). We applied a previously validated frailty index comprising 49 self-reported questionnaire items related to health, presence of disease and disability, and mental wellbeing [26]. Based on this frailty index, we classified participants as being robust (frailty index < 0.12), mildly frail (frailty index 0.12–0.24), or moderate/severely frailty (frailty index > 0.24) [30].

Covariates

Age at baseline was calculated from dates of birth and baseline assessment. Current age was derived from dates of birth and last data from COVID-19 assessment (June 2020). Area-based socioeconomic status (deprivation) was derived from the postcode of residence, using the Townsend score [31]. Ethnicity was self-reported and categorised, in this study, into white and non-white. This approach was selected due to insufficient statistical power in the non-white subgroups. Self-reported smoking status was categorised as never, former, or current smoker. Frequency of alcohol intake was self-reported at baseline via touch-screen questionnaire and categorised as never/special occasions only, 1–3 times per month, 1–4 times per week, or daily/almost daily. Prevalent morbidity was ascertained during a nurse-led interview at baseline. We calculated morbidity count based on 43 LTCs originally developed for a large epidemiological study in Scotland and subsequently adapted for UK Biobank [32, 33]. Further details of these measurements can be found in the UK Biobank online protocol (http://www.ukbiobank.ac.uk).

Ethical approval

UK Biobank was approved by the North West Multi-Centre Research Ethics Committee (Ref: 11/NW/0382).

All participants provided written informed consent to participate in the UK Biobank study. The study protocol is available online (http://www.ukbiobank.ac.uk). This work was conducted under the UK Biobank application number 14151.

Statistical analyses

Descriptive characteristics are presented as means with standard deviations (SD) for quantitative variables and as percentages for categorical variables, broken down by each frailty classification and the presence or absence of severe COVID-19 infection (defined as hospitalisation or death with COVID-19). Poisson regression models with robust standard errors were used to analyse the associations between both the frailty phenotype and the frailty index and severe COVID-19. The results are reported as risk ratios (RRs) with their 95% confidence intervals (CIs) [34]. Poisson regression models with robust standard errors were used because they provide RR estimates, instead of odds ratios, which are easier to interpret [35].

We ran four models including an increasing number of covariates: model 1 (minimally adjusted), adjusted by age and sex; model 2, as per model 1 but also included deprivation, and white versus non-white groups; model 3, included smoking and alcohol intake only; and model 4, included all covariates in models 2 and 3. An additional sensitivity analysis (model 5) was performed aiming to investigate whether the association between the frailty phenotype and COVID-19 was explained by multimorbidity. This model included covariates in model 4, but additionally included multimorbidity (based on a count of 43 diseases and coded as ordinal 0, 1, 2, 3, and ≥ 4 LTCs). This model was carried out for the frailty phenotype only because the frailty index is partly based on the presence of morbidity. All these covariates were selected because they have been recognised as being associated with prognosis of COVID-19 as well as being associated with frailty status, and may therefore potentially confound the relationship between frailty and COVID-19 [1, 4, 5].

Finally, to investigate whether the associations between severe COVID-19 and frailty differed by subgroups, the analyses were re-run stratified by sex and age categories (based on age in June 2020: < 60, 60–70, and > 70 years). An interaction term among the subgroups, the frailty classifications, and severe COVID-19 was fitted into the regression model to test for interaction.

All statistical analyses were performed using R version 3.6.1. Only participants with full data available for both classifications and covariates were included in the analyses.

Results

A total of 420,577 UK Biobank participants in England were eligible for inclusion, of whom 383,845 had data on both frailty phenotype and frailty index. Of these, 802 were either hospitalised with and/or died from COVID-19 and were classified as 'severe COVID-19' (323 deaths and 479 hospitalisations only). The proportion of people identified as frail at baseline, along with the overlap between the frailty phenotype and the frailty index, is shown in Table 1. Out of 383,845 participants, 11,836 (3.1%) participants were frail according to the frailty phenotype, and 15,958 (4.1%) had moderate or severe frailty according to the frailty index. Using the frailty phenotype, and compared with robust individuals, pre-frail and frail individuals with severe COVID-19 were older, more likely to be deprived, non-white, current smoker, to never or occasionally drink alcohol, and to have one or more morbidities (Table 2). Similar characteristics were identified when individuals with mild frailty and moderate/severe frailty were compared with robust individuals using the frailty index (Table S1).

Associations between the frailty phenotype and the frailty index and severe COVID-19 are presented in Fig. 1. Using the frailty phenotype, and compared with non-frail individuals, being pre-frail and frail were associated with 1.69 times [95% CI 1.46; 1.96] and more than four times [RR 4.05 95% CI 3.15; 5.20] higher risk of severe COVID-19, respectively (age- and sex-adjusted model). These associations were attenuated but remained when analyses were adjusted both for sociodemographic and lifestyle factors ($RR_{pre\text{-}frail}$ 1.47 [95% CI 1.26; 1.71] and RR_{frail} 2.66 [95% CI 2.04; 3.47]) (model 4, Fig. 1). Results were similar in analyses using the frailty index, although effect sizes were slightly smaller. In the age- and sex-adjusted model, individuals with mild frailty and moderate/severe frailty had 1.73 [95% CI 1.49; 2.00] and 3.56 [95% CI 2.82; 4.48] times higher risk of severe COVID-19, respectively, compared with robust individuals. When we further adjusted the model for sociodemographic and lifestyle factors, the associations attenuated further, but remained ($RR_{mild\text{-}frail}$ 1.46 [95% CI 1.26; 1.71] and $RR_{mod/severe\ frail}$ 2.43 [95% CI 1.91; 3.10]) (model 4, Fig. 1). In addition, when multimorbidity was included in the sensitivity analysis for the frailty phenotype only (Table S2, model 5), the associations remained but were further attenuated ($RR_{pre\text{-}frail}$ 1.35 [95% CI 1.16; 1.57] and RR_{frail} 1.99 [95% CI 1.51; 2.62]).

For the frailty index, we repeated model 4 treating the frailty index as continuous. There was a RR of 1.53 (95% CI 1.40; 1.67) per 0.1-point increase in the frailty index.

No significant interaction was observed between either frailty definition and age or sex (Fig. 2). When the analyses were stratified by subgroups (sex and age categories), we identified that the associations were similar for both sexes and age categories using both the frailty

Table 1 Overlap between the frailty phenotype and frailty index

	Robust, *n* (%)	Mild, *n* (%)	Moderate or severe, *n* (%)	Total
Robust, *n* (%)	170,964 (44.5)	55,456 (14.5)	2665 (0.7)	229,085 (59.7)
Pre-frail, *n* (%)	75,898 (19.8)	57,719 (15.0)	9307 (2.4)	142,924 (37.2)
Frail, *n* (%)	1770 (0.5)	6080 (1.6)	3986 (1.0)	11,836 (3.1)
Total	248,632 (64.8)	119,255 (31.1)	15,958 (4.1)	**383,845**

Data presented as absolute numbers and prevalence for each frailty measurement

index and the frailty phenotype (Fig. 2). However, the effect of frailty using the frailty phenotype was higher in people aged < 60 at the time of the pandemic (Fig. 2).

Discussion

We demonstrated that people previously identified as frail were at higher risk of severe COVID-19 infection, after adjustment for sociodemographic and lifestyle factors and independent of multimorbidity in the case of the frailty phenotype. These findings were consistent using two different approaches to assessing frailty: the frailty phenotype and the frailty index.

Attenuation following adjustment for multimorbidity using the frailty phenotype is to be expected since morbidity contributes to frailty: 91.9% of frail individuals with severe COVID-19 had multimorbidity versus 75.6% of those classified as robust. On the other hand, we identified that the associations were similar after

Table 2 Characteristics of the population according to their COVID-19 test and the frailty phenotype

	No COVID-19 associated admission or death			Severe COVID-19 infection		
	Robust	Pre-frail	Frail	Robust	Pre-frail	Frail
Total, *n*	228,731	142,550	11,762	354	374	74
Baseline age (years), mean (SD)	56.0 (8.1)	56.5 (8.1)	57.4 (7.7)	60.3 (7.7)	59.8 (7.8)	59.5 (7.9)
Current age (years), mean (SD)	67.1 (8.1)	67.5 (8.1)	68.4 (7.7)	71.3 (7.8)	70.8 (7.8)	70.6 (8.0)
Sex (female), *n* (%)	120,231 (52.6)	83,011 (58.2)	7772 (66.1)	116 (32.8)	145 (38.8)	35 (47.3)
Deprivation, *n* (%)						
Lower	83,333 (36.5)	42,368 (29.7)	2086 (17.7)	92 (26.0)	87 (23.3)	9 (12.1)
Middle	78,557 (34.3)	46,199 (32.4)	2947 (25.1)	123 (34.7)	95 (25.4)	15 (20.3)
Higher	66,841 (29.2)	53,983 (37.9)	6729 (57.2)	139 (39.3)	192 (51.3)	50 (67.6)
Ethnicity, *n* (%)						
White	220,508 (96.4)	132,223 (92.8)	10,204 (86.8)	325 (91.8)	324 (86.6)	63 (85.1)
Non-white	8223 (3.6)	10,327 (7.2)	1558 (13.2)	29 (8.2)	50 (13.4)	11 (14.9)
Smoking status, *n* (%)						
Never	130,457 (57.0)	76,966 (54.0)	5737 (48.8)	134 (37.9)	177 (47.3)	25 (33.8)
Previous	79,074 (34.6)	49,909 (35.0)	4021 (34.2)	173 (48.9)	151 (40.4)	37 (50.0)
Current	19,200 (8.4)	15,675 (11.0)	2004 (17.0)	47 (13.2)	46 (12.3)	12 (16.2)
Alcohol intake, *n* (%)						
Daily or almost daily	53,467 (23.4)	25,316 (17.8)	1176 (10.0)	77 (21.8)	62 (16.6)	9 (12.2)
One to four times a week	119,836 (52.4)	66,267 (46.5)	3711 (31.6)	172 (48.6)	147 (39.3)	24 (32.4)
One to three times a month	23,582 (10.3)	17,695 (12.4)	1487 (12.6)	40 (11.2)	43 (11.5)	10 (13.5)
Never or special occasions	31,846 (13.9)	33,272 (23.3)	5388 (45.8)	65 (18.4)	122 (32.6)	31 (41.9)
Multimorbidity, *n* (%)						
None	93,868 (41.0)	40,383 (28.4)	1068 (9.1)	87 (24.6)	65 (17.4)	6 (8.1)
1	78,185 (34.2)	46,384 (32.5)	2357 (20.0)	119 (33.6)	106 (28.3)	7 (9.5)
2–3	51,407 (22.5)	46,373 (32.5)	5371 (45.7)	133 (37.6)	156 (41.7)	36 (48.6)
≥ 4	5271 (2.3)	9410 (6.6)	2966 (25.2)	15 (4.2)	47 (12.6)	25 (33.8)

The frailty phenotype was derived using an adaptation from the original derived by Fried et al. Participants were classified as frail if they fulfilled three or more criteria, pre-frail if they fulfilled one or two criteria, and robust if they did not fulfil any criteria at baseline
SD standard deviation, *n* number

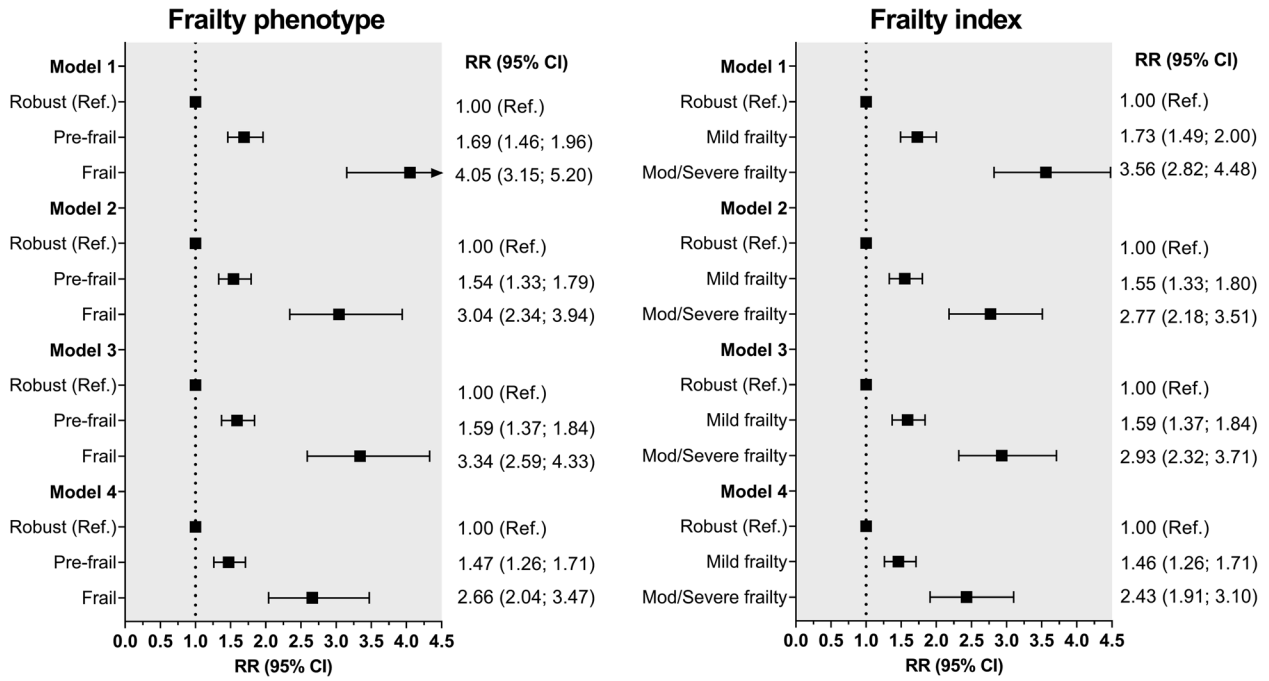

Fig. 1 Associations between the frailty phenotype, the frailty index, and severe COVID-19 infection. Data presented as RRs with their 95% CIs using Poisson regression analyses. Robust individuals were used as the reference group for the frailty phenotype and the frailty index. Model 1, adjusted by age and sex; model 2, as model 1 but also included deprivation, and ethnicity: white versus others; model 3, included smoking and alcohol intake only; model 4, included the covariates in models 2 and 3

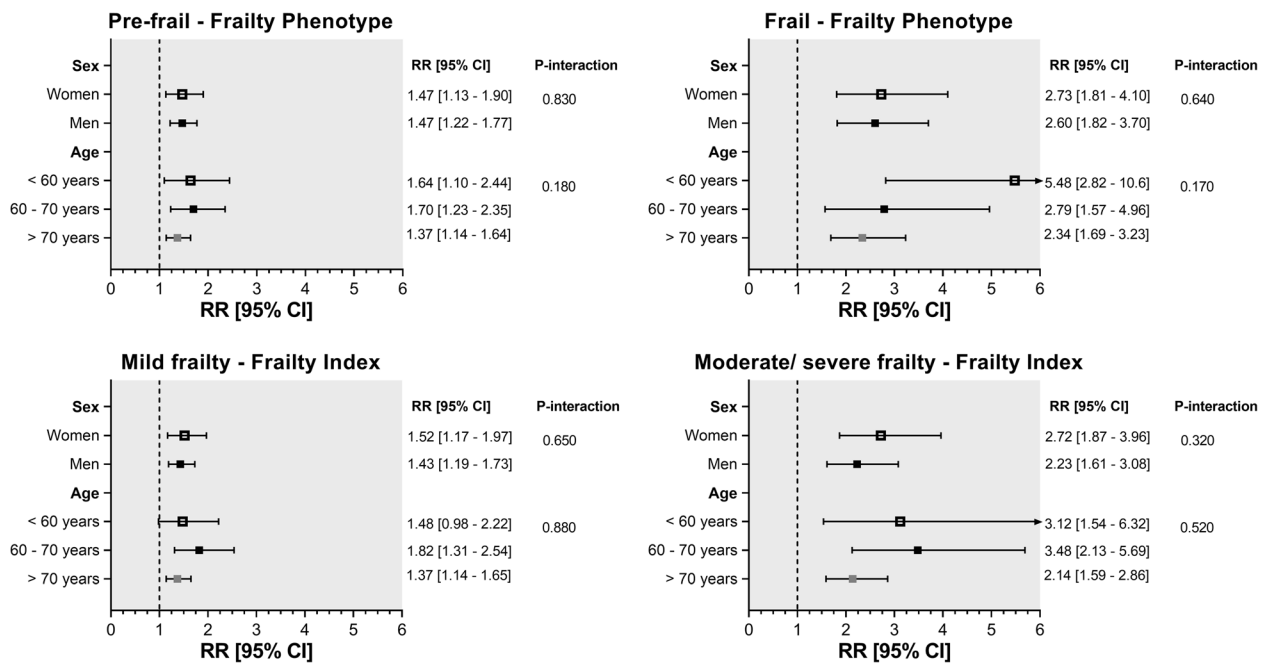

Fig. 2 Associations between the frailty phenotype, the frailty index, and severe COVID-19 infection by subgroups. Data presented as RRs with their 95% CIs using Poisson regression analyses. Robust individuals were used as the reference group for the frailty phenotype and the frailty index. All the analyses were adjusted by age, sex, deprivation, ethnicity, smoking, and alcohol intake when these were not the subgroup used

stratification by sex and age (except for some exceptions probably underpowered). The latter highlights the impact of our findings but also reinforces the implications of frailty beyond ageing [16].

Frailty (either moderate or severe) has been identified among inpatients affected by COVID-19 [6–8, 19–21]. This is consistent with previous findings where frailty has been recognised as a critical prognostic factor of viral pneumonia among inpatients [13]. However, the literature has reported heterogeneous results between frailty and COVID-19 mortality. For example, Miles et al., using data from 377 older inpatients admitted to a London hospital, identified that frailty was not associated with mortality rates after COVID-19 [7]. However, Hewitt et al. and De Smet et al., using the Clinical Frailty Scale (CFS), demonstrated that frail individuals had a higher risk of mortality after adjusting for covariates [19, 20]. Our study is novel since it demonstrates an increased risk of hospitalisation or death from COVID-19 among community-dwelling individuals, but does not investigate prognosis after hospitalisation.

As with COVID-19, frailty is strongly associated with ageing. It also shares some common modifiable risk factors with COVID-19, such as body mass index, muscle strength, respiratory function, and slow gait speed [4, 36]. Although chronological age cannot be modified, key proxies of physical function related to ageing and frailty can. There is evidence that frailty could be reversed with exercise interventions in some older adults [37]. A recent trial conducted in hospitalised frail individuals showed that an exercise intervention was effective at helping to reverse the functional decline associated with ageing [38]. Therefore, there is a need to recognise frail individuals as a higher risk group and determine how best to balance their competing risks, providing greater protection from infection through existing non-pharmaceutical interventions such as physical distancing and shielding, while encouraging and supporting greater physical activity to reduce their frailty. This could potentially be achieved through home training programmes for people with restriction of mobility [39], and perhaps drawing upon the intersection between frailty and respiratory disease [40, 41]. Of note, interventions that prevent, delay, or reverse frailty are likely to have significant public health impact beyond the COVID-19.

Limitations

This study is not without limitations. Firstly, both the frailty phenotype and the frailty index were identified from baseline UK Biobank data (between 10 and 14 years prior to the COVID-19 pandemic). Therefore, we did not have data on subsequent frailty status. Frailty is a dynamic state and is likely to have worsened over time. Consequently, transitioning from a frail to a less frail state is relatively uncommon; however, a proportion of those not identified as frail at baseline are likely to have become frail during the follow-up [42]. Therefore, our results may be an underestimate of the magnitude of the association between frailty and COVID-19. Secondly, while the frailty phenotype and the frailty index are the most widely validated epidemiological measurements of frailty, they are not routinely used within clinical practice. NICE (National Institute for Health and Care Excellence) has recommended using the CFS for the assessment of frailty in the COVID-19 guideline [17]. However, due to the absence of some of the variables included in the CFS in the UK Biobank study, we used a frailty index [26] and an adapted version of the frailty phenotype [16]. While there appears to be a modest degree of overlap between the CFS and other frailty definitions [43], few studies have assessed in detail how the CFS related to measures such as the frailty index or frailty phenotype. The frailty phenotype was an adaptation of the original description by Fried et al. [25], and the frailty index was derived from self-reported data only. Finally, the UK Biobank study is not a nationally representative sample in terms of lifestyle, morbidity, ethnicity, and socioeconomic status [44]. This lack of representativeness is an important limitation, particularly as characteristics such as ethnicity and comorbidities appear to be strongly associated with prognosis in COVID-19 [45]. Therefore, the summary statistics should not be generalised [44], even though effect size estimates are comparable with nationally representative cohorts [46].

Conclusion

Individuals with frailty had a higher risk of severe COVID-19 regardless of the frailty measure used. As the lockdown measures have changed during the course of the pandemic, guidance on how we can protect individuals with frailty should be considered, including whether more protective, preventive measures are required. Moreover, considering we are facing a new COVID-19 outbreak and that confinement could exacerbate frailty [47], further public health policies to minimise the risk of developing this syndrome are more urgent than ever.

Supplementary Information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12916-020-01822-4.

Additional file 1: Table S1. Characteristics of the population according to their COVID-19 test and the frailty index. **Table S2.** Associations between the frailty phenotype and severe COVID-19 infection (sensitivity analysis).

Abbreviations

CFS: Clinical Frailty Scale; CIs: Confidence intervals; FI: Frailty index; LTCs: Long-term conditions; NICE: National Institute for Health and Care Excellence; PHE: Public Health England; RR: Risk ratio; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

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Authors' contributions

F.P-R, P.H, B.I.N, J.P.P, B.D.J, F.K.H, F.S.M, and C.C-M contributed to the conception and design of the study, advised on all statistical aspects, and interpreted the data. F.P-R and P.H performed the literature search. P.H performed the analyses. All authors critically reviewed this and previous drafts. All authors approved the final draft for submission. F.P-R and P.H contributed equally to this work and are joint first authors. B.I.N, J.P.P, B.D.J, F.K.H, F.S.M, and C.C-M contributed equally to this work and are joint senior authors. C.C-M is the guarantor.

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Availability of data and materials

All UK Biobank information is available online on the webpage www.ukbiobank. Data access is available through applications. This research was conducted using the application number 14151.

Ethics approval and consent to participate

UK Biobank was approved by the North West Multi-Centre Research Ethics Committee, and all participants provided written informed consent to participate in the UK Biobank study. The study protocol is available online (http://www.ukbiobank.ac.uk/).

Consent for publication

Non-applicable.

Competing interests

The authors declare no conflicts of interest.

Author details

[1]Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK. [2]British Heart Foundation Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow G12 8TA, UK. [3]Centre of Exercise Physiology Research (CIFE), Universidad Mayor, Santiago, Chile. [4]Laboratorio de Rendimiento Humano, Grupo de Estudio en Educación, Actividad Física y Salud (GEEAFyS), Universidad Católica del Maule, Talca, Chile.

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Publisher's Note

4.5.1 Appendix F

4.5.2 Table S1Characteristics of the population according to their COVID-19 test and the frailty index.

	No COVID-19 associated admission or death			Severe COVID-19 infection		
	Fit	Mild frailty	Moderate/severe frailty	Fit	Mild frailty	Moderate/severe frailty
Total, n	248,242	118,932	15,869 (100)	390	323	89
Baseline age (years), mean (SD)	55.7 (8.1)	57.1 (7.9)	57.8 (7.6)	59.5 (8.2)	60.5 (7.4)	60.2 (7.0)
Current age (years), mean (SD)	66.8 (8.1)	68.2 (7.9)	68.9 (7.6)	70.6 (8.2)	71.5 (7.4)	71.2 (7.2)
Sex (female), n (%)	131,844 (53.1)	69,360 (58.3)	9,810 (61.8)	127 (32.6)	127 (39.3)	42 (47.2)
Deprivation, n (%)						
Lower	88,378 (35.6)	36,042 (30.3)	3,367 (21.2)	102 (26.1)	73 (22.6)	13 (14.6)
Middle	84,840 (34.2)	38,614 (32.5)	4,249 (26.8)	129 (33.1)	90 (27.9)	14 (15.7)
Higher	75,024 (30.2)	44,276 (37.2)	8,253 (52.0)	159 (40.8)	160 (49.5)	62 (69.7)
Ethnicity, n (%)						
White	235,918 (95.0)	112,319 (94.4)	14,698 (92.6)	345 (88.5)	287 (88.9)	80 (89.9)
Non-white	12,324 (5.0)	6,613 (5.6)	1,171 (7.4)	45 (11.5)	36 (11.1)	9 (10.1)
Smoking status, n (%)						
Never	145,907 (58.8)	60,398 (50.8)	6,855 (43.2)	179 (45.9)	127 (39.3)	30 (33.7)
Previous	81,660 (32.9)	44,988 (37.8)	6,356 (40.1)	160 (41.0)	162 (50.2)	39 (43.8)
Current	20,675 (8.3)	13,546 (11.4)	2,658 (16.7)	51 (13.1)	34 (10.5)	20 (22.5)
Alcohol intake, n (%)						
Daily or almost daily	54,536 (22.0)	23,183 (19.5)	2,240 (14.1)	79 (20.3)	55 (17.0)	14 (15.7)
One to four times a week	129,649 (52.2)	54,548 (45.9)	5,617 (35.4)	174 (44.6)	140 (43.3)	29 (32.6)
One to three times a month	26,273 (10.6)	14,357 (12.0)	2,134 (13.4)	47 (12.0)	31 (9.6)	15 (16.9)
Never or special occasions	37,784 (15.2)	26,844 (22.6)	5,878 (37.1)	90 (23.1)	97 (30.1)	31 (34.8)
Multimorbidity, n (%)						

None	120,531 (48.6)	14,593 (12.3)	195 (1.2)	135 (34.6)	23 (7.1)	0 (0)
1	88,526 (35.7)	37,145 (31.2)	1,255 (7.9)	154 (39.5)	74 (22.9)	4 (4.5)
2-3	38,175 (15.4)	57,656 (48.5)	7,320 (46.1)	98 (25.1)	189 (58.5)	38 (42.7)
≥4	1,010 (0.3)	9,538 (8.0)	7,099 (44.8)	3 (0.8)	37 (11.5)	47 (52.8)

Using a previously validated this frailty index, we classified participants as being fit (frailty index <0.12), mildly frail (frailty index 0.12-0.24) or moderate/severely frailty (frailty index >0.24).

SD: standard deviation; n: number

4.5.3 Table S2. Associations between the frailty phenotype and severe COVID-19 infection (sensitivity analysis).

Model 5	RR (95% CI)
Robust	1.00 (Ref.)
Pre-frail	1.35 (1.16; 1.57)
Frail	1.99 (1.51; 2.62)

Data presented as RRs with their 95% Cis using Poisson regression analyses. Robust individuals were used as the reference group. The sensitivity analysis was adjusted as per Model 4, but additionally included multimorbidity.

4.6 Associations between physical frailty and dementia incidence: a prospective study from UK Biobank (Paper 7)

Associations between physical frailty and dementia incidence: a prospective study from UK Biobank

Fanny Petermann-Rocha, Donald M Lyall, Stuart R Gray, Irene Esteban-Cornejo, Terence J Quinn, Frederick K Ho, Jill P Pell*, Carlos Celis-Morales**

Summary

Background Dementia is associated with a high burden of dependency and disability. Physical frailty (hereafter referred to as frailty) is a multisystem dysregulation that has been identified as a risk factor for dementia. The aim of this study was to examine the association of frailty and its individual components with all-cause dementia incidence in a cohort of UK adults.

Methods Participants in UK Biobank with data available for dementia incidence and without any form of dementia at baseline were included in this prospective study. Frailty was defined using a modified version of the frailty phenotype based on five individual components (weight loss, tiredness, physical activity, gait speed, and grip strength), with participants classified as pre-frail if they fulfilled one or two criteria or frail if they fulfilled three or more. Associations between frailty and dementia incidence were investigated using Cox proportional hazard models adjusted for sociodemographic factors, lifestyle factors, and morbidity count. The population attributable fraction was also estimated.

Findings Of 502 535 participants in UK Biobank, 143 215 met the inclusion criteria and were included in our analyses. 68 500 (47·8%) of the participants were pre-frail and 5565 (3·9%) were frail. During a median follow-up period of 5·4 years, 726 individuals developed dementia. Compared with non-frail individuals, the risk of dementia incidence was increased for individuals with pre-frailty (hazard ratio 1·21 [95% CI 1·04–1·42]) and frailty (1·98 [1·47–2·67]) in the fully adjusted model. Of the five components used to define frailty, weight loss (1·31 [1·09–1·58]), tiredness (1·48 [1·18–1·86]), low grip strength (1·38 [1·17–1·63]), and slow gait speed (1·55 [1·22–1·96]) were independently associated with incident dementia. Based on population attributable fraction analyses, in the study sample, pre-frailty and frailty accounted for 9·9% and 8·6% of dementia cases, respectively.

Interpretation Individuals with pre-frailty and frailty were at a higher risk of dementia incidence even after adjusting for a wide range of confounding factors. Early detection and interventions for frailty could translate into prevention or delayed onset of dementia.

Funding None.

Introduction

Dementia is characterised by a progressive deterioration of cognition and the ability to perform activities of daily living. It is a heterogeneous syndrome associated with a high burden of dependency and disability and has a large emotional, economic, and psychological impact on families and society.[1,2] More than 850 000 people have dementia in the UK.[3] Globally, approximately 50 million individuals have dementia, and this number is estimated to increase to 152 million by 2050.[1]

Given that currently available pharmacological interventions can neither cure nor reverse dementia and offer little symptom relief, there is an urgent need to identify potential modifiable risk factors that could prevent or slow development of the disease. A 2020 report[2] on dementia prevention, intervention, and care identified that if 12 major risk factors were modified, 40% of dementias could be prevented or delayed. Physical frailty (hereafter referred to as frailty) has also been proposed as a risk factor.[4] Frailty is a state of high vulnerability to adverse health outcomes, including hospitalisations and deaths.[5] Several studies have reported that frailty is associated with cognitive impairments and a higher risk of dementia,[6–9] which might be explained by frailty and dementia sharing many risk factors and clinical features, including age, inflammation, functional impairment, and multimorbidity.[4]

The evidence from prospective cohort studies regarding the association between frailty and dementia has been conflicting. Some studies have suggested that frailty is an independent risk factor for dementia,[6–9] whereas others have reported that the association between these two conditions is weak and could be explained mainly by confounding factors, including pre-existing health conditions.[10] Discrepancies between existing studies could, in part, be attributable to their relatively small sample sizes (<10 000 participants),[7–9] as well as differences in how frailty has been defined and measured in each

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*Co-senior authors

Institute of Health and Wellbeing (F Petermann-Rocha MSc, D M Lyall PhD, F K Ho PhD, Prof J P Pell MD, C Celis-Morales PhD) **and British Heart Foundation Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences** (F Petermann-Rocha, S R Gray PhD, T J Quinn MD, C Celis-Morales), **University of Glasgow, Glasgow, UK; PROFITH (Promoting Fitness and Health Through Physical Activity) Research Group, Sport and Health University Research Institute (iMUDS), Department of Physical Education and Sports, Faculty of Sport Sciences, University of Granada, Granada, Spain** (I Esteban-Cornejo PhD)**; Centre of Exercise Physiology Research (CIFE), Universidad Mayor, Santiago, Chile** (C Celis-Morales)**; and Laboratorio de Rendimiento Humano, Grupo de Estudio en Educación, Actividad Física y Salud (GEEAFyS), Universidad Católica del Maule, Talca, Chile** (C Celis-Morales)

Correspondence to: Dr Carlos Celis-Morales, British Heart Foundation Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow G12 8TA, UK **carlos.celis@glasgow.ac.uk**

Research in context

Evidence before this study

We searched Web of Science on June 1, 2020, for articles published in English between Jan 1, 1980, and June 1, 2020, using medical subject heading terms for "dementia", "Alzheimer", "neurodegenerative diseases", "pre-frailty", and "frail". Both dementia and frailty have a substantial impact on individuals, families, and society. Several studies have reported that frailty is associated with a higher risk of dementia. However, the evidence from prospective cohort studies regarding this association has been conflicting, in part because of small sample sizes and differences in how frailty has been defined and measured in each study.

Added value of this study

This study provides a better understanding of the association between frailty and dementia incidence in middle-aged and older adults. Individuals with pre-frailty and frailty were at a higher risk of dementia incidence even after adjusting for a wide range of confounder factors, including multimorbidity. We also identified that weight loss, low grip strength, tiredness, and slow gait speed were the main components of the frailty phenotype that were associated with dementia. These findings highlight that public health strategies aiming to improve physical capabilities in middle-aged and older adults could reduce the burden of both frailty and dementia.

Implications of all the available evidence

Given the increased risk of dementia incidence in people with frailty, early assessment and interventions from middle age should be implemented in the general population to prevent frailty, and consequently, reduce the risk of dementia.

study. Moreover, we do not fully understand to what extent the association between frailty and dementia could be explained or moderated by pre-existing and shared risk factors for both conditions, and the components of the frailty phenotype that are most strongly associated with dementia remain to be elucidated. Understanding these features could help to tailor future interventions for dementia prevention. To answer these gaps in the current evidence, we used data from UK Biobank, a prospective cohort study, to investigate the association of the frailty phenotype, along with its individual components, with all-cause dementia incidence.

Methods

Study design and participants

For more on the **UK Biobank protocol** see http://www.ukbiobank.ac.uk

UK Biobank recruited more than 500 000 participants (5·5% response rate), aged 37–73 years, from the general population between 2006 and 2010.[11] Participants attended their closest of 22 assessment centres across England, Wales, and Scotland, where they completed a touchscreen questionnaire, had physical measurements taken, and provided biological samples (blood, urine, and saliva) at a baseline assessment visit. UK Biobank was approved by the North West Multi-Centre Research Ethics Committee (reference 11/NW/0382).

Procedures

See Online for appendix

For more on the **linkage procedure for hospital admissions** see http://content.digital.nhs.uk/services

Record linkage to Health Episode Statistics (England and Wales) and the Scottish Morbidity Records (Scotland) was used to identify the date and cause of hospital admissions. Detailed information regarding the linkage procedure can be found online.

Incident dementia cases were ascertained from two sources. Hospital admission records were available until February, 2018, for the full UK Biobank cohort, whereas linkage to primary care records was available for 45% of the UK Biobank cohort (approximately 230 000 participants) until May, 2017, for Scotland, September, 2017, for Wales, and August, 2017, for England. The detailed linkage procedures relating to primary care records are available online. The analyses of incident cases were restricted to the 230 000 participants with linkage to both primary care and hospital records, and the outcome was defined as either a primary care or hospital record of dementia, whichever occurred first. Follow-up was censored at the primary-care data end date for the relevant country, or the date of incident dementia or all-cause death, if this occurred earlier. Dementia was defined as International Classification of Diseases (10th revision) code F00 (dementia in Alzheimer disease), F01 (vascular dementia), F02 (dementia in other diseases), or F03 (unspecified dementia).

For more on **linkage procedures relating to primary care records** see http://content.digital.nhs.uk/services

Frailty

The Fried frailty phenotype was used in this study because it is based on physical-related frailty, including the following five criteria: weight loss, exhaustion, physical activity, walking speed, and grip strength.[5] However, some of these items were adapted to fit the data available within UK Biobank.[12] Previous studies have suggested that physical capability markers, including low grip strength and slow walking pace, are related to a higher risk of dementia;[13,14] however, little evidence is available regarding their associations as part of the frailty phenotype in the UK. Weight loss, tiredness or exhaustion, gait speed, and grip strength were derived following a similar approach to that of Hanlon and colleagues (appendix pp 1–4).[12] Physical activity was self-reported and collected using the International Physical Activity Questionnaire short form. Total physical activity was computed as the sum of walking, moderate activity, and vigorous activity, measured as metabolic equivalents (MET-h) per week. To derive a proxy for the Fried frailty phenotype, physical activity was categorised into age-specific and sex-specific quintiles, in which the lowest quintile was classified as meeting the physical inactivity criterion for frailty. Participants were

classified as frail if they fulfilled three or more of the five criteria, pre-frail if they fulfilled one or two criteria, and robust (non-frail) if they did not fulfil any criteria at baseline. The three groups were mutually exclusive.

Covariates

Age was calculated from dates of birth and based on the date of baseline assessment. Area-based socioeconomic status (deprivation) was derived from the postcode of residence using the Townsend score.[15] Ethnicity was self-reported and categorised into white, south Asian, black, Chinese, or mixed ethnic background. Education attainment was self-reported and coded as an ordinal variable. Participants were asked which of the following qualifications they held: CSEs, O-levels, A-levels, college or university degree, NVQ, HND, NHC, or equivalent, other professional qualification, or none of these. Self-reported smoking status was categorised as never, former, or current smoker. Total time spent in discretionary sedentary behaviours was derived from the sum of self-reported time spent driving, using a computer, and watching television during leisure time. Body-mass index (BMI) was calculated as weight divided by the square of height (kg/m²) and WHO criteria were applied to define weight categories.[16] Hours of sleep were self-reported and categorised as normal (7–9 h) and long or short sleep (>9 h or <7 h, respectively). Leisure or social activities, frequency of alcohol intake, and frequency of friend and family visits were self-reported at baseline via touchscreen questionnaire. Red meat, processed meat and fruit and vegetable intake were also collected through the touch-screen questionnaire at baseline. Prevalent morbidity was ascertained during a nurse-led interview at baseline. We calculated morbidity count (coded as 1, 2, 3, 4, or ≥5) based on 43 long-term conditions developed initially for a large epidemiological study in Scotland and subsequently adapted for UK Biobank.[17] Total cholesterol and glycated haemoglobin A_{1c} (HbA_{1c}) were analysed from serum and packed red blood cell samples. Systolic and diastolic blood pressure were derived from the mean of two readings recorded in the left arm. Reaction-time tests (timed tests of symbol matching) were completed through a touchscreen tool (Snap). Further details of these measurements can be found in the appendix (pp 3–4). Only participants with complete data available for the five components of frailty and covariates were included in analyses.

Statistical analysis

Descriptive characteristics are presented as means with SDs for quantitative variables that were normally distributed, and as medians with IQRs for those that were non-normally distributed. Categorical variables are presented as frequencies and percentages. STATA 16 statistical software was used for all analyses.

Associations between frailty and dementia incidence were investigated using Cox proportional hazard models.

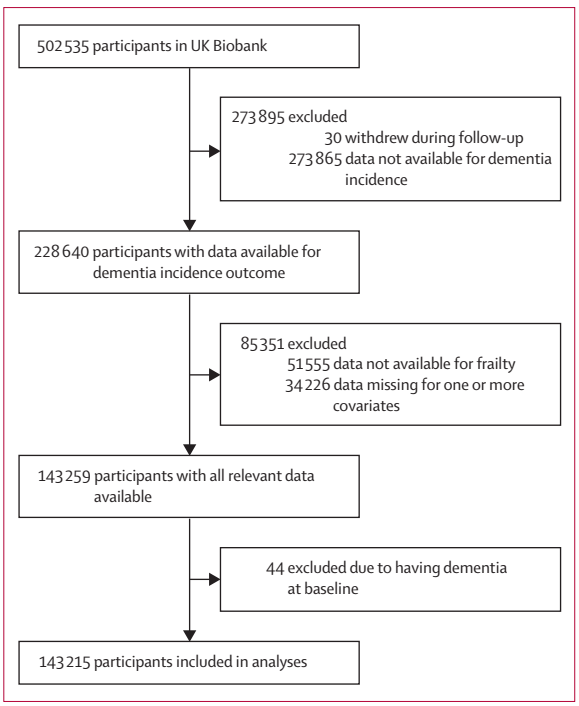

Figure 1: **Participant selection**

Individuals classified as non-frail were used as the reference group. The results are reported as hazard ratios (HRs) with 95% CIs. In addition, a sensitivity analysis was done a posteriori to evaluate associations between frailty and three subtypes of dementia incidence: vascular dementia, non-specific dementia, and Alzheimer's diseases (including early, late, and other non-specified Alzheimer's disease). Associations between the five components of the frailty phenotype and dementia incidence were investigated using the aforementioned analyses. The normal range for each component was used as the reference group. Additionally, non-linear associations between the number of individual components of frailty and the outcome were formally tested using penalised cubic splines fitted in the Cox proportional hazard models.

To avoid a possible reverse causality (ie, a causal relationship operating in the opposite way to that which truly occurs),[18] all analyses were done using a 2-year landmark analysis, excluding participants who experienced events within the first 2 years of follow-up. Participants with all-cause dementia at baseline were also excluded from the follow-up analyses. The proportional hazard assumptions were checked using Schoenfeld residuals.

We ran three models for each outcome, including an increasing number of covariates: model 1 (minimally adjusted) included sociodemographic covariates (age, sex, deprivation, ethnicity, and education); model 2 additionally included lifestyle factors (leisure or social activities, frequency of friend and family visits, smoking, sleep duration, total discretionary sedentary time, alcohol

	Whole population	Non-frail	Pre-frail	Frail
Total	143 215 (100·0%)	69 150 (48·3%)	68 500 (47·8%)	5565 (3·9%)
Sociodemographic factors				
Age at baseline, years	58·0 (50·0–63·0)	57·0 (50·0–63·0)	58·0 (51·0–63·0)	59·0 (53·0–64·0)
Sex				
Female	77 320 (54·0%)	35 216 (50·9%)	38 564 (56·3%)	3540 (63·6%)
Male	65 895 (46·0%)	33 934 (49·1%)	29 936 (43·7%)	2025 (36·4%)
Deprivation				
Lower	49 250 (34·4%)	25 564 (37·0%)	22 478 (32·8%)	1208 (21·7%)
Middle	49 781 (34·8%)	24 627 (35·6%)	23 494 (34·3%)	1660 (29·8%)
Higher	44 184 (30·9%)	18 959 (27·4%)	22 528 (32·9%)	2697 (48·5%)
Ethnicity				
White	137 759 (96·2%)	67 341 (97·4%)	65 425 (95·5%)	4993 (89·7%)
Mixed	1595 (1·1%)	593 (0·9%)	858 (1·3%)	144 (2·6%)
South Asian	2378 (1·7%)	614 (0·9%)	1442 (2·1%)	322 (5·8%)
Black	1167 (0·8%)	472 (0·7%)	607 (0·9%)	88 (1·6%)
Chinese	316 (0·2%)	130 (0·2%)	168 (0·2%)	18 (0·3%)
Education				
CSEs	7617 (5·3%)	3682 (5·3%)	3638 (5·3%)	297 (5·3%)
O-levels	31 238 (21·8%)	15 074 (21·8%)	15 012 (21·9%)	1152 (20·7%)
A-levels	15 970 (11·2%)	7746 (11·2%)	7690 (11·2%)	534 (9·6%)
College or university degree	47 936 (33·5%)	24 865 (36·0%)	21 837 (31·9%)	1234 (22·2%)
NVQ, HND, HNC, or equivalent	9800 (6·8%)	4728 (6·8%)	4666 (6·8%)	406 (7·3%)
Other professional qualification	7612 (5·3%)	3611 (5·2%)	3740 (5·5%)	261 (4·7%)
None of the above	23 042 (16·1%)	9444 (13·7%)	11 917 (17·4%)	1681 (30·2%)
Obesity-related markers				
Bodyweight, kg	77·6 (15·4)	76·3 (14·7)	78·4 (15·8)	82·7 (18·0)
Height, m	1·69 (0·09)	1·70 (0·09)	1·68 (0·09)	1·65 (0·09)
BMI, kg/m²	27·2 (4·5)	26·4 (4·01)	27·8 (4·7)	30·4 (6·0)
BMI category, kg/m²				
<18·5 (underweight)	700 (0·5%)	323 (0·5%)	342 (0·5%)	35 (0·6%)
18·5–24·9 (normal weight)	47 959 (33·5%)	27 197 (39·3%)	19 777 (28·9%)	985 (17·7%)
25·0–29·9 (overweight)	61 985 (43·3%)	30 454 (44·0%)	29 704 (43·4%)	1827 (32·8%)
≥30·0 (obese)	32 571 (22·7%)	11 176 (16·2%)	18 677 (27·3%)	2718 (48·8%)
Fitness and lifestyle				
Total physical activity, MET-h per week	1866·0 (855·0–3750·0)	2493·0 (1422·0–4 506·0)	1222·5 (495·0–2 986·0)	540·0 (346·5–990·0)
Sedentary behaviour, h per day	5·0 (4·0–6·0)	5·0 (3·0–6·0)	5·0 (4·0–6·0)	5·0 (4·0–7·0)
Alcohol intake frequency				
Daily or almost daily	29 872 (20·9%)	15 986 (23·1%)	13 173 (19·2%)	713 (12·8%)
3–4 times a week	34 635 (24·2%)	18 418 (26·6%)	15 519 (22·7%)	698 (12·5%)
Once or twice a week	37 702 (26·3%)	18 269 (26·4%)	18 143 (26·5%)	1290 (23·2%)
1–3 times a month	15 645 (10·9%)	6956 (10·1%)	7957 (11·6%)	732 (13·2%)
Special occasions only	15 076 (10·5%)	5816 (8·4%)	8139 (11·9%)	1121 (20·1%)
Never	10 285 (7·2%)	3705 (5·4%)	5569 (8·1%)	1011 (18·2%)
Red meat intake, portions per week	1·5 (1·5–2·5)	2·0 (1·5–2·5)	2·0 (1·5–2·5)	1·5 (1·5–2·5)
Processed meat intake, portions per week	2·0 (1·0–3·0)	2·0 (1·0–3·0)	2·0 (1·0–3·0)	2·0 (1·0–3·0)
Fruit and vegetable intake, g per day	337·5 (193·5)	341·2 (189·5)	334·6 (195·8)	327·7 (213·7)
Smoking status				
Never	78 961 (55·1%)	38 956 (56·3%)	37 251 (54·4%)	2754 (49·5%)
Previous	50 323 (35·1%)	24 108 (34·9%)	24 275 (35·4%)	1940 (34·9%)
Current	13 931 (9·7%)	6086 (8·8%)	6974 (10·2%)	871 (15·7%)

(Table 1 continues on next page)

	Whole population	Non-frail	Pre-frail	Frail
(Continued from previous page)				
Sleep time				
Normal	106 894 (74·6%)	53 859 (77·9%)	49 708 (72·6%)	3327 (59·8%)
Long or short	35 947 (25·1%)	15 184 (21·9%)	18 565 (27·1%)	2198 (39·5%)
Do not know or prefer not to answer	374 (0·3%)	107 (0·2%)	227 (0·3%)	40 (0·7%)
Social activities				
Sports club or gym	34 635 (24·2%)	27 109 (39·2%)	19 421 (28·4%)	873 (15·7%)
Pub or social club	37 702 (26·3%)	12 235 (17·7%)	13 263 (19·4%)	1116 (20·1%)
Religious group	15 645 (10·9%)	5022 (7·3%)	6721 (9·8%)	777 (14·0%)
Adult education class	15 076 (10·5%)	1839 (2·7%)	2094 (3·1%)	178 (3·2%)
Another group activity	10 285 (7·2%)	5831 (8·4%)	6461 (9·4%)	473 (8·5%)
None of the above	29 872 (20·9%)	17 114 (24·7%)	20 540 (30·0%)	2148 (38·6%)
Frequency of friend or family visits				
Almost daily	17 384 (12·1%)	7942 (11·5%)	8577 (12·5%)	865 (15·5%)
2–4 times a week	45 111 (31·5%)	22 229 (32·1%)	21 210 (31·0%)	1672 (30·0%)
About once a week	50 862 (35·5%)	25 048 (36·2%)	24 025 (35·1%)	1789 (32·1%)
About once a month	18 387 (12·8%)	8853 (12·8%)	8905 (13·0%)	629 (11·3%)
Once every few months	8929 (6·2%)	4119 (6·0%)	4411 (6·4%)	399 (7·2%)
Never or almost never	1869 (1·3%)	724 (1·0%)	998 (1·5%)	147 (2·6%)
No friends or family outside household	259 (0·2%)	73 (0·1%)	154 (0·2%)	32 (0·6%)
Do not know or prefer not to answer	414 (0·3%)	162 (0·2%)	220 (0·3%)	32 (0·6%)
Health status				
Multimorbidity				
None	50 278 (35·1%)	28 473 (41·2%)	21 117 (30·8%)	688 (12·4%)
One or more conditions	92 937 (64·9%)	40 677 (58·8%)	47 383 (69·2%)	4877 (87·6%)
Reaction time, ms	721·6 (119·6)	714·1 (112·0)	726·9 (123·5)	750·4 (151·7)
Total cholesterol, mmol/L	5·7 (1·1)	5·8 (1·1)	5·7 (1·2)	5·4 (1·2)
HbA_{1c}, mmol/L	35·9 (6·5)	35·3 (5·3)	36·3 (7·0)	39·3 (10·7)
Systolic blood pressure, mm Hg	138·0 (18·6)	138·3 (18·7)	137·8 (18·5)	136·7 (18·6)
Diastolic blood pressure, mm Hg	82·3 (10·1)	82·4 (10·1)	82·2 (10·1)	81·6 (10·3)

Data are n (%), median (IQR), or mean (SD). Percentages might not add to 100% due to rounding. BMI=body-mass index. MET-h=metabolic equivalents. HbA_{1c}=glycated haemoglobin A_{1c}.

Table 1: **Baseline characteristics by frailty category**

intake, and consumption of red meat, processed meat, and fruit and vegetables) and BMI; and model 3 additionally included morbidity count (based on 43 diseases and coded as 1, 2, 3, 4, or ≥5; appendix pp 3–4), vascular factors (blood pressure, total cholesterol, and HbA_{1c}), and reaction time (log-transformed to avoid the effect of outliers) at baseline. Model 4 was run only for the analyses of the five individual components of frailty and included mutual adjustment for the other four components of frailty. Percentage risk difference across models was estimated using the formula: $(HR_{model\ 2} - HR_{model\ 1})/(HR_{model\ 1} - 1) \times 100\%$.

The cumulative crude hazard rate of incident dementia and the frailty phenotype by age was estimated using the Nelson-Aalen estimator. The rate advancement period was also estimated, defined as the number of additional chronologic years that would be required to yield the equivalent risk rate for dementia incidence among the frailty phenotype and its individual components. For its estimation, the logarithm HR for incidence of the frailty phenotype and its individual components was divided by the corresponding incidence associated with each yearly increase in age—eg, $\log(HR_{frail})$ divided by $\log(HR_{age})$.[19] Additionally, the population attributable fraction was estimated to calculate the proportion of dementia incident cases that were attributable to both the frailty phenotype (pre-frail and frail) and its individual components, assuming causality. This population attributable fraction was estimated on the basis of the adjusted HR derived from model 3 and prevalence in the sample.

Finally, to investigate whether the associations between frailty and incident dementia differed by subgroups, the models were run stratified by sex, age category (<60 and ≥60 years), deprivation index (below and above median), level of adiposity (normal and overweight or obese), sleep pattern (normal and long or short sleep duration), morbidity count (none and one or more) and smoking status (never and previous or current). A further sensitivity analysis was done in which age was stratified with 65 years as the cutoff.

	Pre-frail (n=68 500)			Frail (n=5565)		
	HR (95% CI)	p value	Risk difference from model 1, %	HR (95% CI)	p value	Risk difference from model 1, %
Model 1	1·20 (1·03–1·40)	0·019	..	2·08 (1·57–2·76)	<0·0001	..
Model 2	1·24 (1·06–1·45)	0·0060	20·0%	2·20 (1·64–2·94)	<0·0001	11·1%
Model 3	1·21 (1·04–1·42)	0·016	5·0%	1·98 (1·47–2·67)	<0·0001	−9·3%

Total number of participants was 143 103; 726 events (incident dementia) occurred. Dementia incidence was estimated using primary care data. Non-frail people were used as the reference group. All analyses were done using a 2-year landmark analysis, excluding participants who experienced events within the first 2 years of follow-up (n=112). Model 1 included sociodemographic covariates (age, sex, deprivation, ethnicity, and education); model 2 additionally included lifestyle factors (leisure or social activities, frequency of friend and family visits, smoking, sleep duration, total discretionary sedentary time, alcohol intake, and consumption of red meat, processed meat, and fruit and vegetables) and body-mass index; model 3 additionally included morbidity count, vascular factors (blood pressure, total cholesterol, and glycated haemoglobin A_{1c}), and reaction time at baseline.

Table 2: **Associations between frailty and dementia incidence**

	HR (95% CI)	p value
Weight loss		
Model 1	1·36 (1·13–1·64)	0·0010
Model 2	1·34 (1·11–1·61)	0·0020
Model 3	1·31 (1·09–1·58)	0·0040
Model 4	1·31 (1·09–1·58)	0·0050
Tiredness or lack of energy		
Model 1	1·61 (1·30–2·01)	<0·0001
Model 2	1·60 (1·28–1·99)	<0·0001
Model 3	1·48 (1·18–1·86)	0·0010
Model 4	1·39 (1·10–1·74)	0·0050
Low physical activity levels		
Model 1	0·95 (0·79–1·14)	0·56
Model 2	0·98 (0·82–1·18)	0·84
Model 3	0·97 (0·80–1·16)	0·73
Model 4	0·93 (0·78–1·12)	0·48
Low grip strength		
Model 1	1·39 (1·18–1·63)	<0·0001
Model 2	1·44 (1·22–1·69)	<0·0001
Model 3	1·38 (1·17–1·63)	<0·0001
Model 4	1·34 (1·13–1·58)	0·0010
Slow gait speed		
Model 1	1·62 (1·30–2·03)	<0·0001
Model 2	1·72 (1·36–2·16)	<0·0001
Model 3	1·55 (1·22–1·96)	<0·0001
Model 4	1·41 (1·10–1·79)	0·0060

Total number of participants was 143 103; 726 events (incident dementia) occurred. Participants with a normal range for each component was used as the reference group. All analyses were done using a 2-year landmark analysis, excluding participants who experienced events within the first 2 years of follow-up (n=112). Model 1 included sociodemographic covariates (age, sex, deprivation, ethnicity, and education); model 2 additionally included lifestyle factors (leisure or social activities, frequency of friend and family visits, smoking, sleep duration, total discretionary sedentary time, alcohol intake, and consumption of red meat, processed meat, and fruit and vegetables) and body-mass index; model 3 additionally included morbidity count, vascular factors (blood pressure, total cholesterol, and glycated haemoglobin A_{1c}), and reaction time at baseline; model 4 additionally included the five individual components when these were not the exposure (sensitivity analysis).

Table 3: **Individual components of frailty and their association with all-cause dementia incidence**

Role of the funding source

There was no funding source for this study. FP-R, FKH, JPP, and CC-M had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 502 535 participants in UK Biobank, 228 640 had data available for dementia incidence, of whom 143 259 had data available for the frailty components and covariates. 44 of these participants had dementia at baseline and were excluded. Therefore, this prospective study included 143 215 participants (figure 1). After excluding the 2-year landmark period, the median follow-up period was 5·4 years (IQR 4·8–6·3) for dementia incidence. Over the follow-up period, 726 (0·5%) of the participants developed dementia.

Cohort characteristics by overall frailty phenotype are presented in table 1; characteristics by individual frailty component are presented in the appendix (pp 5–7). 69 150 (48·3%) of 143 215 participants were in the normal range for all five components; 51 047 (35·6%) had at least one frailty component, and 102 (0·1%) had all components. Of those who had one or more components, 68 500 (47·8%) were classified as pre-frail and 5565 (3·9%) as frail. Compared with non-frail people, those with frailty were more likely to be older, more deprived, more likely to be south Asian, female, obese, and a current smoker, and to report that they never drank alcohol. They were less likely to have a formal education, to take part in social activities, and to have visits from friends or family outside the household. They also had lower levels of physical activity and slower reaction times than non-frail individuals. Lastly, individuals with pre-frailty and frailty were more likely to have long or short sleep, higher levels of HbA_{1c}, and one or more morbidities than non-frail individuals (table 1).

Associations between the frailty phenotype and dementia incidence are shown in table 2. In the minimally adjusted model, individuals with pre-frailty (HR 1·20 [95% CI 1·03–1·40]) and frailty (2·08 [1·57–2·76]) had an increased risk of incident dementia compared with non-frail individuals. The magnitude of these associations was slightly higher if the model was further adjusted for lifestyle factors and BMI (model 2; 20·0% higher risk for pre-frailty and 11·1% higher risk for frailty). However, the associations were attenuated after adjusting for morbidity count and health-related factors (model 3; 1·21 [1·04–1·42] for pre-frailty and 1·98 [1·47–2·67] for frailty). Individuals with frailty had a steeper crude cumulative incidence of dementia compared with non-frail individuals (appendix p 9). When the analyses were stratified by the subtypes of dementia (vascular dementia, non-specific dementia, and Alzheimer's disease), pre-frailty and frailty were

associated with vascular dementia (model 3; 1·70 [1·10–2·62] for pre-frailty, 3·00 [1·54–5·82] for frailty) but not non-specific dementia or Alzheimer's disease (appendix p 10).

Of the five components used to define frailty, weight loss (HR 1·31 [95% CI 1·09–1·58]), tiredness (1·48 [1·18–1·86]), low grip strength (1·38 [1·17–1·63]), and slow gait speed (1·55 [1·22–1·96]) were independently associated with the risk of dementia incidence (model 3; table 3). When the analyses were mutually adjusted by components of frailty (model 4), the associations were attenuated but remained significant. Although we found no evidence of a non-linear association between the number of frailty components and logarithm risk of dementia incidence, the risk for dementia incidence increased markedly for individuals who had two to five components of the frailty phenotype. The hazard for dementia incidence was two-times higher for individuals with five components of the frailty criteria compared with those with none (figure 2, lower panel).

When the analyses were stratified by subgroup, no significant interactions were identified for pre-frailty and dementia incidence (figure 3). However, a significant interaction between frailty and age was observed (p=0·0050); individuals with frailty aged younger than 60 years had an increased risk of dementia incidence compared with those aged 60 years and older (figure 3). When the analyses were performed using a cutoff of 65 years, the associations were attenuated, but a similar pattern of association was observed (appendix p 11).

Based on population attributable fraction analyses, pre-frailty accounted for 9·90% (95% CI 1·61–17·5) of dementia cases and frailty accounted for 8·55% (3·83–13·00; table 4). Among the five individual components, low grip strength had the highest population attributable fraction compared with the other individual components, accounting for 8·84% (3·99–13·40) of incident dementia cases. Based on rate advancement period analyses, individuals with frailty are likely to experience dementia 3·58 years (95% CI 2·33–4·74) earlier than non-frail individuals. Among the frailty components, individuals with slow gait speed have the largest rate advancement (2·3 years [1·20–3·25] before those with normal gait speed).

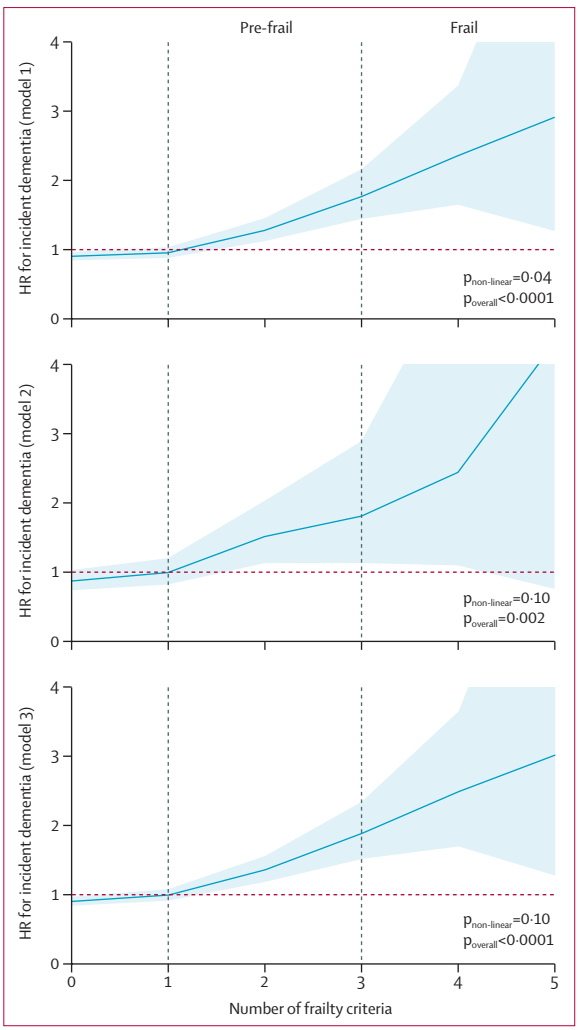

***Figure 2*: Non-linear associations between number of individual components of the frailty phenotype and dementia incidence**
Data are presented as adjusted HR with the 95% CI shown as shading. Non-frail people were used as the reference group. Model 1 included sociodemographic covariates (age, sex, deprivation, ethnicity, and education); model 2 additionally included lifestyle factors (leisure or social activities, frequency of friend and family visits, smoking, sleep duration, total discretionary sedentary time, alcohol intake, and consumption of red meat, processed meat, and fruit and vegetables) and body-mass index; model 3 additionally included morbidity count, vascular factors (blood pressure, total cholesterol, and glycated haemoglobin A_{1c}), and reaction time at baseline. HR=hazard ratio.

Discussion

In this study, using data from 143 215 participants from UK Biobank, we identified that individuals with pre-frailty and frailty were at a higher risk of dementia incidence compared with non-frail individuals, even after adjusting for a wide range of confounding factors, including sociodemographic factors, lifestyle factors, adiposity, morbidity count, and health-related markers. Furthermore, pre-frailty and frailty accounted for 9·9% and 8·6% of dementia cases in the study sample, respectively. Pre-frailty accounts for a greater proportion of dementia cases than frailty because of the higher prevalence of pre-frailty compared with frailty in UK Biobank. Participants with pre-frailty could also be at a milder stage of dementia,[20] which warrants further investigation. Considering that frailty might be a reversible syndrome and that dementia is not part of the natural ageing process, the burden of dementia-related morbidity attributable to frailty might be modifiable by delaying its onset. Therefore, public strategies aiming to improve physical capabilities, especially those related to muscle strength in middle-aged and older adults, might contribute to reducing the burden of frailty and, as a consequence, reduce the dementia risk attributable to frailty.

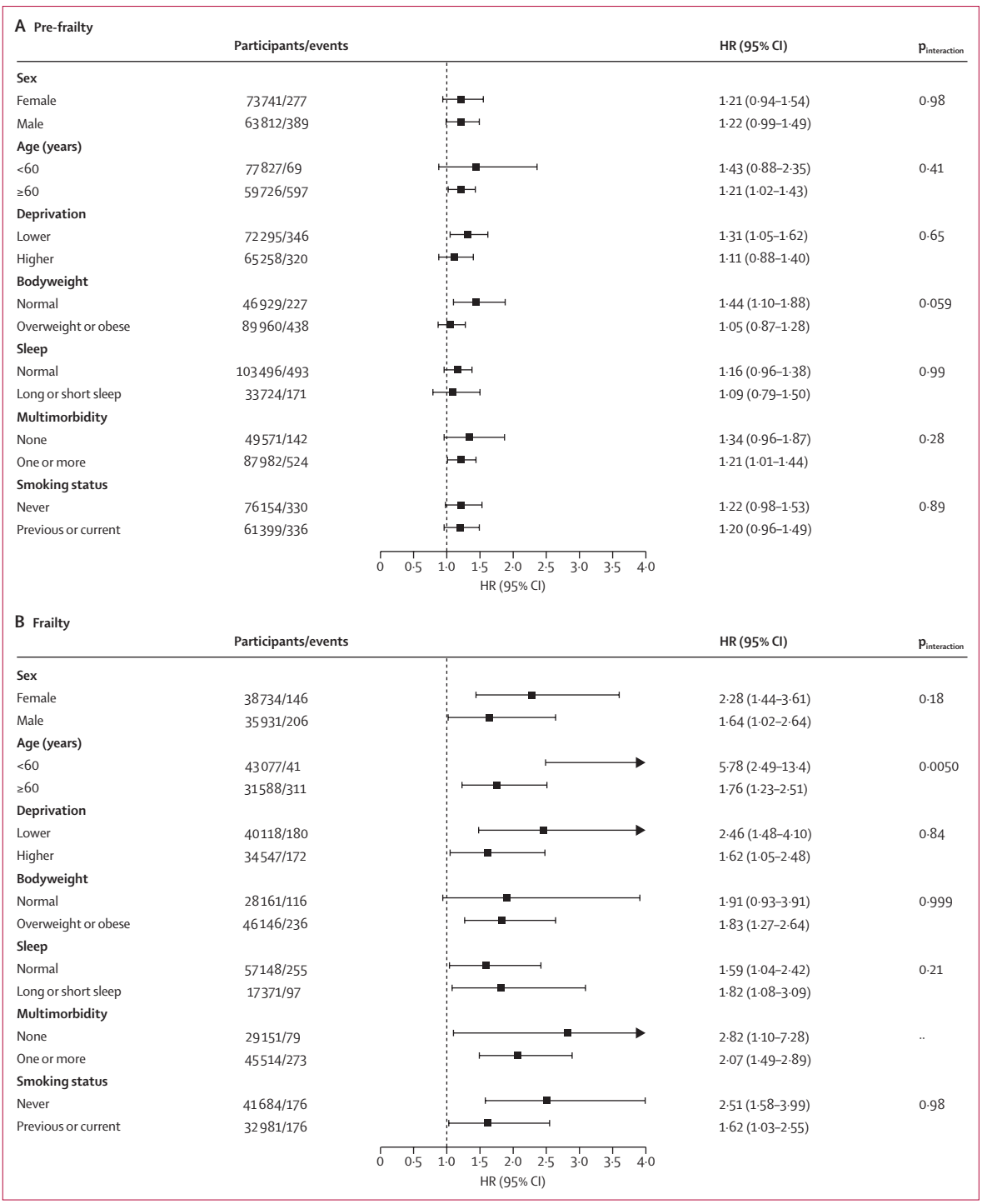

Figure 3: **Associations between all-cause dementia incidence and pre-frailty (A) and frailty (B) by subgroup**
Non-frail people were used as the reference group for each subgroup. All analyses were done using a 2-year landmark analysis, excluding participants who experienced events within the first 2 years of follow-up (n=112). Analyses were adjusted by age, sex, deprivation, ethnicity, education, morbidity count, blood pressure, total cholesterol, glycated haemoglobin A_{1c}, reaction time, body-mass index, leisure or social activities, frequency of friend or family visits, smoking, total discretionary sedentary time, sleep duration, and consumption of alcohol, red meat, processed meat, and fruit and vegetables, when these were not the subgroups used. No $p_{interaction}$ is given for multimorbity because there was not enough power to test for this interaction. HR=hazard ratio.

The associations between dementia and frailty have been previously reported using both multidimensional models (eg, the frailty index),[9] and, as in our study, using the frailty phenotype. However, most studies have used smaller sample sizes and had older populations, in which the risk of dementia could be higher due to the age of the population rather than the frailty status. For instance, Gray and colleagues,[8] who studied 2619 adults older than 65 years, showed that frailty, but not pre-frailty, was associated with a 1·78-times increased risk of incident dementia and a 4·46-times risk of non-Alzheimer dementia, compared with non-frail individuals. These associations were attenuated when the analyses were further adjusted for BMI and health status, and remained significant only for non-Alzheimer's dementia in the maximally adjusted model.[8] Similarly, a study of 2581 Italian adults aged 65–84 years identified that, using the frailty phenotype, individuals with frailty were associated with a 1·85-times risk of overall incident dementia and 2·68-times risk of vascular dementia.[7] In the UK, a dose-response relationship between a frailty index (multidimensional model) and dementia was identified in 8722 older adults from the English Longitudinal Study of Ageing (ELSA).[9] Findings from ELSA were similar to those in our study; individuals who were pre-frail had a 1·60-times increased risk of dementia and individuals who were frail had a 1·60-times increased risk, compared with non-frail individuals. However, in ELSA, dementia cases were self-reported and not clinically diagnosed.[9]

Frailty and dementia are strongly related and share similar common risk factors, such as sociodemographic factors (eg, age and deprivation), morbidities, and lifestyle factors.[21] Of note, in our study, individuals with pre-frailty and frailty with lower levels of deprivation had a higher risk of dementia compared with their counterparts with greater deprivation. This result is discordant with the findings of ELSA, in which individuals who were more deprived (in the lowest quintile) had a 1·68-times increased risk of dementia compared with the least deprived (highest quintile).[22] Individuals with pre-frailty and frailty who are more deprived might have higher resilience than those who are less deprived, allowing for better adaptation or managing of stress situations, trauma, or inequalities.[23] More studies are needed to evaluate the role of deprivation in frailty and dementia. Previous studies have identified that a dysregulation through multiple biological systems is a potential cause for both frailty and dementia.[24] This dysregulation might be caused by the presence of comorbidities, which contribute to both frailty and dementia. However, in our study, an association between frailty and dementia outcomes remained after adjusting for morbidity count, suggesting that the association is not merely the result of confounders.

Consistent with our results, low grip strength and slow gait speed or balance and gait impairment have been attributed to a worse cognitive condition among people with frailty.[21] Previous studies have shown that both gait speed and grip strength could be independent early markers of dementia,[13] and that these two components of frailty are the most strongly associated with cognitive impairment related to frailty.[14] Some of the potential mechanisms implicated are neurodegeneration (which contributes to both dementia and the decrease of physical capability markers); inflammation, described as an increment of pro-inflammatory markers; vascular mechanisms, related to microdamage mainly in the frontal-subcortical region; or a shared brain region (ie, gait speed and cognition could rely on a similar region).[13] Of note, in our study, the strongest association was between frailty and vascular dementia, which highlights that stroke, cerebrovascular disease, or both, could be one of the mechanisms.[25] Additionally, frailty is associated with a reduction in the leisure and social activities that contribute to the wellbeing and life satisfaction of individuals.[26] This lower social interaction could increase the risk of dementia, as has been previously shown.[27]

The assessment and surveillance of frailty could help to decrease its associated adverse health outcomes, including dementia. Of note, according to our rate advancement period analyses, individuals with frailty could experience dementia approximately 3 years earlier than non-frail individuals. However, frailty is not routinely assessed in clinical practice. A multicentre study of 388 clinicians (mainly medical doctors) from 44 countries showed that only 52·8% routinely assessed frailty in daily practice.[28] The assessment rate was higher among geriatricians than other medical specialties,[28] consistent with frailty being normally associated with ageing. However, its development begins earlier in life, and an association between frailty and cognition has been recognised independent of age.[29] Although in our study, only older individuals with pre-frailty had a higher risk of dementia compared with non-frail individuals, individuals with frailty younger than 60 years had

	Population attributable fraction, % (95% CI)	Rate advancement period, years (95% CI)
Weight loss	4·54% (1·08 to 7·88)	1·42 (0·50 to 2·21)
Tiredness	4·27% (1·50 to 6·96)	2·06 (0·95 to 3·00)
Low physical activity	–0·65% (–4·36 to 2·93)	–0·16 (–1·28 to 0·72)
Low grip strength	8·84% (3·99 to 13·40)	1·77 (0·95 to 2·46)
Slow gait speed	4·48% (1·67 to 7·21)	2·30 (1·20 to 3·25)
Pre-frailty	9·90% (1·61 to 17·50)	1·00 (0·24 to 1·69)
Frailty	8·55% (3·83 to 13·00)	3·58 (2·33 to 4·74)

All analyses were done using a 2-year landmark analysis, excluding participants who experienced events within the first 2 years of follow-up (n=112). Analyses were adjusted by age, sex, deprivation, ethnicity, education, morbidity count, blood pressure, total cholesterol, glycated haemoglobin A_{1c}, reaction time, body-mass index, leisure or social activities, frequency of friend or family visits, smoking, total discretionary sedentary time, sleep duration, and consumption of alcohol, red meat, processed meat, and fruit and vegetables (model 3).

Table 4: **Population attributable fraction and rate advancement periods of incident dementia attributable to frailty and its components**

a 5·78-times increased risk of incident dementia compared with a 1·76-times increased risk among those aged 60 years and older. This finding highlights the association between frailty and dementia as modified by age, and also shows that the onset of frailty could start much earlier in life. Therefore, our study provides novel evidence regarding the association between frailty and dementia incidence, not only in older adults as has been previously shown, but also in middle-aged adults. These findings are supported by a study by Gil-Salcedo and colleagues,[30] which showed that a healthier lifestyle (eg, not smoking, moderate alcohol consumption, 2·5 hours per week of physical activity) during the middle age (at 50 years) of participants from the UK Whitehall II cohort was associated with a lower risk of frailty during 20 years of follow-up. In this context, considering that previous studies have shown that frailty might be reversed with exercise interventions in some older adults,[31] early assessment and interventions from middle age should be implemented among the general population to prevent frailty, and consequently, reduce the risk of dementia. However, further studies in the field are still needed.

For more on **applying for access to UK Biobank data** see http://www.ukbiobank.ac.uk

UK Biobank is a large, prospective, general population cohort with data available on a wide range of potential confounders and health outcomes. As a result, our analyses could be adjusted for multiple confounders and stratified by different subgroups. However, UK Biobank participants are not representative of the UK population because they are more likely to have healthier behaviours than the general UK population;[32] therefore, the summary statistics should not be generalised even though the effect sizes estimated from UK Biobank were generally consistent with those from population-representative cohorts. In addition, the frailty phenotype was created using similar but not identical variables to those suggested by Fried and colleagues,[5] and four of the five variables were self-reported. Furthermore, the frailty phenotype was derived from baseline UK Biobank data, and these data could have changed over time. Our analysis might have underestimated the associations because frailty might not develop until older age for some people. Although we were able to adjust our model for one cognitive test, UK Biobank does not have other cognitive measurements, such as the Mini-Mental State Examination or the Instrumental Activities of Daily Living. Therefore, residual confounding might have occurred due to baseline cognitive ability, which could overestimate the association. Similarly, our study did not adjust for apolipoprotein E polymorphism, a major risk factor for dementia. However, a previous study found no association between apolipoprotein E polymorphism and frailty.[33] Additionally, we note that our sample might not have sufficient power for dementia subtype analysis. Finally, although we performed a 2-year landmark analysis excluding participants who experienced events in the first 2 years after recruitment, reverse causality is possible in any observational study.

In conclusion, frailty (both the pre-frail and frail status) was associated with a higher risk of dementia incidence. Furthermore, among the five components used to define frailty in this study, slow gait speed and low grip strength made the largest contributions to dementia incidence. Considering that frailty is a modifiable syndrome in middle age, its early detection and treatment might represent a target for prevention or delayed onset of neurodegenerative diseases, including dementia.

Contributors

FP-R, FKH, JPP, and CC-M contributed to the conception and design of the study, advised on all statistical aspects, and interpreted the data. FP-R did the literature search. FP-R did the analyses with support from FKH, JPP, and CC-M. All authors critically reviewed previous drafts. All authors approved the final draft for submission. CC-M is the guarantor.

Declaration of interests

We declare no competing interests.

Data sharing

Applications for access to UK Biobank data can be made online.

Acknowledgments

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4.6.1 Appendix G

4.6.2 Supplementary methods

a Frailty definition and measures

An adapted version of the frailty classification derived by Fried et al. was used in this study. The Fried classification uses the following five criteria: weight loss, exhaustion, physical activity, walking speed and grip strength. Participants were classified as frail if they fulfilled three or more criteria, prefrail if they fulfilled one or two criteria and robust if they did not fulfil any criteria.

Weight loss was derived from self-report of weight loss in the previous year, dichotomised into yes or no (same weight or gained weight). Exhaustion was derived from the self-report of tiredness in the last two weeks categorised as: not at all; several days; more than half the days; nearly every day. Those participants who reported tiredness more than half the days or nearly every day were identified as meeting the Fried criterion for exhaustion (Fried et al., 2001b). Physical activity was based on self-report, collected using the International Physical Activity Questionnaire (IPAQ) short form(Guo et al., 2015). Total physical activity was computed as the sum of walking, moderate and vigorous activity, measured as metabolic equivalents (MET-hours/week). To derive a proxy for the Fried frailty criteria, this variable was categorised into age-sex-specific quintiles where the lowest quintile (20%) was classified as meeting the physical inactivity criterion for frailty. Walking speed was categorised as slow, average or brisk. To derive a proxy for gait speed, this was then dichotomised into slow or normal (average or brisk pace). Grip strength was measured using a Jamar J00105 hydraulic hand dynamometer. Isometric grip force was assessed from a single 3-second maximal grip effort, separately in the right and left arms, with the participant seated upright with their elbow by their side and flexed at 90º so that their forearm was facing forwards and resting on an armrest. The average of the right and left values were expressed in absolute units (kg) and used in subsequent analyses. The specific cut-off points by sex are presented Supplementary Table 1.

Finally, we have conducted a sensitivity analysis to examine how misclassification of frailty may influence the effect size estimates. We assumed

the sensitivity and specificity of the exposure conservatively to be 80%. The misclassification corrected risk ratio for prefrailty (including frailty) were 1·87, compared with 1·44 without correction. Therefore, we are confident that misclassification would non-significant alter the conclusions of this study.

b More information about some covariates

Education attainment was self-reported and coded as an ordinal variable. Participants were asked, 'Which of the following qualifications do you have? (you can select more than one),' with the options 'college or university degree, A levels or equivalent, O levels or GCSEs or equivalent, CSEs, NVQ/HND/HNC, or equivalent'. Height and body weight were measured by trained nurses during the initial assessment. Body mass index (BMI) was calculated as (weight in kg)/(height in m)^2 and the WHO criteria were applied to categorise participants into underweight <18·5 kg.m^{-2}, normal weight 18·5-24·9 kg.m^{-2}, overweight 25·0-29·9 kg.m^{-2} and obese ≥30·0 kg.m^{-2} (WHO, 2000). Frequency of alcohol intake was self-reported at baseline via touch-screen questionnaire and categorised as daily/almost daily, 3-4 times a week, once/twice a week, 1-3 times a month, special occasions only and never. Leisure/social activities was self-reported. Participants were asked 'Which of the following do you attend once a week or more often? (you can select more than one)', whit the options 'sports club or gym', 'pub or social club', 'religious group', 'adult education class', 'other group activity', 'none of the above'. Frequency of friend and family visits was also self-reported. Participants were asked 'how often do you visit friends or family or have them visit you?', with the options 'almost daily' '2-4 times a week' 'about once a week', 'about once a month', 'once every few months', 'never or almost never', 'no friend/family outside household'. Reaction-time test (timed test of symbol matching) was completed through a touch-screen test (Snap) in milliseconds across trials which contained matching pairs. More information is available here
http://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/Snap.pdf

Prevalent morbidity was ascertained during a nurse-led interview at baseline. We calculated morbidity count based on 43 long-term conditions originally developed for a large epidemiological study in Scotland and subsequently

adapted for UK Biobank (Barnett et al., 2012). The complete list of this morbidities is found below:

List of morbidities: count of 43 chronic illness groups including cancer

1. Hypertension
2. Depression
3. Painful condition
4. Asthma
5. CHD
6. Dyspepsia
7. Diabetes
8. Thyroid
9. Inflammation (rheumatoid arthritis/ other inflammation)
10. COPD
11. Anxiety
12. Irritable bowel syndrome
13. Alcohol problems
14. Other psychoactive substance abuse
15. Constipation
16. Stroke
17. Chronic Kidney disease
18. Diverticular disease of the intestine
19. Atrial fibrillation
20. Peripheral vascular disease
21. Heart failure
22. Prostate disorders
23. Glaucoma
24. Epilepsy
25. Dementia
26. Psoriasis or eczema
27. Inflammatory bowel disease
28. Migraine
29. Chronic sinusitis
30. Anorexia or bulimia
31. Bronchiectasis
32. Parkinson's disease
33. Multiple sclerosis
34. Chronic liver disease
35. Osteoporosis
36. Chronic fatigue syndrome
37. Endometriosis
38. Polycystic ovary syndrome
39. Pernicious anaemia
40. Cancer

c More information about PAF

The population attributable fraction (PAF) is defined by Mansournia MA as 'the fraction of all cases of a particular disease or other adverse condition in a

population that is attributable to a specific exposure; PAF equals (O – E)/O, where O and E refer to the observed number of cases and the expected number of cases under no exposure, respectively'(Mansournia and Altman, 2018). In other words, the proportion of the population that can be attributed to a particular exposure (Porta, 2014). In our study, PAF was estimated to calculate the proportion of dementia incidence cases that were attributable to both the frailty phenotype (pre-frail and frail) and its individual components assuming causality (Mansournia and Altman, 2018).

4.6.3 Supplementary Table 1. Frailty and sarcopenia definition and cut-off points

Individual components	Frailty (adapted from Halton et al. (Hanlon et al., 2018b) and used in this manuscript)
Weight Loss	Self-reported: "Compared with one year ago, has your weight changed?" **Options:** Yes: weight loss in the previous year. No: another option.
Exhaustion	Self-reported: "Over the past two weeks, how often have you felt tired or had little energy" **Options:** Yes: more than half time or every day No: another option
Low physical activity	Quintiles of sex- age-specific levels of total PA in derived from IPAQ **Options:** Yes: Lowest level of PA No: low/middle to highest levels of PA
Slow walking speed	Self-reported: How do you describe your usual walking pace? (a proxy for gait speed) **Options:** Yes: slow No: average or brisk pace
Low grip strength	Measured grip strength expressed in kg by sex-and BMI adjusted cut-off points. **Cut-off points:** **Men** If BMI ≤24 & grip strength ≤ 29 If BMI 24·1 - 26 & grip strength ≤ 30 If BMI 26·1 - 28 & grip strength ≤ 30 If BMI >28 & grip strength ≤ 32 **Women** If BMI ≤23 & grip strength ≤ 17 If BMI 23·1 - 26 & grip strength ≤ 17·3 If BMI 26·1 - 29 & grip strength ≤ 18 If BMI >29 & grip strength ≤ 21

Table adapted from Halton et al. (Hanlon et al., 2018b)

4.6.4 Supplementary Table 2. Sociodemographic characteristics of the study population by the individual components of frailty at baseline

	All components normal	One component only	Two components	Three components	Four components	Five components
Socio-demographics						
Total n (%)	69 150 (48·3)	51 047 (35·6)	17 453 (12·2)	4 538 (3·2)	925 (0·6)	102 (0·1)
Age (years), median (IQR)	57·0 (50 – 63)	58·0 (50·0 – 63·0)	59·0 (51·0 – 64·0)	59·0 (53·0 – 64·0)	59·0 (52·0 – 65·0)	56·0 (52·0 – 63·0)
Sex (female) n (%)	35 216 (50·9)	28 013 (54·9)	10 551 (60·4)	2 894 (63·8)	585 (63·2)	61 (59·8)
Deprivation n (%)						
Lower	25 564 (37·0)	17 373 (34·0)	5 105 (29·1)	1 033 (22·7)	164 (17·7)	11 (10·8)
Middle	24 627 (35·6)	17 783 (34·9)	5 711 (32·7)	1 378 (30·4)	254 (27·5)	28 (27·4)
Higher	18 959 (27·4)	15 891 (31·1)	6 637 (38·0)	2 127 (46·9)	507 (54·8)	63 (61·8)
Ethnicity n (%)						
White	67 341 (97·4)	49 045 (96·1)	16 380 (93·8)	4 109 (90·6)	795 (86·0)	89 (87·2)
Mixed	593 (0·9)	580 (1·1)	278 (1·6)	109 (2·4)	31 (3·4)	4 (3·9)
South Asian	614 (0·9)	902 (1·8)	540 (3·1)	239 (5·3)	77 (8·3)	6 (5·9)
Black	472 (0·7)	402 (0·8)	205 (1·2)	67 (1·5)	19 (2·0)	2 (2·0)
Chinese	130 (0·1)	118 (0·2)	50 (0·3)	14 (0·3)	3 (0·3)	1 (1·0)
Education, n (%)*						
CSEs	3 682 (6·1)	2 66 (6·0)	972 (6·4)	242 (6·1)	51 (6·2)	4 (4·4)
O-levels	15 074 (24·8)	11 235 (25·1)	3 777 (24·7)	938 (23·6)	197 (23·9)	17 (18·5)
A-levels	7 746 (12·7)	5 816 (13·0)	1 874 (12·3)	438 (11·0)	83 (10·1)	13 (14·1)
College/University degree	24 865 (40·9)	16 803 (37·5)	5 034 (32·9)	1 047 (26·3)	166 (20·2)	21 (22·8)
None of the above	9 444 (15·5)	8·286 (18·5)	3 631 (23·8)	1 318 (33·1)	326 (39·6)	37 (40·2)
Obesity-related markers						
Body weight (kg) mean (SD)	76·3 (14·7)	78·0 (15·5)	79·7 (16·6)	82·4 (17·7)	84·2 (19·4)	81·5 (19·7)
Height (m) mean (SD)	1·70 (0·09)	1 68 (0·09)	1·66 (0·09)	1·65 (0·09)	1·64 (0·09)	1·64 (0·09)
BMI mean (SD)	26·4 (4·01)	27·4 (4·5)	28·7 (5·2)	30·2 (5·9)	31·1 (6·5)	30·5 (6·9)
BMI Categories n (%)						
Underweight (<18·5 $kg \cdot m^{-2}$)	323 (0·5)	242 (0·5)	100 (0·6)	26 (0·6)	8 (0·9)	1 (0·9)
Normal weight (18·5-24·9 $kg \cdot m^{-2}$)	27 197 (39·3)	15 587 (30·5)	4 190 (24·0)	810 (18·8)	153 (16·5)	22 (21·6)
Overweight (25·0 to 29·9 $kg \cdot m^{-2}$)	30 454 (44·0)	22 717 (24·5)	6 987 (40·0)	1 532 (33·8)	264 (28·5)	31 (30·4)

Obese (≥30·0 kg·m^{-2})	11 176 (16·2)	12 501 (24·5)	6 176 (35·4)	2 170 (47·8)	500 (54·0)	48 (47·1)
Fitness and Lifestyle						
Total PA (MET·h^{-1}·week^{-1}), median (IQR)	2 493·0 (1 422·0 – 4 506·0)	1 413·0 (594·0 –3 262·0)	693·0 (412·5 – 2 079·0)	577·5 (360·0 – 1 177·5)	480·0 (330·0 – 693·0)	406·2 (330·0 – 577·5)
Sedentary behaviour (h·day^{-1}), median (IQR)	5·0 (3·0 – 6·0)	5·0 (4·0 – 6·0)	5·0 (4·0 – 6·0)	5·0 (4·0 – 7·0)	5·0 (4·0 – 7·0)	5·0 (4·0 – 6·0)
Alcohol frequency intake n (%)						
Daily or almost daily	15 986 (23·1)	10 331 (20·2)	2 842 (16·3)	618 (13·6)	85 (9·2)	10 (9·8)
3-4 times a week	18 418 (26·6)	12 119 (23·7)	3 400 (19·5)	588 (13·0)	102 (11·0)	8 (7·8)
Once or twice a week	18 269 (26·4)	13 565 (26·6)	4 578 (26·2)	1 091 (24·0)	182 (19·7)	17 (16·7)
1-3 times a month	6 956 (10·1)	5 751 (11·3)	2 206 (12·6)	605 (13·3)	119 (12·9)	8 (7·8)
Special occasions only	5 816 (8·4)	5 579 (10·9)	2 560 (14·7)	882 (19·4)	210 (22·7)	29 (28·4)
Never	3 705 (5·4)	3 702 (7·2)	1 867 (10·7)	754 (16·6)	227 (24·5)	30 (29·4)
Red meat (portion·week-1), median (IQR)	2·0 (1·5 – 2·5)	1·5 (1·5 – 2·5)	1·5 (1·5 – 2·5)	1·5 (1·5 – 2·5)	1·5 (1·0 – 2·5)	1·5 (1·0 – 2·5)
Processed meat intake (portion·week-1), median (IQR)	2·0 (1·0 – 3·0)	2·0 (1·0 – 3·0)	2·0 (1·0 – 3·0)	2·0 (1·0 – 3·0)	2·0 (1·0 – 3·0)	2·0 (1·0 – 3·0)
Fruit and vegetable intake (g·day-1) mean (SD)	341·2 (189·5)	336 4 (193·8)	329·2 (201·2)	327·6 (205·7)	323·0 (232·6)	375·4 (342·7)
Smoking status n (%)						
Never	38 956 (56·3)	28 010 (54·9)	9 241 (53·0)	2 274 (50·1)	434 (46·9)	46 (45·1)
Previous	24 108 (34·9)	18 096 (35·4)	6 179 (35·4)	1 587 (35·0)	316 (34·2)	37 (36·3)
Current	6 086 (8·8)	4 941 (9·7)	2 033 (11·6)	677 (14·9)	175 (18·9)	19 (18·6)
Sleep time n (%)**						
Normal	53 859 (78·0)	37 791 (74·2)	11 917 (68·7)	2 792 (62·0)	483 (52·6)	52 (52·5)
Long/short sleep	15 184 (22·0)	13 126 (25·8)	5 439 (31·3)	1715 (38·0)	436 (47·4)	47 (47·5)
Social activities, n (%)						
Sports club or gym	27 109 (39·2)	15 470 (30·3)	3 951 (22·6)	764 (16·8)	100 (10·8)	9 (8·8)
Pub or social club	12 235 (17·7)	9 712 (19·0)	3 551 (20·4)	916 (20·2)	185 (20·0)	15 (14·7)
Religious group	5 022 (7·3)	4 770 (9·3)	1 951 (11·2)	630 (13·9)	134 (14·5)	13 (12·8)
Adult education class	1 839 (2·6)	1 528 (3·0)	566 (3·2)	143 (3·2)	27 (2·9)	8 (7·8)
Another group activity	5 831 (8·4)	4 728 (9·3)	1 733 (9·9)	377 (8·3)	80 (8·6)	16 (15·7)
None of the above	17 114 (24·8)	14 839 (29·1)	5 701 (32·7)	1 708 (37·6)	399 (43·1)	41 (40·2)
Frequency of friend/family visits, n (%)***						
Almost Daily	7 942 (11·5)	6 248 (12·3)	2 329 (13·4)	683 (15·1)	162 (17·6)	20 (19·6)
2-4 times a week	22 229 (32·2)	15 805 (31·1)	5 405 (31·1)	1 368 (30·3)	274 (29·8)	30 (29·4)

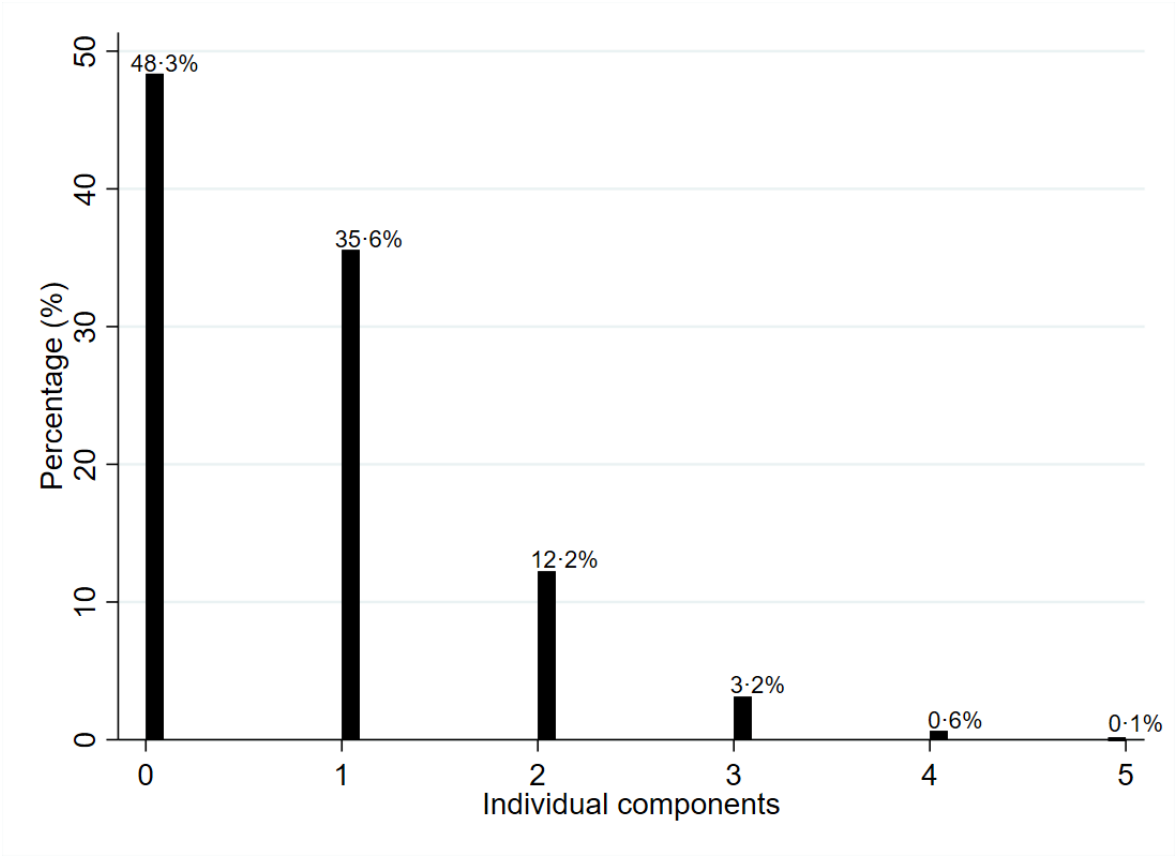
About once a week	25 048 (36·3)	18 142 (35·6)	5 883 (33·8)	1 475 (32·7)	288 (31·3)	26 (25·5)
About once a month	8 853 (12·8)	6 729 (13·2)	2 176 (12·5)	512 (11·4)	105 (11·4)	12 (11·8)
Once every few months	4 119 (6·0)	3 204 (6·3)	1 207 (6·9)	340 (7·5)	50 (5·4)	9 (8·8)
Never or almost never	724 (1·1)	676 (1·3)	322 (1·8)	111 (2·5)	31 (3·4)	5 (4·9)
No friends/family outside household	73 (0·1)	77 (0·2)	66 (0·4)	23 (0·5)	9 (1·0)	0
Health status						
Multimorbidity n (%)						
None	28 473 (41·2)	17 002 (33·)	4 115 (23·6)	630 (13·9)	54 (5·8)	4 (3·9)
≥ 1	40 677 (58·8)	34 045 (66·7)	13 338 (76·4)	3 908 (86·1)	871 (94·2)	98 (96·1)
Reactive time test (time/ms), mean (SD)	714·1 (112·0)	723·6 (120·2)	736·3 (132·3)	747·6 (147·5)	765·3 (167·9)	742·4 (173·3)
Total cholesterol (mmol/l), mean (SD)	5·8 (1·1)	5·7 (1·2)	5·6 (1·2)	5·5 (1·2)	5·3 (1·3)	5·3 (1·6)
HbA1c (mmol/l), mean (SD)	35·3 (5·3)	36·0 (6·6)	37·0 (7·9)	39·0 (10·4)	40·7 (12·0)	40·9 (11·0)
SBP (mmHg), mean (SD)	138·3 (18·7)	137·9 (18·5)	137·3 (18·6)	137·0 (18·6)	135·3 (18·1)	135·6 (20·9)
DBP (mmHg), mean (SD)	82·4 (10·1)	82·3 (10·1)	82·0 (10·2)	81·7 (10·3)	81·6 (10·2)	80·7 (11·1)

BMI: body mass index; PA: physical activity; MET: metabolic equivalents; SBP: systolic blood pressure; DBP: diastolic blood pressure; ms: millisecond; IQR: interquartile range.

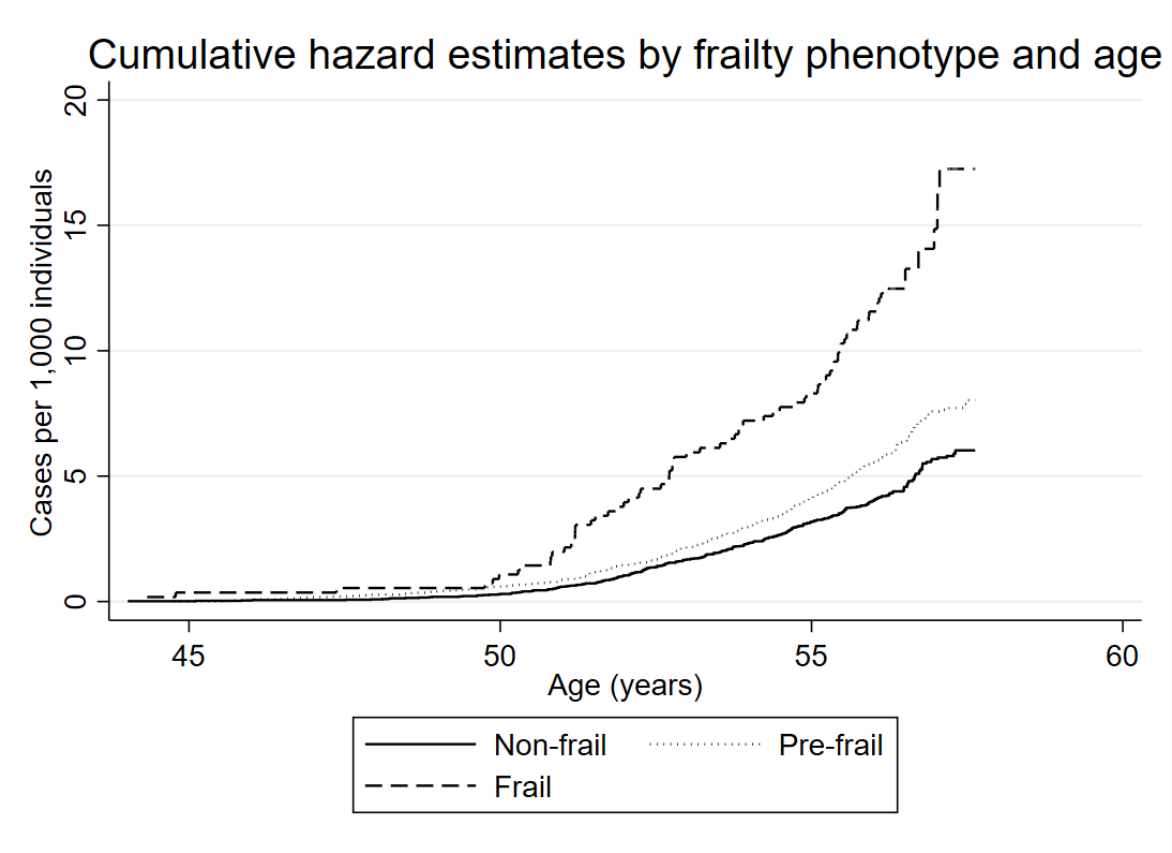
*9800 participants declared had NVQ/HND/HNC or equivalent and 7612 other professional qualification.

** 374 participants preferred not to answer or did not know.

***414 participants preferred not to answer or did not know.



4.6.5 Supplementary Figure 1. Prevalence of individuals components of the frailty phenotype at baseline.



4.6.6 Supplementary Figure 2. Cumulative survival plot of incident dementia by frailty phenotype and age

Data presented as crude HR by the frailty phenotype. All analyses were performed using a 2-year landmark analysis, excluding participants who experienced events within the first two years of follow-up and those with all-cause dementia at baseline (n=44).

4.6.7 Supplementary Table 3. Associations between frailty and specific dementia incidence

			Non-frail/robust	Pre-frail		Frail	
	Total n	Death / events	HR (95%CI)	HR (95% CI)	p-value	HR (95% CI)	p-value
Vascular dementia							
Model 1	143 115	116	1·00 (Ref)	1·98 (1·30; 3·02)	0·002	4·86 (2·64; 8·97)	<0·001
Model 2	143 115	116	1·00 (Ref)	1·94 (1·26; 2·97)	0·002	4·42 (2·34; 8·35)	<0·001
Model 3	143 115	116	1·00 (Ref)	1·70 (1·10; 2·62)	0·016	3·00 (1·54; 5·82)	0·001
Non-specific dementia							
Model 1	143 111	171	1·00 (Ref)	1·08 (0·79; 1·47)	0·647	1·11 (0·55; 2·24)	0·765
Model 2	143 111	171	1·00 (Ref)	1·15 (0·84; 1·58)	0·381	1·30 (0·64; 2·66)	0·464
Model 3	143 111	171	1·00 (Ref)	1·14 (0·83; 1·57)	0·419	1·23 (0·59; 2·55)	0·577
Alzheimer's disease							
Model 1	143 112	432	1·00 (Ref)	1·00 (0·83; 1·22)	0·957	1·10 (0·70; 1·72)	0·674
Model 2	143 112	432	1·00 (Ref)	1·06 (0·88; 1·30)	0·526	1·26 (0·80; 1·99)	0·308
Model 3	143 112	432	1·00 (Ref)	1·07 (0·88; 1·31)	0·486	1·26 (0·79; 2·00)	0·323

Data presented as adjusted hazard ratio (HR) and its 95% confidence interval (95% CI) by the frailty phenotype. Non-frail people were used as the reference group.

All analyses were performed using a 2-year landmark analysis, excluding participants who experienced events within the first two years of follow-up and those with all-cause dementia at baseline (n=44). Model 1 included sociodemographic covariates (age, sex, deprivation, ethnicity, and education); model 2 additionally included lifestyle factors (leisure/social activities, frequency of friend/ family visit, smoking, sleep duration, total discretionary sedentary time, alcohol intake and consumption of red meat, processed meat and fruit and vegetable) and BMI; and model 3, which additionally included morbidity count (based on 43 diseases and coded as 1, 2, 3, 4 and ≥5), vascular factors (blood pressure, total cholesterol, and HbA1c) and reaction time (transformed at logarithm to avoid the effect of outliers) at baseline.

4.6.8 Supplementary Table 4. Associations between all-cause dementia incidence and pre-frail and frail by age group (< and ≥ 65 years)

Age category	Non-frail	Pre-frail	Frail	$P_{interaction}$
< 65 years	1·00 (Ref.)	1·14 (0·89; 1·46)	2·37 (1·44; 3·89)	0·089
≥ 65 years	1·00 (Ref.)	1·29 (1·05; 1·58)	1·76 (1·13; 2·74)	

Data presented as adjusted hazard ratio (HR) and its 95% confidence interval (95% CI) by the frailty phenotype. Non-frail people were used as the reference group.

All analyses were performed using a 2-year landmark analysis, excluding participants who experienced events within the first two years of follow-up and those with all-cause dementia at baseline (n=44). Analyses were adjusted by sex, deprivation, ethnicity, education, morbidity count, blood pressure, total cholesterol, and HbA1c, reaction time, BMI, leisure/social activities, frequency of friend/ family visit, smoking, total discretionary sedentary time, sleep duration, alcohol, red meat, processed meat and fruit & vegetable.

Chapter 5 Discussion

5.1 Summary of key findings

Worse physical capability markers - and their combinations: sarcopenia and frailty - are associated with worse health outcomes as well as a higher economic burden and health care cost (~£2.5 billion/year associated with sarcopenia and around a total additional cost of £5.8 billion/year in the whole UK associated with frailty)(Pinedo-Villanueva et al., 2019, Han et al., 2019). Therefore, early detection and intervention are key to reduce the impact of these clinical conditions. As it has been shown, sarcopenia and frailty are complex syndromes that share a common cellular mechanism between themselves and with ageing itself and are associated with increased risk of osteoporosis, CVD, respiratory disease, dementia, cancer, COVID-19, and all-cause mortality (Petermann-Rocha et al., 2020b, Petermann-Rocha et al., 2020a, Petermann-Rocha et al., 2020c, Petermann-Rocha et al., 2021b, Petermann-Rocha et al., 2021c, Petermann-Rocha et al., 2021d).

The prevalence of frailty across the globe has been already estimated using its main classifications: the Frailty Index and the Frailty Phenotype (O'Caoimh et al., 2020). In contrast, despite some attempts, the overall prevalence of sarcopenia was lacking. To address this, by performing a comprehensive systematic review and meta-analyses of the published literature, the overall prevalence of sarcopenia was estimated as ranging from 10% to 27% according to different definitions (Chapter 2). In addition, for the first time, the overall prevalence of severe sarcopenia was assessed as ranging from 2% to 9% (paper 1, Chapter 2) (Petermann-Rocha et al., 2021a). In this context, considering the wide variation in the prevalence of sarcopenia and severe sarcopenia according to the classification used to define it, the use of a single diagnostic should be considered in future studies.

Across the manuscripts included in this thesis (Chapter 4), the associations between different combinations of sarcopenia, frailty, and individual physical capabilities were determined for each outcome studied (Petermann-Rocha et al., 2020b, Petermann-Rocha et al., 2020a, Petermann-Rocha et al., 2020c, Petermann-Rocha et al., 2021b, Petermann-Rocha et al., 2021c, Petermann-

Rocha et al., 2021d). When the individual markers were investigated in isolation, in comparison to individuals with these markers in the normal range, slow gait speed, low grip strength and low muscle mass were all associated with a higher risk of incident COPD and respiratory disease as well as all-cause, CVD and respiratory disease mortality. In all cases, the strongest association was found for slow gait speed (Petermann-Rocha et al., 2020b). For incident CVD, the only association identified was for slow gait speed (paper 2, Chapter 4). When osteoporosis was the outcome of interest, low muscle mass, followed by gait speed, were associated with a higher risk in both sexes. Furthermore, low grip strength was only associated with a higher risk in men; not in women (paper 3, Chapter 4) (Petermann-Rocha et al., 2021b). Therefore, considering slow gait speed and grip strength were consistently associated with various important outcomes, these markers should be assessed more frequently in clinical practice.

This thesis also investigated all potential combinations of physical capability markers to examine which combination may have the strongest associations with the outcomes of interest in the cohort of UK Biobank participants. The combination of slow gait speed plus low muscle mass, followed by severe sarcopenia, demonstrated the strongest associations with incident respiratory disease and all-cause mortality. Even for those outcomes that were associated with low grip strength combined with low muscle mass - the current definition of sarcopenia – the magnitude of the associations was lower compared with the other combinations (Petermann-Rocha et al., 2020b). Consequently, a definition, and diagnosis, based on slow gait speed and/or low grip strength may be more meaningful for use in clinical practice and research since both can be completed quickly and predicts health outcome reliably.

Following the study of sarcopenia with health outcomes, pre-sarcopenic men and sarcopenic women showed a stronger and independent association with incident osteoporosis. These associations were found in osteoporosis without pathological fractures, but were weaker for those with pathological fractures (paper 3, Chapter 4) (Petermann-Rocha et al., 2021b). As sarcopenia can be prevented, there is a window of opportunities to pick people up and intervene before pre-sarcopenia or sarcopenia starts and, consequently, decrease the osteoporosis risk (assuming causality between sarcopenia and osteoporosis).

Frailty and its categories were also included as exposures in this thesis. Firstly, using the Frailty Phenotype, the combined associations between categories of sarcopenia and frailty were investigated. Using this approach, this thesis identified a higher risk of CVD and respiratory disease among frail and sarcopenic people than those without frailty or sarcopenia (paper 4, Chapter 4) (Petermann-Rocha et al., 2021c). Secondly, and considering that both sarcopenia and frailty share similar diagnostic criteria with cachexia and malnutrition, the overlap within these exposures showed that frailty was the most prevalent clinical condition in the cohort. Moreover, individuals with frailty plus ≥ 2 other conditions had the highest risk of all-cause mortality, i.e., the risk of all-cause mortality increasing incrementally with the number of conditions in addition to frailty (paper 5, Chapter 4)(Petermann-Rocha et al., 2021d). Finally, frailty was used as an exposure to investigate the risk of COVID-19 as well as incident dementia. In the first case, frailty was demonstrated to be a risk factor for COVID-19 hospital admission and mortality risk irrespective of the classification used to define frailty (paper 6, Chapter 4)(Petermann-Rocha et al., 2020a). In the second case, pre-frailty and frailty were associated with an incremented risk of incident all-cause and vascular dementia. Among the individual components of frailty, weight loss, tiredness, low grip strength, and slow gait speed were all associated with a higher risk of incident all-cause dementia (paper 7, Chapter 4)(Petermann-Rocha et al., 2020c).

5.2 Comparison with existing evidence

As discussed in each manuscript (Petermann-Rocha et al., 2020b, Petermann-Rocha et al., 2020a, Petermann-Rocha et al., 2020c, Petermann-Rocha et al., 2021b, Petermann-Rocha et al., 2021c, Petermann-Rocha et al., 2021d), previous studies have investigated the associations of individuals physical capability markers, sarcopenia, and frailty with a variety of different adverse health outcomes. Of the wide-ranging outcomes included in this thesis, incidence and mortality for CVD and respiratory disease and all-cause mortality are the most common outcomes investigated in previous longitudinal studies (Jones et al., 2015, Bone et al., 2017, Chin et al., 2013, Kim and Choi, 2015, Zhang et al., 2018, Liu et al., 2017, Li et al., 2019, Hanlon et al., 2018b). Nonetheless, incident osteoporosis and COVID-19 are rarely included in prospective studies (Yu et al., 2014a, Scott et al., 2016b).

On the other hand, previous studies of sarcopenia or frailty as the exposure of interest have primarily been carried out in older adults, which limit our understanding of these associations in middle-aged people who might present a higher risk. In fact, when the joint association between sarcopenia and frailty was investigated by subgroups of age (≥ and < 60 years), the associations were stronger in younger individuals (paper 4, Chapter 4)(Petermann-Rocha et al., 2021c). Similar findings were found in frail individuals younger than 60 years when the association between frailty categories and incident dementia, as well as between frailty and COVID-19, were analysed (Petermann-Rocha et al., 2020a, Petermann-Rocha et al., 2020c).

Furthermore, previous studies have demonstrated the individual associations of frailty and sarcopenia with CVD, respiratory disease and cancer. However, to my knowledge, this thesis included the second longitudinal study to investigate their joint association and the first to do so in a large study population. The previous study was carried out in 197 older Italian adults and was focused on all-cause mortality only (Landi et al., 2013). Similarly, this is one of the first studies reporting the overlap and combined associations between four common clinical conditions: frailty, sarcopenia, cachexia, and malnutrition. Although the clustering between these conditions was previously reported (Gingrich et al., 2019), this was done in older inpatients; therefore, there was lack of evidence in non-institutionalised older adults. As it was previously mentioned, these conditions are recognised to start earlier in life.

The association between sarcopenia and osteoporosis has been previously described in cross-sectional studies. Indeed, the literature using this type of study design is extensive and has consistently shown a higher likelihood between the exposures included in this thesis and these outcomes (Verschueren et al., 2013, He et al., 2016a, Yoshimura et al., 2017, Sjöblom et al., 2013, Scott et al., 2019). Yet, prospective studies in this field using a larger sample size (>10,000 individuals) were limited (Yu et al., 2014a, Scott et al., 2016b). As a result, these results contribute to the current gaps in the literature and reinforce the relevance of this thesis. Yet, since sarcopenia and osteoporosis share many common pathways (including the sensitivity to reduced anabolic hormone secretion and increased inflammatory cytokine activity), a future prospective study using the UK biobank data should also investigate the

combined association of osteoporosis with sarcopenia, i.e., ‘osteosarcopenia’ over adverse health outcomes such as all-cause mortality. Even if the concept has been further explored since its first definition in 2009, prospective studies are limited.

Other comparisons associated with the outcomes included in this thesis can be found in each article throughout Chapter 4.

5.3 Strengths and limitations

5.3.1 Of the studies

As it has been highlighted in each paper included in this thesis, the use of UK Biobank provides the unique opportunity to test the research questions in a large and well-characterised population cohort study of middle-aged and older adults. Furthermore, UK Biobank has data on a wide range of potential confounders and health outcomes. Additionally, muscle strength was objectively measured using grip strength. The EWGSOP2 also recommends using the chair stand test for this measurement (Cruz-Jentoft et al., 2019b) but this information is not available in the UK Biobank study. However, this thesis is not exempt from limitations. Firstly, the investigation of physical capability markers, sarcopenia, and frailty and different health outcomes was carried out using only UK Biobank data, i.e., only one database, which is not representative of the overall UK population in terms of lifestyle and sociodemographic factors (Fry et al., 2017). Therefore, whilst the effect size estimates could be generalisable to the general population, the incidence and prevalence, as well as population attributable fractions, may not be. Although other two databases were also considered at the beginning, the Whitehall study and the ALSPAC study, these databases were then dismissed as they did not measure physical capability markers at baseline or, in the case of the ALSPAC study, did not have the outcomes of interest yet due to the young age of the population. Consequently, I decided to conduct the analyses using only the UK Biobank data because it had these two conditions: available physical capability markers at baseline and linked data regarding the outcomes of interest. Moreover, data were already available under one of my supervisors' applications. Secondly, muscle mass, a key component of the sarcopenia definition, was measured using BIA. Although DXA is the most

common method to measure muscle mass, only 5,000 participants were assessed using this approach in the UK Biobank study. A strong correlation was observed in the 5,000 participants with data available for both measurements. However, the mean difference among muscle mass (as index) measured using BIA and DXA was -8.5 (95% CI: -13.0 to -3.99). Thus, BIA clearly tended to underestimate the skeletal muscle mass of participants, consistent with a systematic bias. Therefore, we cannot confirm or conclude that the results would have the same direction and association for the whole database if we use DXA instead of BIA. Even if BIA is an affordable, portable and widely available instrument, the estimation of muscle mass using this method can be influenced by the hydration status of the participants. Moreover, the prediction models are more relevant for the population in which they have been derived. Consequently, DXA is more recommended to measure muscle mass. Thirdly, physical performance was assessed using self-reported walking pace instead of gait speed in all analyses conducted using this variable as exposure or as a criterion for defining severe sarcopenia or frailty. While this is a potential source of reporting bias because it is a self-reported measure, it is more easily replicated in clinical practice. In fact, previous studies have demonstrated that walking pace is a good market for walking speed. This market is strongly associated with adverse health outcomes (like the results of this thesis) (Ganna and Ingelsson, 2015, Celis-Morales et al., 2019). The literature also recommends other objective measurements to assess physical performance such as the short physical performance battery, the timed-up-and-go test and the 400-meter walk; however, these variables were not available in the UK Biobank study. Therefore, considering that gait speed is the measurement recommended for the EWGSOP2 for physical performance evaluation (Cruz-Jentoft et al., 2019b), future studies still need to consider if walking pace is a reasonable proxy of objectively measured gait speed. Fourthly, analyses were adjusted using a single self-reported measure of diet and alcohol at baseline, which may change over time. In terms of diet, I could not adjust the analyses by protein intake (associated with the exposures) since this information was available in a smaller proportion of the population. Processed and red meat intake were self-reported as a categorical variable (categorised as never, less than once a week, 2-4 times a week, 5-6 times a week and once or more daily) and were used as a proxy in the analyses. Yet, these variables were not validated in the UK Biobank study nor in the analyses conducted. Therefore,

some associations might change using protein intake measured in grams/per day instead of the self-reported variables. I conducted a sensitivity analysis in paper 3 (association of sarcopenia with incident osteoporosis: a prospective study of 168,682 UK biobank participants (Petermann-Rocha et al., 2021b)) where protein intake was included as a confounder. In that case, even if the HR was over 1, the associations were non-significant, probably due to power issues. Additionally, although these categorical variables could discriminate between people with low and high intakes, they cannot assess accuracy in quantity, preparation, food combinations, or even time when the food was consumed. A 24-h recall applied to the whole population might be a better approach to collect data about alcohol and diet in future studies to avoid these limitations. Moreover, both diet and alcohol intake were self-reported and subjected to recall and misclassification bias. Hence, results need to be considered with caution. Finally, sarcopenia and frailty were defined using baseline UK Biobank data. Yet, both conditions are dynamic and are likely to have worsened over time. Therefore, some part of my results may underestimate the true magnitude of the associations between the exposures and outcomes of interest. Two-year landmark analyses were carried out in the majority of the studies to minimise the risk of reverse causation. However, due to the observational nature of the studies included, causality cannot be confirmed.

5.3.2 Strengths and limitations in relation to other studies

Previous studies investigating similar questions have included fewer participants, have focused mainly on older adults, and/or used weaker studies designs such as cross-sectional studies with limited data on potential confounding factors. Compared to these previous studies, I was able to include a larger number of participants, covering both middle-aged and older ages, using prospective data and including a large list of potential confounding factors. However, among the limitations, other studies have used DXA to determine muscle mass instead of BIA. Although MRI is the gold standard measure, DXA is widely accepted and recommended to determine muscle mass (Cruz-Jentoft et al., 2019b). In addition, this thesis used walking pace as a proxy of gait speed which is the recommended measure to assess physical performance. This variable is required both for the definition of severe sarcopenia and frailty as it is measured as a continuous variable. Finally, even though this thesis included older age and

middle-aged participants, most of the study population was still too young at the baseline assessment to have developed the exposures of interest, which limited in part our statistical power to identify associations with other less common health outcomes. Consequently, the prevalence and number of individuals in some classifications (e.g., sarcopenic men) was lower than in other studies. Therefore, some analyses might be underpowered.

5.4 Implications of findings for research and practice

Throughout the articles included, this thesis fills gaps in the existing evidence base. Furthermore, I highlighted the relevance of studying these clinical conditions early in life as they are risk factors for adverse health outcomes that need to be investigated beyond ageing. We cannot modify chronological age; however, proxies of physical function related to ageing, such as sarcopenia and frailty, can be modified.

Even if it is uncommon, both frailty and sarcopenia might be reversible in some individuals with the proper diet and exercise intervention, and progression may be able to be slowed or halted in the remainder. Early assessment and interventions from middle age should be implemented among the general population to prevent or reverse sarcopenia and frailty, and consequently, reduce the burden of adverse health outcomes.

However, several challenges remain. Regarding sarcopenia, the lack of a single classification and definition remains one of the greatest problems for research into sarcopenia. This lack of a single classification inhibits the proper comparison of findings between studies and makes it harder to estimate the overall prevalence across the globe, as it was demonstrated in Chapter 2. Achieving a consensual definition would facilitate comparing results across studies that use a common definition and would help translate the findings into clinical practice.

Regarding frailty, even though there are multiple classifications and definitions, only a few are used in research, making results more comparable than sarcopenia. Nevertheless, although frailty's implications for people's health are known, frailty is not routinely assessed in clinical practice.

Finally, considering that sarcopenia and frailty share many of the parameters used for their definitions and, therefore, overlap between them is highly probable, creating a unique and global definition could have a high impact in clinical practice, including improved diagnoses.

5.5 What I learnt during my PhD

During the three years of my PhD, I had the opportunity to improve my writing skill across the different manuscripts developed both as first author and co-author. Even if in this thesis only seven manuscripts where I was the first author were included, since September 2018 (the month when I started my PhD), I wrote 31 papers as first or joint first author in topics of ageing, diet and lifestyle (see the publications section of this thesis). As it is shown in that section, these manuscripts are available in high impact factor journals and have been highly cited due to their contribution to the literature, research, and clinical practice. Two of these manuscripts were selected as the ‘paper of the month’ or ‘the editor choice of the month’. Moreover, I contributed as a co-author in other 81 papers, as is highlighted in Appendix H of this thesis. I consider this a high achievement considering my young age.

From the first day, I knew the relevance of making known my work. Consequently, I actively attended more than 15 conferences where I contributed with 23 poster and oral presentations, improving my presentation skills and networking (see the Poster and Abstract section).

I also had the opportunity to develop and further improve different skills and techniques. In fact, I attended 15 external and 11 internal courses in statistics, data analysis, epidemiology, nutrition, and leadership (See Appendix I). As I know that we need more leaders for the scientist of tomorrow, I want to highlight the contribution of the Oxford Women's Leadership Development Programme in my training. In the programme, I learnt that I am an affiliative leader, the strengths and limitations of my leadership style, and also improved my negotiation abilities.
Fortunately, I have implemented this new knowledge in voluntary and exchange activities that go beyond my PhD such as: i) deputy director of my Chilean Research Team (ELHOC); ii) PhD representative of the Institute of Health and

Wellbeing (2020 to September 2021); iii) participation in the Leader in Science programme (support member to foster STEAM in schools in Glasgow); iv) as an editorial member of the Spanish Journal of Nutrition and Dietetics; and v) reviewer of different journals.

Finally, although COVID-19 has been a tough situation, I could continue my progress without many problems. However, as part of my training, I was selected for an internship in the Ageing unit of the World Health Organisation, headquarters Europe (Copenhagen) for six months. Unfortunately, due to the pandemic situation, and as my exchange period should have started on the 17th of March 2020, I could not complete this activity. Apart from that, I had a great PhD experience.

5.6 Final conclusion and future work

This thesis has demonstrated and highlighted that individuals with lower physical capability, sarcopenia and/or frailty had a higher risk of adverse health outcomes, including: incidence and mortality for osteoporosis, CVD, respiratory disease, cancer, COVID-19, dementia, and all-cause mortality. These associations remained even after adjustment for a large range of potential confounders and existed both in middle-aged and older adult sub-groups. Considering that the decline in physical capability markers, and therefore, sarcopenia and frailty could be prevented, health interventions to improve physical capability may delay or prevent the onset of these outcomes.

Despite the huge progress concerning physical capability markers, sarcopenia and frailty, there is a need for a more comprehensive approach to a better understanding of all these conditions, how to identify them at an earlier stage, and a more in-depth study of the age-related changes in physical capability, body composition and associated health beyond the ageing progress.

Prospective studies are an excellent resource to investigate the association between different lifestyle exposures (including physical capability markers) and multiple health outcomes providing meaningful statistics results (e.g., RR and HR). They are also a good resource to investigate rare exposures, which may be difficult in case-control studies. Cohort studies are less prone to bias than other

observational studies. For instance, repeated measures can be used in contrast to cross-sectional data collected at only one point. Moreover, the temporal sequence and incidence can be determined, unlike case-control and cross-sectional studies. Yet, the loss to follow-up and unmeasured confounders are still possible in any cohort study like the UK Biobank. In the particular case of the UK Biobank study, only 0.04% of the population have been lost due to follow-up; however, some unmeasured confounders might change the associations. Among them, the Mini-Mental State Examination, gait speed measured as a continuous variable, physical activity objectively reported in the whole database, and the use of the 24h recall to measure diet and alcohol intake. Even if this type of study is costly and takes a long time to have the outcomes of interest, following people from early ages enables a better understanding of the risk factors associated with ageing and preventing or delaying them from early stages of life. That would be the case of the ALSPAC study (Avon Longitudinal Study of Parents and Children), which is following parents and children born in Avon, England, between 1991 and 1992 (Golding et al., 2001). The study was initially designed to determine how the combination of environment and individual's genotype influence health. Those children are between 29 and 30 years today. Yet, in the coming years will be an excellent resource to link early development with adverse health outcomes.

Finally, as healthy ageing should be achievable for each older adult and is one of the priorities of the WHO, public strategies should be implemented to prevent or delay known risk factors against healthy ageing, such as sarcopenia and frailty. Consequently, the findings identified in each article in Chapter 4 will need further corroboration in different cohort studies that can provide external validation of my findings.

Other appendices

Appendix H Co-author publications during the PhD period

Benítes-Brito, N. *et al (2021).* 'Estigmatización de la obesidad: un problema a erradicar'. Rev Esp Nutr Hum Diet.25(1). Article in Spanish.

Boonpor, J., Parra-Soto, S., Petermann-Rocha, F. *et al (2021).* 'Associations Between Grip Strength and Incident Type 2 Diabetes: Findings from the UK Biobank Prospective Cohort Study'. BMJ Open Diabetes Res Care.9(1):e001865.

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Concha, Y. *et al (2019)*. 'Patterns of physical activity in Chilean adults across the lifespan'. Nutr. Hosp.; 36(1): 149-158. doi: 10.20960/nh.1942. Article in Spanish.

Concha, Y. *et al (2018)*. 'Levels of physical activity and excess body weight in University students". Rev. med. Chile; 146 (8). doi: 10.4067/s0034-98872018000800840. Article in Spanish.

Cristi-Montero, C. *et al (2018)*. 'Joint effect of physical activity and sedentary behaviour on cardiovascular risk factors in Chilean adults'. J Public Health; 40(3): 485-492. doi: 10.1093/pubmed/fdx134.

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Appendix I Training courses

External courses

- Oxford Women's Leadership Development Programme. Oxford University.
- Introduction to Epidemiology. Oxford University.
- Advance topic in statistics. EEPE.
- Principles of prevention in the precision medicine, Big Data, and Covid-19 time. EEPE.
- Multiple imputation for missing data. Bristol University.
- Nutrient type and timing for optimal exercise output. The Nutrition Society.
- NIHR Cambridge Biomedical Research Centre: Anthropometry Webinar. Cambridge University.
- Introduction to Human Nutrition. The Nutrition Society.
- Causal Inference in Epidemiology: Concepts and Methods. Bristol University.
- Word: Creating a Dissertation or Thesis. Glasgow University.
- Equality and Diversity Essentials Course & Certificate. Glasgow University.
- Advance use of Stata. Bristol University.
- Research Data Management Sciences Course. Glasgow University.
- Research Integrity for Sciences. Glasgow University.
- Systematic Reviews & Meta-Analysis. Bristol University.

Internal courses from the College (University of Glasgow)

- Discovering and Managing Information at PhD Level
- Emergency First Aid at Work
- Postgraduate Research Student Induction Course
- MOOC On-line Course “Research Impact: Making a Difference”
- Statistics- Logistic Regression
- Successful Writing
- Mental Health First Aid Training
- Statistics - Survival Analysis
- Job Hunting & Successful Applications
- Introduction to Writing your thesis
- Preparing for the Viva

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