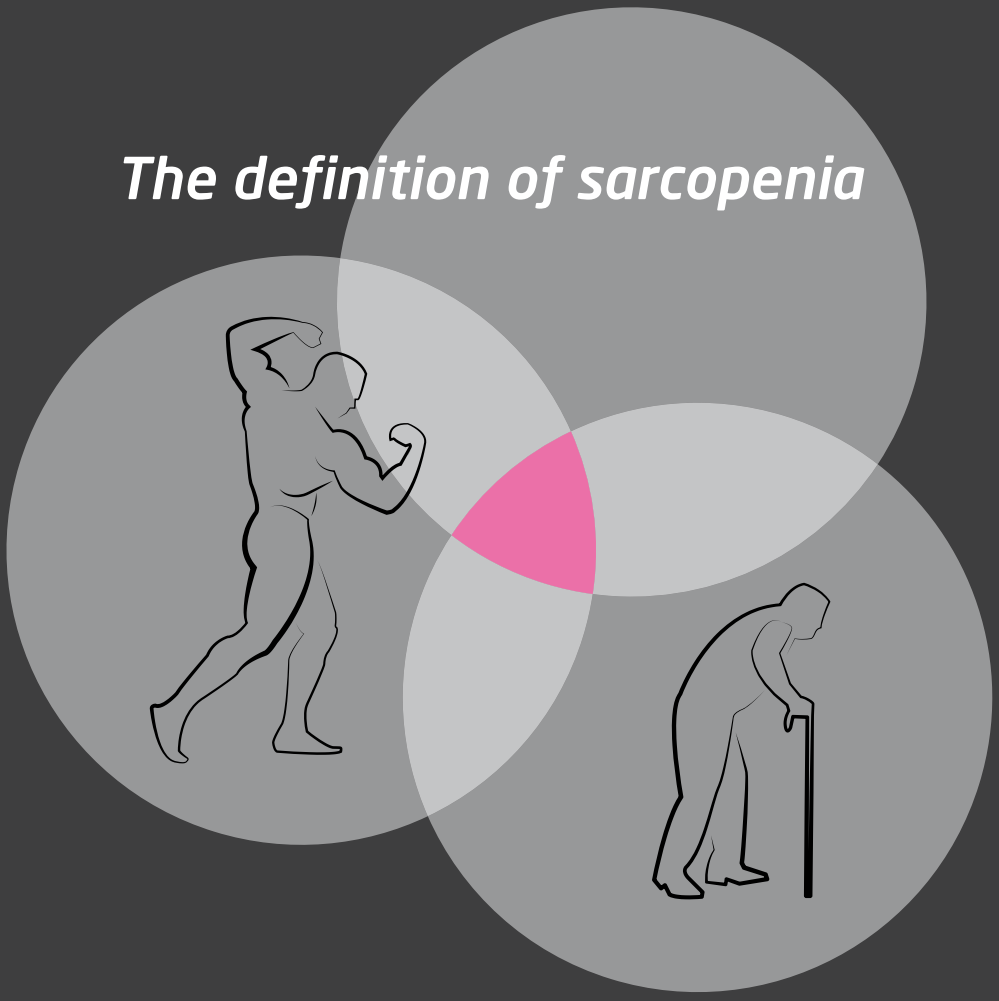
The definition of sarcopenia



Astrid Y. Bijlsma

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...The sixth age shifts
Into the lean and slipper'd pantaloon,
With spectacles on nose, and pouch on side,
His youthful hose well sav'd, a world too wide,
For his shrunk shank...

(Shakespeare, The Seven Ages of Man)

Contents

Chapter 1

General introduction and outline of thesis

General introduction

In developed countries, life expectancy is increasing and the elderly population is expanding rapidly. In the past 40 years the population of adults aged over 65 years has doubled to almost 2.6 million in 2011 in the Netherlands only (1). In this ageing society sarcopenia is an emerging problem. The term sarcopenia was coined in 1988 to describe the 'deficiency' (penia) of 'flesh' (sarx) as is often observed in old age. Annual loss of muscle mass has been reported as 1 to 2 percent from the age of 50 years onwards (2;3). While the loss of muscle mass seems to be accelerated in the presence of chronic disease, even in life-long trained athletes muscle mass is much lower in old as compared to young age (2).

The introduction of the term sarcopenia contributed to research aimed to understand the consequences. There is a growing body of evidence that low muscle mass at old age is associated with self-reported physical disability and physical performance (4-6). The change of muscle mass is related to changes in muscle strength. However, to generate muscle strength other factors are important in addition to muscle mass, such as neural control, cognition, cardiovascular and joint function (7). Reduced muscle strength has been found to be associated with dependency in activities of daily living (8;9), cognitive decline (10-12), and mortality (13;14). Next to the generation of muscle strength, muscle tissue is an important reserve of body proteins and energy that can be used in extreme conditions of stress or malnutrition. Low muscle mass is associated with higher drug toxicity (15;16) and reduced insulin sensitivity (17). Because of the multiple functions of muscle tissue, biological aspects as well as functional and mechanical aspects can be considered as muscle related clinical outcome of interest when studying sarcopenia.

Despite increasing knowledge about the consequences of sarcopenia, there is no consensus on the definition of sarcopenia. Since the coining of the term sarcopenia, researchers have been searching for diagnostic criteria for sarcopenia. This has lead to the use of a variety of diagnostic criteria for sarcopenia. In general, currently used diagnostic criteria for sarcopenia can be divided into criteria based on (1) low muscle mass (4;6), (2) low muscle strength (18), and (3) low walking speed (19;20). Muscle mass can be further divided into relative muscle mass and absolute muscle mass (figure 1) (21). With currently used diagnostic criteria for sarcopenia, the reported prevalence of sarcopenia varies extremely between elderly cohorts ranging from 7 to over 50% (22). It remains unknown whether this range can be explained by true differences between cohorts, or by the application of various diagnostic criteria to define sarcopenia in these cohorts.

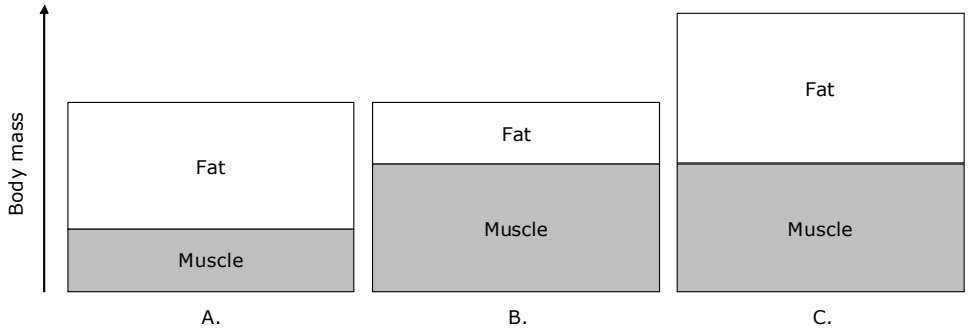

Figure 1. *Hypothetical example of the distribution of fat and muscle mass in three different persons with equal height, for visualization of differences between relative and absolute muscle mass. Person A and B have the same amount of body mass with a different amount of muscle mass and fat mass. Person B has a higher absolute (kg) amount of muscle mass and also a higher relative (percentage) amount of muscle mass compared to person A. Person C has the same absolute amount of muscle mass as person B, but with a higher body mass. Therefore person C has a lower relative muscle mass as compared to person B.*

Currenty, clinical awareness of the signs and consequences of sarcopenia is lacking. To diagnose sarcopenia in clinical practice a clear definition for sarcopenia is needed. The aim of this thesis is to assess the implications of the use of different diagnostic criteria for sarcopenia, and to define the most accurate criteria for sarcopenia.

Outline of this thesis

In **chapter two** the literature is reviewed for current knowledge on sarcopenia, concerning the diagnostic criteria for sarcopenia, the pathophysiology of sarcopenia, and its clinical implications. **Chapter three** compares the chronology in the history of defining osteoporosis with sarcopenia. This comparison is used to detect milestones needed to define both age-related disease definitions, and missing milestones still needed to reach consensus on the definition of sarcopenia. In **chapter four** the impact of the use of different diagnostic criteria on the prevalence of sarcopenia is assessed. This chapter answers the question whether differences in the reported prevalence of sarcopenia can be explained by the use of different diagnostic criteria within one study cohort. In the following four chapters diagnostic criteria for sarcopenia are compared in their association with different aspects of muscle related clinical outcome. The diagnostic criteria that are compared comprise relative muscle mass, absolute muscle mass, muscle strength, and walking speed. The muscle related

outcome of interest is: physical performance tested with the Timed get Up and Go test (TUG) and walking speed in **chapter five**; measures of insulin resistance derived from an oral glucose tolerance test in **chapter six**; whole body bone mineral density in **chapter seven**; and standing balance in **chapter eight**. In **chapter nine** the key findings of this thesis are summarized with a reflection, and recommendations for the definition of sarcopenia and future research are provided.

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Chapter 2

Sarcopenie: Op weg naar klinische toepasbaarheid

AY Bijlsma, CGM Meskers, RGJ Westendorp, AB Maier

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English abstract

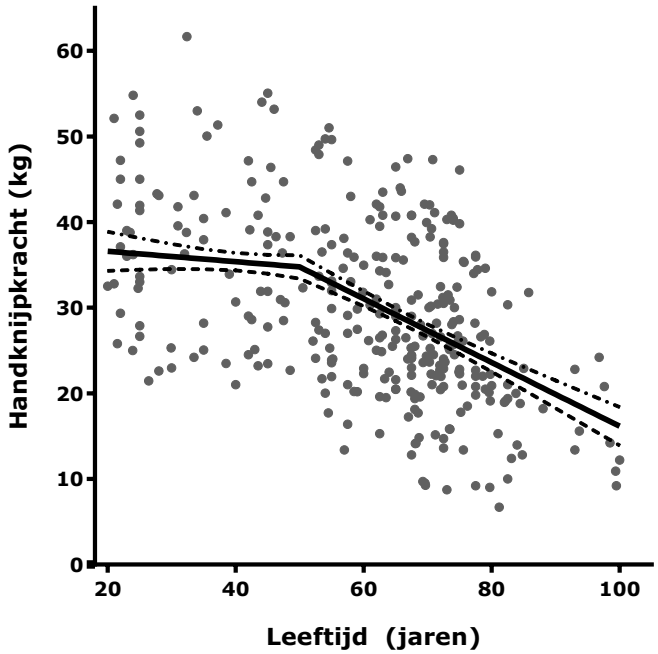
Sarcopenia is a term introduced to describe 'low muscle mass'. There is no consensus definition for sarcopenia; a variety of criteria are being used to establish the diagnosis of 'sarcopenia'. Depending on the criteria used, the prevalence of sarcopenia in elderly varies from 7 to over 50 percent. The presence of sarcopenia often remains unrecognized when the loss of muscle mass is replaced by fat and connective tissue; body weight thus remains stable or even increases. Sarcopenia can be detected by measuring muscle mass with dual-energy X-ray absorptiometry (DXA) or bioimpedance analysis (BIA). Besides the generation of strength, muscle tissue is an important internal organ involved in protein storage, glucose regulation, hormonal homeostasis and cellular communication. Systemic, cellular, neuromechanical factors and lifestyle are linked to the pathophysiology of sarcopenia. Sarcopenia is associated with higher mortality, dependency in activities of daily living, toxicity of chemotherapy, and disturbed glucose regulation.

Dutch abstract

Sarcopenie is geïntroduceerd als term voor 'lage spiermassa'. Er is geen eenduidige definitie van sarcopenie. Er wordt een verscheidenheid aan criteria gebruikt om de diagnose ´sarcopenie´ te stellen. Afhankelijk van de gehanteerde definitie worden prevalentiecijfers van 7 tot meer dan 50 procent bij ouderen gerapporteerd. Sarcopenie blijft vaak onopgemerkt als de afnemende spiermassa wordt opgevuld door vet en bindweefsel; het gewicht blijft hierbij gelijk of neemt zelfs toe. Spiermassa kan worden gemeten met 'dual-energy X-ray' absorptiometrie (DEXA) of bio-elektrische impedantie-analyse (BIA). Spierweefsel is behalve krachtsleverancier ook als intern orgaan betrokken bij eiwitopslag, glucoseregulatie, hormoonhuishouding en cellulaire communicatie. Bij de pathofysiologie van sarcopenie zijn systemische, cellulaire en neuromechanische factoren en leefstijl betrokken. Sarcopenie houdt verband met een hogere sterfte, afhankelijkheid in dagelijks functioneren, toxiciteit van chemotherapie en verslechterde regulatie van de glucoseconcentratie.

Introductie

In onze vergrijzende samenleving is sarcopenie een veelvoorkomende maar voor velen onbekende aandoening. De term 'sarcopenie' is in 1988 geïntroduceerd om het verlies van spiermassa op oudere leeftijd te beschrijven (1). Dit woord is afgeleid van de Griekse woorden 'sarx' (vlees) en 'penia' (behoeftigheid).
Uit observationele studies is gebleken dat spiermassa tot het 30e levensjaar wordt opgebouwd en na een plateaufase afneemt met de leeftijd. Geschat wordt, dat na het 50e levensjaar de spiermassa ongeveer met 1 á 2 procent per jaar afneemt (2). Een vergelijkbaar beloop wordt gezien voor de spierkracht. De gemiddelde spierkracht bij 80-jarigen is bijna de helft van de spierkracht op jonge leeftijd, zo bleek uit cross-sectionele studies (figuur 1) (3). Ziekte en immobiliteit kunnen dit proces versnellen, maar de spiermassa neemt ook af bij mensen die hun hele leven lichamelijk zeer



Figuur 1: *Het verband tussen spierkracht en leeftijd, weergegeven in een strooidiagram van 330 studies onder de algemene bevolking; rond de meta-regressielijn is het 95%-betrouwbaarheidsinterval met onderbroken lijnen aangegeven (gestandaardiseerd op 50% vrouwen). De handknijpkracht in de algemene bevolking is lager bij ouderen, met een omslagpunt op de leeftijd van 50 jaar (figuur afkomstig uit eerdere publicatie) (3).*

actief zijn geweest (2).
De klinische relevantie van sarcopenie betreft niet alleen het fysieke functioneren door het genereren van kracht, maar ook de rol van spieren als intern orgaan dat betrokken is bij de glucoseregulatie en productie van energie en dat als lichaamsreserve dient voor eiwitten (2). Voordat de diagnose 'sarcopenie' in de klinische praktijk toegepast kan worden is een goede definitie noodzakelijk. Voor het vormen van een goede definitie is kennis over de betekenis van sarcopenie en inzicht in de pathofysiologie noodzakelijk. In dit artikel bespreken wij het huidig gebruik van verschillende definities van sarcopenie, het onderscheid tussen sarcopenie, kwetsbaarheid ('frailty') en cachexie, de pathofysiologie en tot slot de klinische relevantie van sarcopenie.

Definitie van sarcopenie

De afname van spiermassa is een geleidelijk proces. Het verlies van spiermassa blijft vaak onopgemerkt indien het gewicht hetzelfde blijft of toeneemt. De afnemende spiermassa wordt doorgaans opgevuld door weefsel zonder contractiele eigenschappen zoals vet en bindweefsel (in de spier en rond de spier). Derhalve is de body mass index (BMI) in deze gevallen geen betrouwbare maat om de hoeveelheid spiermassa vast te stellen. De spiermassa kan in de klinische praktijk eenvoudig gemeten worden met 'dual-energy X-ray' absorptiometrie (DEXA) of bio-impedantie (BIA) (4). Voor een afspiegeling van de spierkracht kan een handknijpkrachtmeter worden gebruikt (3).
Tot op heden is er nog geen WHO-classificatie voor sarcopenie. In de literatuur wordt de term 'sarcopenie' gebruikt voor verschillende parameters: een lage spiermassa, een lage spierkracht, een lage loopsnelheid of een combinatie van deze factoren, met toepassing van verschillende correctiefactoren, zoals gewicht of lengte. De betekenis van deze term is dus niet altijd direct duidelijk. De Tabel geeft de gehanteerde formules en afkappunten voor het stellen van de diagnose sarcopenie weer (5).
Om de discussie rond de definitie van sarcopenie te stimuleren en consensus te bereiken zijn er internationale werkgroepen voor sarcopenie opgericht. Momenteel wordt voorgesteld sarcopenie als combinatie van een lage spiermassa en een lage loopsnelheid of knijpkracht te definiëren (6;7). Hier vallen echter kritische kanttekeningen bij te plaatsen. Gebruik van afgeleide factoren van spiermassa, namelijk spierkracht en loopsnelheid, maakt het onderscheid tussen sarcopenie en kwetsbaarheid ('frailty') moeilijk. Spierkracht en loopsnelheid worden naast spiereigenschappen ook bepaald door andere factoren zoals neurale aansturing, cardiovasculair functioneren, motivatie en pijn.

Tabel: Voorbeelden van veel gebruikte formules en afkapwaarden om een lage spiermassa of lage spierkracht vast te stellen.

Eerste auteur (meetmethode)[a]	Formule	Afkapwaarde		Afkapwaarde gebaseerd op
		Mannen	Vrouwen	
Baumgartner (8) (DEXA)	ALM/lengte^2	7.26 kg/m^2	5.45 kg/m^2	2 SD onder het gemiddelde van 229 personen tussen de 18 en 40 jaar oud.
Janssen (16) (BIA)	SLM/gewicht * 100%	31%	22%	2 SD onder het gemiddelde van 6414 personen tussen de 18 en 39 jaar oud.
Janssen (17) (BIA)	SLM/ lengte^2	8.50 kg/m^2	6.75 kg/m^2	ROC-curve analyse voor afkapwaarden gerelateerd aan fysieke beperkingen in 4502 personen ouder dan 60 jaar oud.
Prado (29) (CT)	Dwarsdoorsnede spiermassa	52.4 cm^2/m^2	38.5 cm^2/ m^2	0.30x(dwarsdoorsnede spiermassa op L3)+6.06; Afkapwaarden gerelateerd aan mortaliteit
Lauretani (7)	Handkrijpkracht	30.3 kg	19.3 kg	ROC-curve voor afkapwaarden gerelateerd aan loopsnelheid minder dan 0.8 m/sec in 1030 personen tussen 20 en 102 jaar oud.

ALM=som van de vet-vrije wekedelen massa van alle ledematen; SLM=geschatte skeletspiermassa van het gehele lichaam; SD=standaarddeviatie; ROC-curve=receiver operating characteristics curve (deze laat het verband zien tussen de sensitiviteit en de specificiteit van een test); DEXA=dual-energy x-ray absorptiometrie; BIA=bio-impedantie analyse. [a]Deze methoden zijn in de aangehaalde onderzoeken gebruikt om de afkapwaarden vast te stellen.

Het toepassen van verschillende definities voor sarcopenie, met verschillende afkappunten en correctiefactoren, leidt tot een sterke variatie in prevalentiecijfers: bij ouderen boven de 60 jaar worden prevalenties van 7 tot 40 procent gemeld, tot meer dan 50 procent bij ouderen boven de 80 jaar (5;8).

Sarcopenie in relatie tot kwetsbaarheid en cachexie

Sarcopenie wordt onderscheiden van cachexie en kwetsbaarheid. 'Cachexie' wordt gekenmerkt door 'wasting'; bepaalde ziektes gaan vaak gepaard met cachexie. Ook bij cachexie wordt spierweefsel afgebroken, wat betekent dat cachectische patiënten eveneens aan de voorwaarden voor sarcopenie voldoen.

Kwetsbaarheid is een geriatrisch syndroom dat gekenmerkt wordt door achteruitgang in meerdere domeinen. Hierbij spelen fysieke, psychische en sociale factoren een belangrijke rol. Tot op heden is het niet gelukt een eenduidige definitie voor kwetsbaarheid te vormen. In de praktijk betekent dit dat er vele testen en

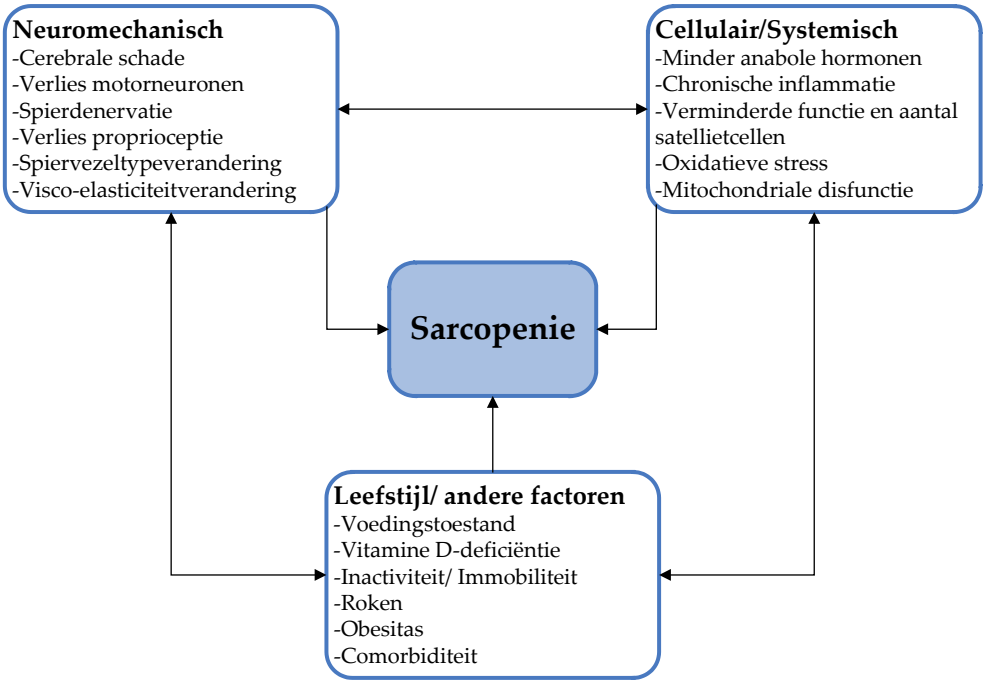
definities ontwikkeld zijn om kwetsbaarheid te meten, waaronder loopsnelheid en handknijpkracht (9).

Pathofysiologie van sarcopenie

In de afgelopen was er een flinke toename van kennis over veranderingen in systemische, cellulaire, neuromechanische factoren en leefstijl die bijdragen aan de afname van spiermassa. Aangezien de meeste studies naar de pathofysiologie van sarcopenie nog kleinschalig en het veelal om cross-sectioneel onderzoek gaat, is causaliteit nog niet aangetoond. Wel zijn er veelbelovende verbanden ontdekt. Een overzicht van factoren die bijdragen aan het ontstaan van sarcopenie is schematisch weergegeven in figuur 2. Een aantal factoren wordt hieronder toegelicht.

Neuromechanische factoren

Een typische dwarsgestreepte skeletspier bestaat uit vele spiervezels die worden



Figuur 2: *Schematische weergave van factoren die bijdragen aan de pathofysiologie van sarcopenie. Dit overzicht is niet compleet. Ook is er nog onvoldoende bewijs voor causaliteit van de verbanden.*

aangestuurd door een kleiner aantal motorneuronen. De hoeveelheid spierkracht die gegenereerd kan worden hangt af van het aantal parallel gelegen sarcomeren (ofwel het oppervlak van de dwarsdoorsnede van de spier), terwijl de snelheid van contractie afhangt van het aantal in serie gelegen sarcomeren (ofwel de vezellengte). De structuur en functie van spiervezels wordt aangetast door verlies van spinale motorneuronen, bijvoorbeeld door apoptose. Wanneer gedenerveerde spiervezels opnieuw geïnnerveerd worden door collaterale uitgroei ('sprouting') van nabij gelegen motoraxonen of motoreindplaten, ontstaan zeer grote motorunits. Dit is een mogelijke oorzaak van het verlies van fijne motoriek op oudere leeftijd (10). Ook zijn er aanwijzingen dat door verlies van motorneuronen het aantal spiervezels vermindert (hypoplasie) en het volume van de overgebleven spiervezels afneemt (atrofie) (10).

Systemische en cellulaire factoren

Op hogere leeftijd worden gemiddeld hogere bloedspiegels gedetecteerd van ontstekingsmediatoren zoals interleukine-6 (IL-6), tumornecrosefactor-alpha (TNF-α) en C-reactief proteïne (CRP). De twee- tot viervoudige verhoging van deze waarden op oudere leeftijd vergeleken met de waarden op jongere leeftijd duidt op een laaggradig chronisch systemisch ontstekingsproces. Deze geringe verhoging op oudere leeftijd is hiermee goed te onderscheiden van acute infectie, waarbij veel hogere waarden worden gevonden (11). In longitudinale studies is er een verband aangetoond tussen hoge bloedwaarden van deze ontstekingsmediatoren en verlies van spiermassa (12).

De capaciteit van spierweefsel om te groeien of te herstellen van opgelopen schade hangt voor het grootste gedeelte af van satellietcellen, de myogene stamcellen. In spierweefsel van oudere personen worden aanzienlijk lagere aantallen satellietcellen aangetroffen dan in het spierweefsel van jongere personen (13). De proliferatieve capaciteit van satellietcellen is beperkt, net als die van andere delende celtypen in het lichaam (14). Als een satellietcel niet in staat is tot proliferatie kan de cel of in een senescente staat gaan, of in apoptose. Aangezien spieren bestaan uit veelkernige cellen, kan apoptose van een enkele myonucleus en het bijbehorende sarcoplasma optreden terwijl de spiervezel behouden blijft. Apoptose is hiermee, mits goed gereguleerd, een geschikt middel om beschadigd weefsel te verwijderen. Deze regulatie kan op hoge leeftijd verstoord zijn, bijvoorbeeld door het disfunctioneren van mitochondriën en door verhoogde concentraties van TNF-α (11).

In tegenstelling tot bij apoptose, blijft bij cellulaire senescentie de niet-functionele cel aanwezig in het weefsel, waardoor accumulatie van senescente cellen optreedt.

Leefstijl en andere factoren

Lichamelijke inactiviteit zorgt voor atrofie van de spier en hierdoor uiteindelijk tot functionele beperkingen. Functionele beperkingen leiden echter ook tot inactiviteit, waardoor wederom spiermassa verloren gaat en een negatieve spiraal ontstaat. De mate van inactiviteit wordt in de klinische praktijk vaak onderschat bij gebruik van (gevalideerde) vragenlijsten. Met bewegingsmonitors kan daadwerkelijke activiteit in de thuissituatie gemeten worden gedurende meerdere dagen. Op deze manier kan de invloed van dagelijkse bewegingspatronen op het ontstaan van sarcopenie worden opgehelderd.

Ook andere leefstijlfactoren zoals dieet, zonexpositie en intoxicaties kunnen invloed hebben op het ontstaan van sarcopenie. De voedingstoestand speelt hierbij een zeer belangrijke rol. Uit studies naar dagelijkse eiwitinname bij ouderen blijkt dat een eiwitrijk dieet geassocieerd is met een hogere spiermassa (15). Door verminderde voedselinname, verminderde zonexpositie en verminderde capaciteit om vitamine D3 te synthetiseren, kan vitamine D-deficiëntie ontstaan, wat ook gepaard gaat met een verhoogd risico op sarcopenie (15).

Klinische relevantie van sarcopenie

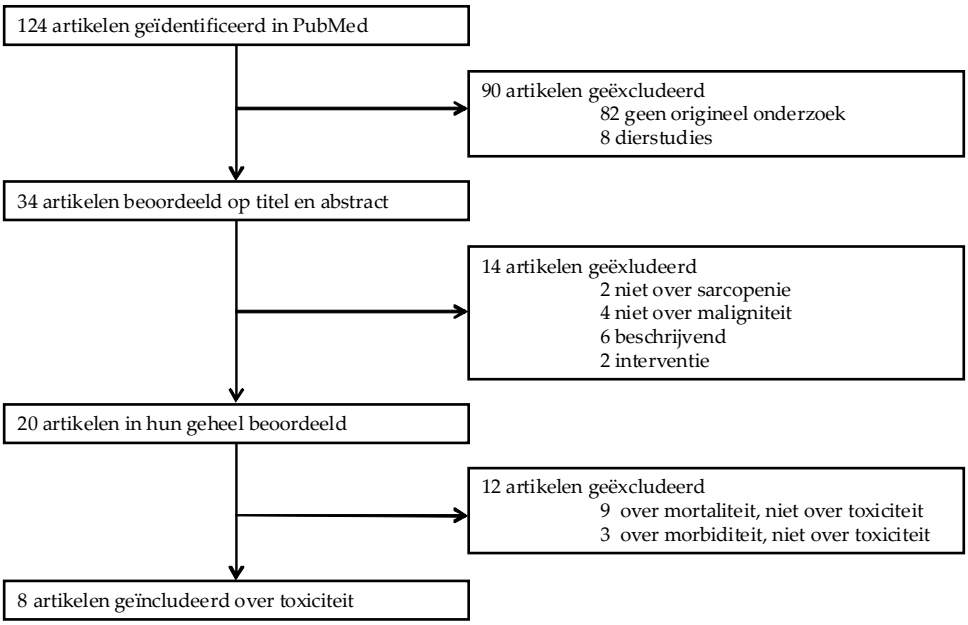
Uit observationeel onderzoek is gebleken dat spiermassa een voorspeller is van klinisch zeer relevante uitkomstmaten zoals fysiek functioneren, ADL (activiteit dagelijks leven)-afhankelijkheid (8;16;17), het vermogen om te herstellen van operaties (18;19), en mortaliteit (20).

Klinische relevant is ook de spier als belangrijke speler in cellulaire en mechanische interactie met omliggende weefsels, zoals vet en bot. Zo speelt spiermassa een rol bij het ontstaan van osteoporose, aangezien mechanische stimulatie door spieren de aanmaak van bot via osteocyten bevordert (21). Tevens is spierweefsel belangrijk voor glucoseregulatie, aangezien het grootste deel van de insulinegestimuleerde opname van glucose in spierweefsel plaatsvindt.

Spiermassa en (geriatrische) oncologie

De spiermassa van een individu kan directe klinische consequenties hebben. Een voorbeeld hiervan zien we bij de dosering van chemotherapeutica. Het verdelingsvolume van medicijnen hangt significant af van de lichaamssamenstelling. Chemotherapeutica worden vaak op basis de body surface area (BSA) gedoseerd, waarbij geen rekening met spiermassa wordt gehouden.

Wij deden een literatuurstudie naar de toxiciteit van chemotherapie en spiermassa



Figuur 3: *Schematische weergave van een literatuurstudie naar sarcopenie als risicofactor voor toxiciteit van chemotherapie bij bestaande maligniteit. Wij gebruikte hiervoor de volgende zoekstrategie: ("Sarcopenia"[Mesh] AND "Neoplasms"[Mesh]) OR ("sarcopenia"[All Fields] AND ("neoplasm"[All Fields] OR "malignancy"[All Fields] OR "cancer"[All Fields])) AND ("1989/01/01"[PDAT] : "2012/11/15"[PDAT]).*

(Figuur 3). De geïncludeerde artikelen betroffen grotendeels kleine studies met minder dan 55 patiënten. In drie studies werd een positief verband tussen een lage spiermassa en toxische verschijnselen die dosisreductie noodzakelijk maakten (22-24). In twee studies werd geen significante relatie gevonden tussen enerzijds een lage spiermassa en anderzijds het wel of niet afmaken van neoadjuvante chemotherapie (25) of toxiciteit bij hepatisch arterieel toegediende chemotherapeutica (26). In twee studies wordt niet direct het verband tussen spiermassa en toxiciteit beschreven, maar wel de waarneming dat de toediening van chemotherapie gepaard gaat met verlies van spiermassa (27;28), en met een nog sterkere afname van spiermassa als er al sprake was van een lage spiermassa voordat de chemotherapie was gestart (28). Op oudere leeftijd bleek er een slechte correllatie tussen de spiermassa en het lichaamsoppervlak (29). Dit betekent dat als men doseert op basis van het lichaamsoppervlak, patiënten met een zeer lage spiermassa een hogere dosis krijgen per kilogram spiermassa dan patiënten met een hoge spiermassa.

Conclusie

De term sarcopenie beschrijft een lage spiermassa op oudere leeftijd. Een lage spiermassa blijft vaak onopgemerkt als de BMI gelijk is gebleven of zelfs is toegenomen. Sarcopenie gaat gepaard met fysieke beperkingen, morbiditeit en toegenomen mortaliteit. Recent onderzoek biedt meer inzicht in de pathofysiologie en klinische relevantie van sarcopenie. Consensus over een goede definitie van sarcopenie is wenselijk om de toepassing van dit begrip in de klinische praktijk te bevorderen.

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Chapter 3

Chronology of age-related disease definitions: Osteoporosis and Sarcopenia

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Abstract

Low muscle mass at older age has been associated with functional impairments, cognitive decline and mortality. The term sarcopenia, coined in 1988, has been used interchangeably to describe low muscle mass, strength, and function. Without a well defined definition, results of studies using the term sarcopenia cannot be compared. Difficulties in defining sarcopenia parallel the history of defining osteoporosis. To understand critical steps that are needed to reach consensus in defining age-related diseases, we have identified milestones in the history of defining osteoporosis and compared these to sarcopenia. As a result, the main missing steps in the process of defining sarcopenia are: specific treatment options, pharmaceutical interest, and public awareness. Similar to osteoporosis being defined as 'low bone mineral density', the term sarcopenia should be reserved for 'low muscle mass'. Consensus must be reached regarding the diagnostic criteria to quantify muscle mass, correction factors, and reference populations used to define cut-off values of muscle mass.

Introduction

Over the past decades, scientists have reached consensus on an exclusive definition of osteoporosis, which was instrumental in developing clinical protocols for early diagnosis and tailored treatment. Sarcopenia, a much younger term, was first used in 1988 to describe the deficiency of muscle tissue often observed in older age (1). The term sarcopenia is still largely unknown among clinicians and researchers. Identifying and treating sarcopenia is becoming increasingly important, since research has shown that low muscle mass is associated with functional and cognitive impairment (2-4) and increased mortality (5). After the age of 50 years, an average annual decline of 1 to 2 percent of muscle mass has been reported (6), leading to a 50 percent reduction of muscle mass among those aged 80 years and older (3). It is estimated that a 10.5 reduction of the prevalence of sarcopenia could lead to a reduction of healthcare costs by 1.1 billion US dollars per year in the United States (7). However, the prevalence and measurable impact of sarcopenia depends crucially on how sarcopenia is defined. A proper definition is the necessary base for clinical diagnosis and development of tailored treatment.

Over the past years the term sarcopenia has been used interchangeably to describe low muscle mass as well as low muscle strength and physical performance. Loss of muscle mass cannot fully explain loss of muscle strength and vice versa (8). While it has been proposed to define sarcopenia based on the presence of low muscle mass together with low muscle strength or function (9), it has also been suggested to restrict the term sarcopenia to low muscle mass and to use another term for low muscle strength: 'dynapenia' (10). The prevalence of sarcopenia in elderly populations was found to vary substantially (11;12). The use of various diagnostic criteria of sarcopenia is most likely to account for the differences. Consequently, difficulties arise when comparing different cohorts and individual patients (13).

The medical community did not agree on a definition of osteoporosis from its first medical interest in the early 1940s until the mid 1990s. The aim of this paper is to learn from the similarities and differences in defining sarcopenia with respect to osteoporosis. By identifying and comparing milestones in the process of decision making we aim to get insights into the required steps to be taken to reach a clinically applicable definition of sarcopenia.

Chronology of osteoporosis and sarcopenia

Milestones in the definition of osteoporosis

The term 'osteoporosis' (porous bone) was most probably launched by the French pathologist Lobstein 'the Younger' in 1830 (milestone 1: coining of a term, figure 1). This term was derived from the Greek 'osteon' (bone) and 'poros' (little hole), and was initially used to describe cavities observed in human bone of his patients during autopsy (14). Though the term was widely accepted and described in medical dictionaries from that moment on, it was not until the 20th century that osteoporosis was considered a treatable disorder instead of an unavoidable condition just occurring with ageing. This was probably due to Albright and colleagues, who first made a medical definition for osteoporosis and described conditions associated with osteoporosis (milestone 2: understanding of consequences, figure 1). Since the presence of osteoporosis was mainly observed in postmenopausal women, treatment with estrogen was suggested (15) (milestone 3: available medication, figure 1). Albright defined osteoporosis as "too little formation of calcified bone", with the bone itself being normally calcified, and exhibiting a normal rate of bone destruction (16;17).

After Albright's definition, the interest of researchers in osteoporosis increased. However, researchers assigned different meanings to 'osteoporosis', with varying emphases on clinical, physiological, and biochemical factors. Until 1994, different definitions of osteoporosis were described in medical dictionaries (interchangeable use of the term osteoporosis, figure 1)(18). Furthermore, the definition of osteoporosis in Harrison's 'Principles of internal medicine' varied over the years. In the Harrison of 1950, age was considered as one of the causal factors leading to atrophy of tissue. It was recognized that all tissues atrophy with age, and skeletal atrophy was termed osteoporosis (19). An age based distinction was made between 'senile' and 'postmenopausal' osteoporosis. Women under the age of 65 years were diagnosed with postmenopausal osteoporosis; above 65 years of age they were diagnosed with senile osteoporosis (19-21). This definition was held until 1970, when osteoporosis was distinguished from 'normal age-related bone loss' and recognized as a disease (22). Age was considered the causal factor in 'primary' osteoporosis. If an underlying cause was identified such as immobilization, steroid use or gonadal insufficiency, it was called 'secondary' osteoporosis (22). Although there was no universal definition of osteoporosis, besides the estrogen therapy introduced by Albright, other drug therapies (e.g. bisphosphonates in 1960) were developed and introduced in patient care (23).

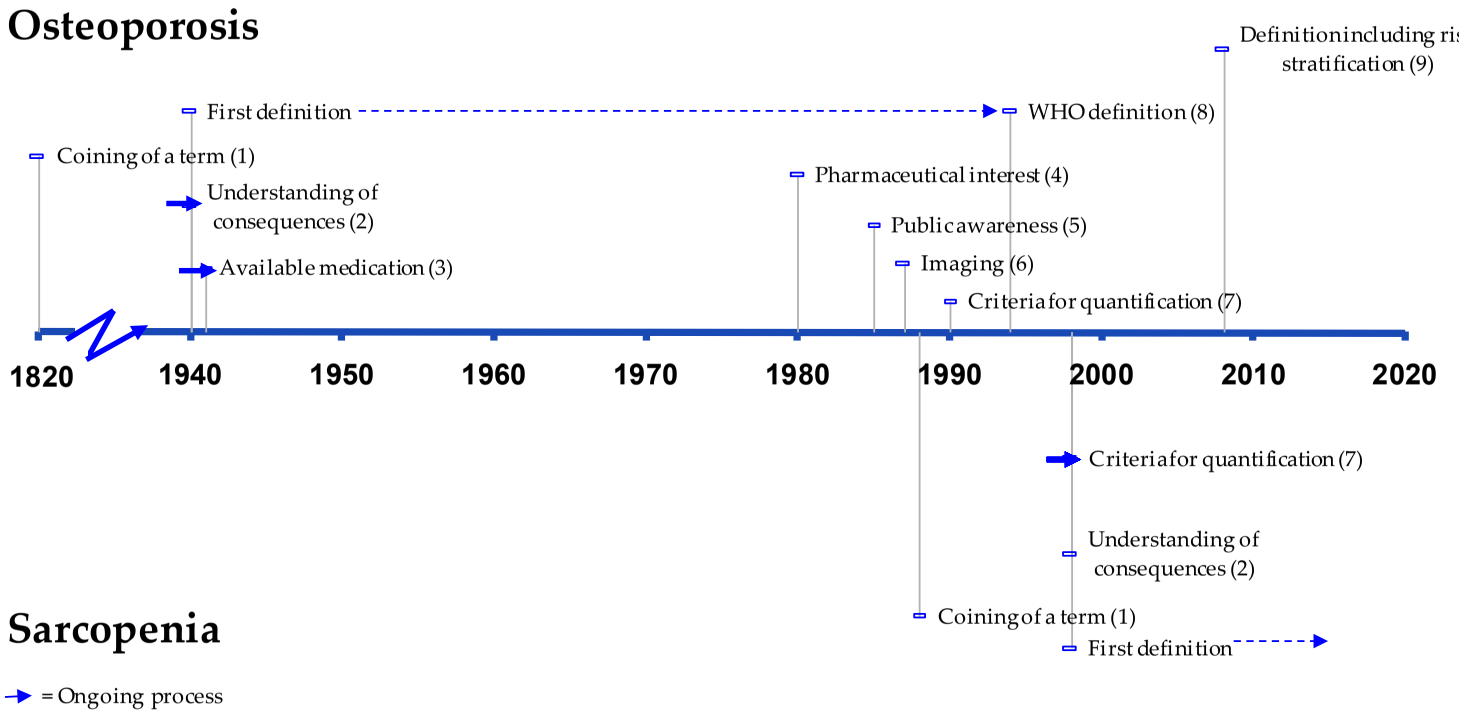

Figure 1: *Chronology of osteoporosis and sarcopenia. Milestones in defining osteoporosis / sarcopenia: (1) coining of a term, (2) understanding of consequences, (3) available medication, (4) pharmaceutical interest, (5) public awareness, (6) imaging, (7) criteria for quantification, (8) World Health Organisation (WHO) definition, (9) definition including risk stratification. For the definition of sarcopenia, crucial milestones are missing such as (3) available medication, (4) pharmaceutical interest and (5) public awareness. First definitions for sarcopenia have been proposed, using criteria to quantify muscle mass, strength and function (7). There is no universal consensus on which criteria to use to define sarcopenia.*

Before the introduction of dual-energy x-ray absorptiometry (DXA) scanners in 1987, osteoporosis was diagnosed in a rather crude way, for example, when there was evidence of deformity of a vertebral body or fracture or other bone from minor trauma, or the bones were extensively demineralized, readily recognized on routine diagnostic x-ray films. Without the ability to detect osteoporosis in an early stage, osteoporosis was a disease with a sudden onset after a fracture in patients. Without a proper method to measure bone mineral density, no consensus was reached on how to define osteoporosis without the presence of fractures. In the 1980s, a massive public awareness campaign regarding osteoporosis was launched in the United States, largely funded by the pharmaceutical industry producing hormone replacement therapy and dairy industry promoting their products as bone-building treatments (milestone 4: pharmaceutical interest, figure 1) (18). The awareness was so widespread that by 1987, 85% of Americans knew what osteoporosis was, as compared to 15% in 1982 (milestone 5: public awareness, figure 1) (18). Investments were also made in imaging technology to measure bone-density in routine clinical practice, leading to the introduction of the DXA scanners in 1987 (milestone 6: imaging) (24). Effort was made to define a reference standard against which a certain bone mineral density could be measured. Fracture risk was taken into account to define osteoporosis, to be able to start treatment before the onset of adverse events (milestone 7: criteria for quantification, figure 1) (25).

After the introduction of DXA, it was recognized that the clinically important cut-off points for bone mineral density varied according to a number of parameters such as sex, age, and racial origin (25;26). A definition was formulated at the WHO Consensus Conference of Osteoporosis in Copenhagen in 1990, where osteoporosis was defined 'a disease characterized by low bone mass, microarchitectural deterioration of bone tissue leading to enhanced bone fragility, and a consequent increase in fracture risk' (27). In 1994 the World Health Organization (WHO) operationally defined osteoporosis as a bone density measured with DXA, 2.5 standard deviations (SD) below the mean for healthy women aged 20 – 29 years, also referred to as a T-score of -2.5 (milestone 8: WHO definition, figure 1) (28). These cut-off points, although arbitrarily defined based on sensitivity and specificity of the occurrence of fractures, are still being used today.

Optimal risk assessment in osteoporosis still remains under debate in research. When the WHO diagnostic criteria were provided, the prevalence of osteoporosis was considered roughly equal whether assessed at the hip, lumbar spine or forearm (high degree of agreement between sites). However, with the introduction of new technologies (peripheral DXA, quantitative ultrasound, quantitative computed

tomography, and other radiographic techniques) applied to different skeletal sites of the body, it became clear that the same T-score from different skeletal sites and techniques yielded different information on the prevalence of osteoporosis and on fracture risk (29). Moreover, it has been recognized that using the same reference values for different races is far from optimal (29-31). After the introduction of a clinically applicable WHO definition of osteoporosis, other risk factors of fractures have been assessed to optimize the assessment of fracture risk in osteoporosis. The fracture risk depends not only on the bone mineral density but also on other factors like the level of being at risk for trauma (risk behavior or cognitive functioning), severity of the trauma, and underlying conditions such as rheumatoid arthritis (32). The Fracture Risk Assessment Tool (FRAX) was initiated and enables physicians to assess the 10-year probability of fracture for individual patients based on information about a patient's clinical risk factors combined with a hip DXA scan (milestone 9: definition including risk stratification, figure 1) (32). While convenient in risk assessment, the definition of osteoporosis as defined by the WHO in 1994 remained unchanged.

Milestones in the definition of sarcopenia

In 1988, Rosenberg coined the term 'sarcopenia' to describe 'deficiency of muscle mass' as a literal translation from Greek, where 'sarx' means 'flesh' and 'penia' means 'deficiency' (milestone 1: coining of a term, figure 1) (1). Since the introduction of the term, the attention of the medical community to sarcopenia has grown. Nowadays the use of the term sarcopenia in literature has reached a level comparable to the use of the term osteoporosis 50 years ago (figure 2).

For sarcopenia, the techniques to measure the amount of muscle mass were already in use at the time the term was coined, but there was little intention for application, since the clinical consequences were unknown. In 1998, Baumgartner et al. suggested a formula to define sarcopenia as appendicular lean mass (sum of lean mass of both arms and legs) divided by height squared. Values more than two standard deviations below the mean of a young reference population were classified as sarcopenia (3). Other researchers introduced different formulas to define sarcopenia using muscle mass corrected for a combination of height, fat mass, or total body mass (milestone 7: criteria for quantification, figure 1) (4;33;34).

The introduction of diagnostic criteria contributed to the understanding of the consequences of having low muscle mass. There is a growing body of evidence that muscle mass is associated with self-reported physical disability (3;4;35) and functional impairment (4;35) (milestone 2, understanding of consequences).

Sarcopenia has also been defined by muscle strength represented by knee extension isometric torque or handgrip strength, lower extremity muscle power or physical performance such as gait speed (36) (milestone 7: criteria for quantification, figure 1). It has also been proposed to define sarcopenia by combining muscle mass with muscle strength or function, such as a combination of low muscle mass with low gait speed (9;37;38). Interchangeable use of the term sarcopenia makes it impossible to compare studies on sarcopenia due to very little concordance between different used diagnostic criteria (13).

Reflection

We have identified milestones in the history of the definition of osteoporosis and compared these to milestones that have been reached for the definition of sarcopenia. Both disease definitions relate to chronological age and started with the identification, recognition, and branding of a phenomenon (milestone 1, coining of a term, figure 1). A relevant question is at what stage to consider the gradual decline in bone mass or muscle mass as a disease, instead of a condition normal for

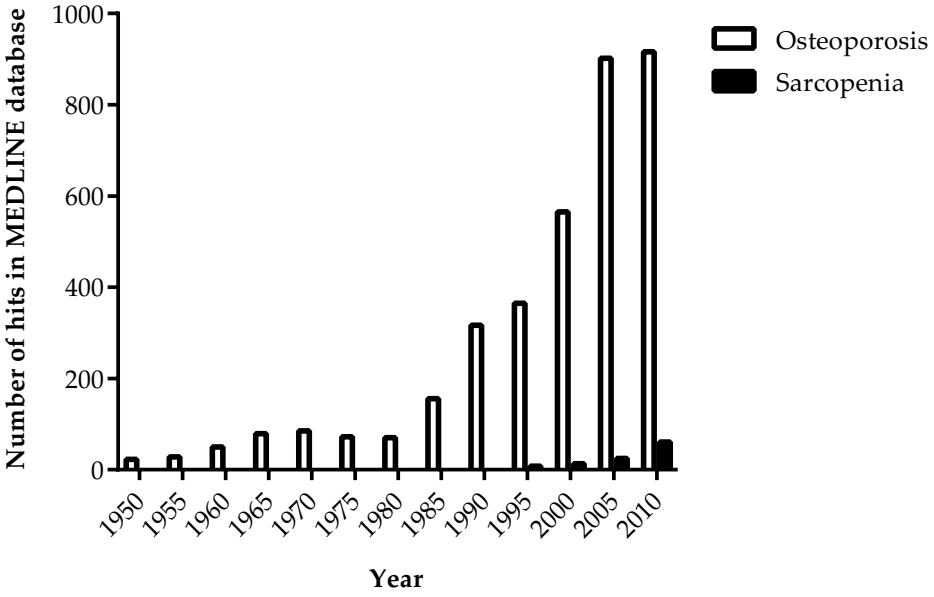

Figure 2: *Amount of hits in the MEDLINE database with the term "osteoporosis" (white bars) and "sarcopenia" (black bars). Both terms were entered as a single term in the MEDLINE database search engine per year with 5 year intervals.*

chronological ageing. In the past, the terms 'disease', 'disorder', and 'condition' have been used as synonyms in literature for osteoporosis, while they describe different phenomena. 'Disease' is a definite morbid process with characteristic symptoms, whereas a 'disorder' describes an abnormality of function and a 'condition' is a state or mode of being, especially a state of health (39). The severity and development of the process and the underlying pathophysiological process determines the term to be chosen. The detrimental outcome associated with sarcopenia justifies defining sarcopenia as a disease, comparable to osteoporosis (milestone 2: understanding of consequences, figure 1).

The difficulty in defining cut-off points for the amount of bone mineral density and muscle mass accounts for both osteoporosis and sarcopenia. Which reference populations should be used to decide whether the amount of muscle mass or bone mineral density is normal or abnormal? Concerning osteoporosis, cut-off points are based on the optimal combination of sensitivity and specificity to determine the occurrence of fractures. As in osteoporosis, for sarcopenia it is crucial to define reference groups, based on gender, ethnicity, and race.

An important difference between osteoporosis and sarcopenia is a clearly defined clinical consequence, which is needed for evaluation of the diagnostic criteria and development of treatment. In case of osteoporosis the risk of fractures is used as clinical outcome parameter. For sarcopenia, a clear clinical outcome parameter is still lacking. It is undesirable to evaluate muscle quality in terms of physical performance and strength, since this is also dependent on other parameters such as the neural controller, cardiovascular fitness and joint function. Although the amount of muscle mass is associated with muscle strength (4;33;34;40), there is accumulating evidence that muscle mass and muscle strength are two different entities (10;41;42) and therefore the term 'dynapenia' was coined by Clark in 2008 to describe the loss of muscle strength occurring with age (10). Besides a generator of strength, muscle tissue is an important internal organ. Next to mechanical consequences, loss of muscle mass has physiological consequences. These include protein storage, glucose regulation, hormone production and other cellular mechanisms (6). Recent studies have shown that the ability to recover from life-threatening disease is dependent on a higher amount of muscle mass, as sarcopenia was associated with higher mortality rates after liver transplantation (43) and higher chemotoxicity, independent of confounding factors (44). This might also be of clinical relevance in determining whether or not a patient is suitable for organ transplantation or chemotherapy.

In conclusion, it appears that crucial milestones are missing in the development of a clinically applicable definition of sarcopenia. Obvious main lacking milestones are

the availability of specific drug therapy (and therewith pharmaceutical interest), public awareness of clearly defined disease consequences, and a universally accepted definition. Interchangeable use of the definition of sarcopenia makes it impossible to compare studies, to understand the pathophysiological process and to develop targeted therapies. Since muscle tissue is involved in multiple processes, we suggest defining sarcopenia as 'low muscle mass' without use of functional or metabolic outcome parameters. Consensus must be reached regarding reference values of the general population of different ethnicities and race and applied correction factors. Furthermore, proper outcome measures should be defined for valid risk assessment. Understanding of the underlying pathophysiological processes will lead to first treatment possibilities and introduction of the disease in clinical care. It is necessary to create public awareness and accelerate the process of reaching a universally accepted definition of sarcopenia.

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Chapter 4

Defining sarcopenia: the impact of different diagnostic criteria on the prevalence of sarcopenia in a large middle aged cohort

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Abstract

Sarcopenia, low muscle mass, is an increasing problem in our aging society. The prevalence of sarcopenia varies extremely between elderly cohorts ranging from 7 to over 50%. Without consensus on the definition of sarcopenia, a variety of diagnostic criteria are being used. We assessed the degree of agreement between seven different diagnostic criteria for sarcopenia based on muscle mass and handgrip strength, described in literature. In this cross-sectional study, we included men (n=325) and women (n=329) with complete measurements of handgrip strength and body composition values as measured by bioimpedance analysis within the Leiden Longevity Study. Prevalence of sarcopenia was stratified by gender and age. In men (mean age 64.5 years) the prevalence of sarcopenia with the different diagnostic criteria ranged from 0% to 20.8% in the lowest age category (below 60 years), from 0% to 31.2% in the middle (60 to 69 years) and from 0% to 45.2% in the highest age category (above 70 years). In women (mean age 61.8 years) the prevalence of sarcopenia ranged from 0% to 15.6%, 0% to 21.8% and 0% to 25.8% in the lowest, middle and highest age category respectively. Only one participant (0.2%) was identified having sarcopenia according to all diagnostic criteria that marked prevalence above 0%. We conclude that the prevalence of sarcopenia is highly dependent on the applied diagnostic criteria. It is necessary to reach a consensus on the definition of sarcopenia in order to make studies comparable and for implementation in clinical care.

Introduction

Sarcopenia, low muscle mass at older age, is an increasing problem in our aging society. Annual loss of muscle mass has been reported as 1 to 2 percent at the age of 50 years onwards (1;2), and it exceeds over 50% among those aged 80 years and older when compared to younger adults (3). The change of muscle mass is closely related to changes in muscle strength. Reduced muscle strength has been found to be associated with dependency in activities of daily living (4;5), cognitive decline (6-8), and mortality (9;10). Next to the generation of muscle strength, muscle tissue is an important reserve of body proteins and energy that can be used in extreme conditions of stress or malnutrition. Low muscle mass is associated with higher drug toxicity (11;12) and reduced insulin sensitivity (13).

Since the coining of the term 'sarcopenia' in 1989 by Rosenberg (14), many suggestions have been made to try to establish a clinically applicable definition. In general, three possible approaches in defining sarcopenia have been suggested. According to the first, the amount of muscle mass, measured with dual-energy x-ray absorptiometry (DXA) or bioimpedance analysis (BIA), compared to a younger reference population determines whether a person has sarcopenia. Correction factors applied using this approach are height (3;15), body mass (16), or both body height and body fat (17). In the second approach, muscle function is used as diagnostic criterion to define sarcopenia as compared to a younger reference population (18). The third approach combines both muscle mass and muscle function in the definition (19;20).

Little is known about the degree of agreement between the diagnostic criteria and their effects on estimates of the prevalence of sarcopenia, which appears to vary extremely between different cohorts ranging from 7 to over 50% in the elderly (3;16-18;21). The use of different diagnostic criteria may lead to different conclusions and may have different implications for treatment. To the best of our knowledge the differences in prevalence of sarcopenia in middle aged people comparing different diagnostic criteria has not been previously reported. In the present paper we explore the prevalence of sarcopenia using seven different diagnostic criteria in a large cohort of Dutch middle aged people. Furthermore, we assess the degree of concordance within individuals using the different criteria. Therewith, we aim to show the importance of reaching a consensus on the definition of sarcopenia, for clinical research and patient care.

Methods

Study cohort

The Leiden Longevity Study (LLS) consists of long-living Caucasian siblings of 420 families together with their middle aged offspring, and the partners of the offspring as controls (22). The study included 674 participants of the middle aged to older offspring and their partners, who were assessed in the period from 2006 to 2008. The sample of partners in the study was representative of the Dutch population (22). Participants (n=20) with missing data for body composition measured with Direct Segmental Multi-frequency Bioelectrical Impedance Analysis (DSM-BIA) were excluded from the present analysis. There were no selection criteria on health or demographic characteristics (23). The Medical Ethics Committee of the Leiden University Medical Centre approved the study, and written informed consent was obtained from all participants.

Participant characteristics

At baseline, information on common chronic diseases and medication use was obtained from the participants' general practitioner, pharmacist's records, and from blood sample analyses. The chronic diseases recorded were diabetes mellitus, chronic obstructive pulmonary disease, malignancy, myocardial infarction, stroke, and hypertension. Health behaviour variables included current smoking status and excessive alcohol use (male > 210 g/week and female > 140 g/week).

Body composition

Body mass and body height were measured. DSM-BIA was performed using the In-Body (720) body composition analyser (Biospace Co., Ltd, Seoul, Korea). We have previously shown this technique to be a valid tool for the assessment of whole body composition and segmental lean mass measurements in our sample of a middle aged people (24). Excellent agreements were observed between the DSM-BIA technique and DXA in whole body lean mass (intraclass correlation coefficient (ICC) female=0.95, $p<0.001$, ICC male=0.96, $p<0.001$) and fat mass (ICC female 0.97 $p<0.001$, ICC male 0.93 $p<0.001$) (24). The DSM-BIA technique is based on the assumption that the human body is composed of 5 interconnecting cylinders and takes direct impedance measurements from the various body compartments. A tetrapolar eight point tactile electrode system is used, which separately measures impedance of the participant's trunk, arms, and legs at six different frequencies (1 kHz, 5 kHz, 50 kHz, 250 kHz, 500 kHz, and 1000 kHz) for each of the body segments. The

spectrum of electrical frequencies is used to predict the intracellular water (ICW) and extracellular water (ECW) compartments of the total body water (TBW) in the various body segments. Lean body mass is estimated as TBW (ICW + ECW)/0.73. Body fat mass is calculated as the difference between total body mass and lean mass. The machine gives immediate detailed results including quantitative values of total body and segmental lean mass, fat mass, and percentage fat mass. Appendicular lean mass (ALM) calculation was based on the sum of lean mass in all four limbs. Relative ALM was calculated as ALM divided by body height in meters squared (3). Participants wore normal indoor clothing and were asked to stand barefoot on the machine platform with their arms abducted and hands gripping on to the handle of the machine.

Handgrip strength

Handgrip strength was measured to the nearest kilogram using a Jamar hand dynamometer (Sammons Preston, Inc., Bolingbrook, IL, USA). All participants were instructed to maintain an upright standing position, arms down by the side, and holding the dynamometer in the dominant hand without squeezing the arm against the body. The width of the dynamometer's handle was adjusted to the hand size of the participants such that the middle phalanx rested on the inner handle. Participants were allowed to perform one test trial, followed by three trials, and the best measurement was taken for analysis.

Diagnostic criteria of sarcopenia

An overview of different diagnostic criteria of sarcopenia (coded A to G) as described in the literature, which included muscle mass and handgrip strength is given in table 1 (3;15;16;18;25). Only diagnostic criteria based on measurements of muscle mass by BIA (definition E and F) or DXA (definition A, B, C, and D) scanning were used in this comparison. For each of these formulas, a different reference population had been used to derive a cut-off point for sarcopenia. For the formula ALM divided by height squared (definition A, B, and C), we found three different cut-off points for men and women, established in different reference populations (3;25;26). Reference populations were different in age and ethnicity, consisting of younger participants of the Rosetta study (definition A)(3), the NHANES survey (definition C)(26), and the NHANES III study (definition E)(16); elderly participants were included as reference population in the Health ABC study (definition B)(25), and the NHANES III study (definition F)(15); the whole adult age range was included in the reference population in the InCHIANTI study (definition G)(18). The formula described in

definition D, was applied to our cohort, using the 20th percentile as cut-off point for sarcopenia (25). Consequently, we used a total of seven different diagnostic criteria of sarcopenia in our analysis.

Statistical analysis

Data were analysed for men and women separately. Because there was no significant difference in fat percentage, relative ALM, and handgrip strength between offspring and partners of the LLS, data for both groups were combined (27). The prevalence of sarcopenia in this population was assessed for all seven diagnostic criteria as described in table 1. For definition D, the residuals of linear regression of ALM with height and fat mass were calculated.

After assigning the status of sarcopenia being present or not present in the participants according to each of the seven diagnostic criteria, participants were stratified by gender and age. The lowest age category included participants aged below 60 years, the middle age category included participants aged 60 to 69 years and the highest included participants aged 70 years and above. Differences between age groups in characteristics were assessed with linear regression or binary logistic regression. The degree of concordance within individuals using the different diagnostic criteria of sarcopenia was assessed in all participants.

All statistical analyses were performed using SPSS for Windows (SPSS Inc, Chicago), version 17. P values <0.05 were considered statistically significant.

Results

Baseline characteristics of the study participants stratified by gender and age are presented in Table 2. Overall, the prevalence of comorbidity was slightly higher in older participants (statistically not significant). Skeletal lean mass as a percentage of body mass and grip strength were significantly lower in the older age groups. ALM divided by height squared was significantly different between the age groups in men, but not in women.

The prevalence of sarcopenia using the seven different diagnostic criteria is shown in Table 3. In men, the prevalence ranged from 0% to 20.8% in the lowest age category, from 0% to 31.2% in the middle age category and from 0% to 45.2% in the highest age category. In women, percentages ranged from 0% to 15.6%, 0% to 21.8% and 0% to 25.8% in the lowest, middle and highest age category respectively.

Definitions A, B, and C are based on the same formula taking height into account, but each comprised different reference populations and strategies to define cut-

Tabel 1 Seven different diagnostic criteria to define sarcopenia

Code	Formula	Cut-off point			Cohort used as reference population	Reference[a]
		Sarcopenia present	Men	Women		
A	ALM/height^2	> 2 SD below reference population	7.26 kg/m^2	5.45 kg/m^2	Rosetta Study (1986-1992)m 229 non-Hispanic white men and women aged 18-40 years	Baumgartner et al., 1998
B	ALM/height^2	Under 20th percentile	7.25 kg/m^2	5.67 kg/m^2	Health ABC Study (1997/1998), 2976 men and women 70-79 years old black and white, Pittsburgh, Pennsylvania and Memphis, Tenessee	Delmonico et al., 2007
C	ALM/height^2	> 2 SD below reference population	6.19 kg/m^2	4.73 kg/m^2	NHANES survey (1999 - 2004) white men and women aged 20 years	Kelly et al., 2009
D	Residuals of linear regression of ALM with height and fat mass	Under 20th percentile	NA	NA	NA	Delmonico et al., 2007[b]
E (1)(2)	Skeletal lean mass/ body mass * 100%	1-2 SD below reference population is class I sarcopenia >2 SD below reference population is class II sarcopenia	37% 31%	28% 22%	NHANES III (1988-1994), 6414 men and women aged 18-39 years non-Hispanic white, non-Hispanic black and	Janssen et al., 2002
F (1)(2)	Skeletal lean mass/ height^2	ROC analysis was used to develop cutpoints associated with moderate (1) and high (2) physical disability	10.75 8.50 kg/m^2	6.75 5.75 kg/m^2	NHANES III (1988-1994), 4502 subjects aged 60 years plus, non-Hispanic white, non-Hispanic black and Mexican-American	Janssen et al., 2004
G	Optimal cutpoint for grip strength, identified in the ROC curve, predicting walking slower than 0.8 m/s	Below optimal cutpoint	30.3 kg	19.3 kg	InCHIANTI (1998-2000), 1030 subjects aged 20 - 102 years, Tuscany, Italy	Lauretani et al., 2003

[a]Reference describes the formula and cut-off points, unless indicated otherwise. [b]Reference describes the formula which was applied to the Leiden Longevity Study population. ALM=appendicular lean mass, sum measurement of lean mass in all 4 limbs; ROC=receiver operating characteristics; NA=not applicable.

off points. In men prevalence varied from 0% to 3.9% (lowest age category), 0% to 4.3% (middle age category) and 0% to 6.5% (highest age category). In women this variation for definitions A, B, and C was 0% to 3.1% (lowest age category), 0% to 3.5% (middle age category) and 0% (highest age category). When applying cut-off points for definition E class II, two men (0.6%) and 1 woman (0.3%) were classified as sarcopenic. The prevalence of sarcopenia was higher when applying cut-off points for definition E class I. Only one of the men (0.3%) was sarcopenic according to definition F class II criteria, based on muscle mass and height. The prevalence was higher using definition F class I criteria. The use of definition G which included handgrip strength gave a prevalence of less than 4% in this middle aged cohort.
Figure 1 shows the distribution of participants identified as sarcopenic according to the different diagnostic criteria. Definition C, which gave zero prevalence of sarcopenia is omitted. For definition E and F, class I and class II sarcopenia are combined. Out of the 654 participants, 436 did not have sarcopenia according to any definition. For 218 participants, the diagnosis of sarcopenia depended on the diagnostic criteria applied. Only one of the participants (0.2%) was sarcopenic according to all six definitions.

Discussion

In this large middle aged Dutch cohort, the prevalence of sarcopenia varied widely depending on which diagnostic criteria were used. Criteria based on low grip strength and skeletal lean mass failed to match with criteria based on appendicular lean mass. There was substantial overlap between diagnostic criteria A and B which are both based on the amount of appendicular lean mass, yet another cut-off point for the amount of appendicular lean mass resulted in the absence of sarcopenia (diagnostic criterium C). These findings clearly demonstrate the highly different selection of participants with the diagnosis sarcopenia using various criteria. Consequently, there are concerns about the validity of comparisons between studies using different criteria to diagnose sarcopenia.
The question arises which properties of skeletal muscle are represented by the term sarcopenia. Besides the production of force, muscle tissue is also an important regulator of biological processes. For instance, as a protein store it provides a homeostatic reserve to recover from disease (28). Furthermore, skeletal muscle has been identified as the major tissue involved in glucose metabolism (29;30). Current evidence suggests that lean body mass may be a better measure for normalising dosages of drugs that are distributed and metabolised in lean tissue, compared

Table 2: Baseline characteristics of study participants, stratified for gender and age.

Variables[a]	Men				Women			
	<=59 y (n=77)	60-69 y (n=186)	>=70 y (n=62)	P trend	<=59 y (n=128)	60-69 y (n=170)	>=70 y (n=31)	P trend
Age (y, mean, range)	56.1 (45-59)	64.9 (60-69)	73.5 (70-82)		55.6 (38-59)	64.5 (60-69)	72.3 (70-78)	
Height (m)	1.81 (0.07)	1.78 (0.06)	1.76 (0.07)	<0.001	1.67 (0.06)	1.66 (0.1)	1.64 (0.6)	0.02
Body mass (kg)	86.7 (11.0)	85.5 (11.8)	84.1 (10.1)	0.17	71.7 (12.5)	72.6 (13.1)	76.0 (11.4)	0.15
Body Mass Index (kg/m^2)	26.6 (3.3)	27.0 (3.2)	27.2 (2.9)	0.25	25.8 (4.4)	26.4 (4.7)	28.2 (4.0)	0.01
Total body fat mass (%)	23.4 (6.1)	25.8 (5.9)	28.0 (7.1)	<0.001	33.7 (7.5)	35.2 (7.1)	39.4 (6.7)	<0.001
Skeletal lean mass (kg)	37.2 (4.1)	35.3 (4.0)	33.3 (3.9)	<0.001	25.7 (3.3)	25.3 (3.3)	24.7 (3.0)	0.10
Skeletal lean mass (%)[b]	43.1 (3.5)	41.5 (3.4)	39.8 (4.0)	<0.001	36.2 (4.1)	35.3 (3.9)	32.8 (3.8)	<0.001
ALM[c] (kg)	28.0 (3.3)	26.7 (3.2)	25.5 (3.3)	<0.001	19.3 (2.7)	18.9 (2.7)	18.9 (2.5)	0.31
Relative ALM[d] (kg/m2)	8.6 (0.6)	8.4 (0.6)	8.2 (0.6)	0.002	6.9 (0.7)	6.9 (0.8)	7.0 (0.7)	0.78
Handgrip strength (kg)	51.1 (7.9)	46.8 (7.2)	41.7 (8.1)	<0.001		29.0 (5.0)	26.6 (4.8)	<0.001
Comorbidities (n %)								
Myocardial infarction	1 (1.3)	8 (4.3)	3 (4.8)	0.25	0	1 (0.6)	1 (3.2)	0.11
Stroke	1 (1.3)	5 (2.7)	5 (8.1)	0.04	2 (1.6)	3 (1.8)	0	0.70
Hypertension	10 (13.0)	50 (26.9)	20 (32.3)	0.006	25 (19.5)	47 (27.6)	13 (41.9)	0.008
Diabetes Mellitus	5 (6.5)	16 (8.6)	6 (9.7)	0.48	6 (4.7)	7 (4.1)	4 (12.9)	0.25
Neoplasm	2 (2.6)	12 (6.5)	6 (9.7)	0.08	6 (4.7)	14 (8.2)	3 (9.7)	0.18
COPD	3 (3.9)	7 (3.8)	5 (8.1)	0.26	5 (3.9)	3 (1.8)	2 (6.5)	0.99
Rheumatoid arthritis	1 (1.3)	1 (0.5)	1 (1.6)	0.90	1 (0.8)	2 (1.2)	0	0.91
Medicatione, median (IQR)[e]	0 (0-0)	0 (0-1)	0 (0-1)	<0.001	0 (0-1)	0 (0-1)	0 (0-2)	0.02
Smoking (n %)	10 (13.0)	24 (12.9)	6 (9.7)	0.61	21 (16.4)	16 (9.4)	1 (3.2)	0.02
Excessive alcohol use (n %)[f]	20 (26.0)	57 (30.6)	14 (22.6)	0.95	19 (14.8)	24 (14.1)	5 (16.1)	0.90

[a]Variables are presented in mean, SD, unless indicated otherwise. P values for trend were calculated using linear or logistic regression. [b]skeletal lean mass/total body mass•100%. [c]Appendicular lean mass, sum measurement of lean mass in all 4 limbs. [d]Appendicular lean mass adjusted for height (appendicular lean mass/height^2). [e]Sum score of total number of oral medication, data available in males (n=272) and females (n=268). [f]Male>210 g/week and female>140 g/week.

Table 3: Prevalence of sarcopenia (n %) in the middle aged study population stratified by gender and age.

Code[a]	Men				Women			
	<=59 y (n=77)	60-69 y (n=186)	>=70 y (n=62)	Total (n=325)	<=59 y (n=128)	60-69 y (n=170)	>=70 y (n=31)	Total (n=329)
A	3 (3.9)	8 (4.3)	4 (6.5)	15 (4.6)	2 (1.6)	5 (2.9)	0	7 (2.1)
B	3 (3.9)	8 (4.3)	4 (6.5)	15 (4.6)	4 (3.1)	6 (3.5)	0	10 (3.0)
C	0	0	0	0	0	0	0	0
D	12 (15.6)	35 (18.8)	18 (29.0)	65 (20.0)	20 (15.6)	37 (21.8)	8 (25.8)	65 (19.8)
E1	3 (3.9)	17 (9.1)	16 (25.8)	36 (11.1)	4 (3.1)	8 (4.7)	4 (12.9)	16 (4.9)
E2	1 (1.3)	0	1 (1.6)	2 (0.6)	0	0	1 (3.2)	1 (0.3)
F1	16 (20.8)	58 (31.2)	28 (45.2)	102 (31.4)	0	0	1 (3.2)	1 (0.3)
F2	0	0	1 (1.6)	1 (0.3)	0	0	0	0
G	1 (1.3)	2 (1.1)	5 (8.1)	8 (2.5)	3 (2.3)	6 (3.5)	0	9 (2.7)

[a]The letters represent codes for the applied definition. The code is fully described in Table 1.

with body surface area alone (11;12;31). This underlines the importance to evaluate muscle mass in aging subjects.

In the present study, there was little overlap between individuals with low grip strength and low muscle mass using the diagnostic criteria. A possible explanation is that muscle strength is not only determined by muscle mass. The amount of muscle mass represents the number of sarcomeres that are in parallel. As each sarcomere is capable of exerting an amount of force, the number of sarcomeres in parallel, together with the quality of proteins and connective tissue determines the amount of force that a muscle can potentially exert. Additionally, muscle function is dictated by energy supply and neural control. Consequently, the terms muscle mass and muscle strength cannot be used interchangeably (32). The rate of decline in muscle strength at older age appears to be higher than the decline in muscle mass in a 3-year longitudinal study, suggesting that factors other than muscle mass are influential (33). Additionally, the increase of strength after resistance training is higher than the increase in muscle mass in older adults (34-37). In a recent meta-analysis it was shown that handgrip strength decreases each year with 0.37 kg (95% CI 0.31-0.44) after 50 years of age (38). Still, the low prevalence of sarcopenia in our cohort based on cut-off points for handgrip strength can possibly be explained by the fact that our cohort was middle aged and not over 80 years of age, where lower muscle strength becomes even more apparent (39). Recently a new term, dynapenia, has been developed to describe low muscle strength at old age (32). The use of the terms dynapenia for low muscle strength, and sarcopenia for low muscle

mass, emphasises the differences between muscle strength and mass. However, this terminology might overcomplicate the situation unnecessarily, since muscle mass is also needed to generate strength. In other words, low muscle strength is one of the possible consequences of low muscle mass.

The prevalence of sarcopenia determined by diagnostic criteria using ALM corrected for height was not related to chronological age in women. However, the total lean mass as a percentage of total body mass was lower in all older subjects. This provides evidence that the interpretation of the amount of muscle mass is highly dependent on applied correction factors, such as fat mass and height. This is supported by Newman et al., who found that correction for height only could lead to an overestimation of sarcopenia in underweight individuals, compared to an underestimation of sarcopenia in obese individuals (17). Furthermore, recent

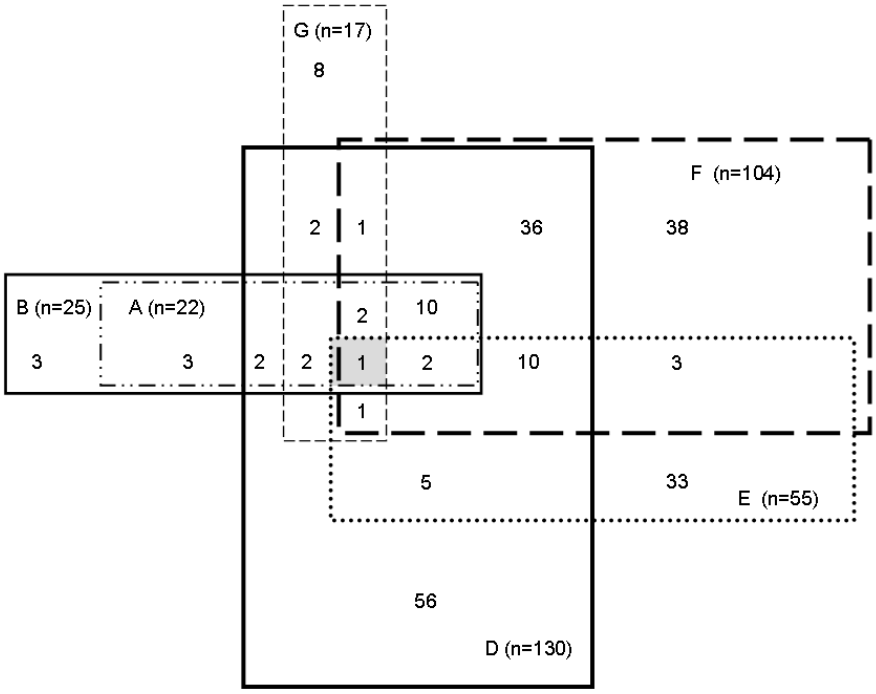

Figure 1: *Number of participants identified as having sarcopenia according to various definitions, represented by letter codes. A description of the codes can be found in table 1. A total of 654 were evaluated. Definition C, in which no participants were sarcopenic, is not shown. In definition E and F, class I and II sarcopenia are combined. Two subjects, one in whom sarcopenia was diagnosed according to F, G and E, and one in whom sarcopenia was diagnosed according to B and D are not shown in the figure.*

studies suggest that high fat mass is an important and independent determinant of functional status in elderly, even after adjustment for the level of physical activity (40-43).

Next to a valid assessment of the amount of muscle mass, some variability emerges from the comparison to different reference populations and different cut-off points. Even with this variability, the degree of agreement between diagnostic criteria with the same formula but different cut-off points (definition A and B) was substantial. The prevalence of sarcopenia of zero percent using definition C can be explained by differences in reference populations. Furthermore, the prevalence of sarcopenia with definition A in this study cohort was much lower than reported in the same age categories by Baumgartner et al. (1998). In that study, using the same cut-off points in non-Hispanic whites, the prevalence of sarcopenia was found to be 13.5%-23.1% below 70 years, and 19.8%-33.3% between 70-74 years, in men and women respectively. Differences in reference groups may be caused by age, ethnicity, genetic background, and environmental factors such as the level of physical activity. Therefore, it is important to agree on reference populations that can be used in specific ethnic groups. Establishing reference databases generally requires a large sample size to achieve reliable results. Reference databases established to diagnose osteoporosis could function as a role model. Furthermore, it remains important to invest in longitudinal studies including the general population assessing the relation between muscle mass and functional outcomes to establish possible critical thresholds of muscle mass needed for muscle function.

Until now, attempts to approve on a consensus definition for sarcopenia failed. To the best of our knowledge, three international consortia have agreed on distinct definitions, which have not been generally accepted in the medical community. The first consensus definition was published by the Special Interest Groups (SIG) in 2009 (20). Here, the diagnosis sarcopenia is based on a combination of low muscle mass as defined by Janssen in 2002 (definition E)(16), together with low gait speed, which is walking speed below 0.8 m/s in the 4-m walking test, or another functional test (20). The second consensus definition was published by The European Working Group on Sarcopenia in Older People (EWGSOP) in 2010. The EWGSOP included a degree of severity of sarcopenia in the definition. 'Presarcopenia' was defined as low muscle mass, 'sarcopenia' as low muscle mass together with either low muscle strength or performance and 'severe sarcopenia' as a combination of all three. In addition, it was proposed that sarcopenia should be considered 'primary' when no other cause is evident but aging itself, and 'secondary' when one or more other causes are evident (19). This terminology is not acceptable in modern gerontology, as age in itself is no

longer considered a causal factor of disease (44). In the third consensus definition, Fielding et al. based the diagnosis of sarcopenia on low muscle mass as defined by Delmonico et al. (definition B)(25), together with low gait speed defined as less than 1 m/sec (45).

In our opinion, these consensus definitions are not clinically applicable. First of all, using the SIG definition none of the participants in the present study fulfilled the criteria for low muscle mass. Furthermore, gait speed is not a parameter of muscle function alone, but also dependent on other factors such as cognition, neural control, joint function, and cardiovascular fitness (46). The EWGSOP definition lists different ways to diagnose sarcopenia, without making a choice which measurement should be used. Consequently, the huge variability of prevalence of sarcopenia highlighted in the present study would therefore still be present. Defining sarcopenia based solely on the amount of muscle mass avoids all afore mentioned problems.

The strength of the present study is that the currently used diagnostic criteria of sarcopenia were applied to one study population. Previously, we have shown an excellent correlation between BIA and DXA measurements (24); therefore we were able to apply diagnostic criteria based on both DXA and BIA measurements. A possible limitation of this study is selection bias of the participants, since only the partners of the offspring of nonagenarian siblings are considered to be representatives of the general population. However, the offspring of long-lived families did not differ significantly from their partners in fat percentage, muscle mass, and handgrip strength (27). Therefore, this would not influence conclusions made in the present study. Moreover, participants were middle aged; the degree of agreement between the different diagnostic criteria for sarcopenia might be different in an oldest old population. Another limitation is that we had no functional outcome measures available for participants in this study. We were not able to apply diagnostic criteria for sarcopenia based on gait speed.

In conclusion, the prevalence of sarcopenia varies widely depending on the applied diagnostic criteria. A consensus definition is necessary in order to make studies comparable and for implementation in clinical care. We suggest defining sarcopenia as 'low muscle mass', to do justice to the multifunctionality of muscle tissue. 'Low muscle mass' can be diagnosed with DXA and BIA, while 'loss of muscle mass with aging' cannot be measured in an individual at one time point. Further research should focus on establishing an appropriate formula to correct the amount of muscle mass for factors such as height and fat mass, and take into account differences in ethnicity when subjects are compared to reference populations.

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Chapter 5

Diagnostic criteria for sarcopenia and physical performance

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Submitted

Abstract

Relative and absolute muscle mass and muscle strength are used as diagnostic criteria for sarcopenia. We aimed to assess which diagnostic criteria are most associated with physical performance in 180 young (18-30 years) and 281 healthy old participants (69-81 years) of the European study MYOAGE. Diagnostic criteria included relative muscle mass (total or appendicular lean mass (ALM) as percentage of body mass), absolute muscle mass (ALM/height^2 and total lean mass), knee extension torque, and handgrip strength. Physical performance comprised walking speed, Timed Up and Go test (TUG), and in a subgroup physical fitness. Diagnostic criteria for sarcopenia and physical performance were standardized and the associations were analyzed using linear regression models stratified by age category, with adjustments for age, gender, and country. In old participants, relative muscle mass was associated with faster walking speed, faster TUG, and higher physical fitness (all $p < 0.001$). Absolute muscle mass was not associated with physical performance. Knee extension torque and handgrip strength were associated with faster walking speed (both $p \leq 0.003$). Knee extension torque was associated with TUG ($p = 0.001$). Knee extension torque and handgrip strength were not associated with physical fitness. In young participants, there were no significant associations between diagnostic criteria for sarcopenia and physical performance, except for a positive association between relative muscle mass and physical fitness ($p < 0.001$). Relative muscle mass, defined as lean mass or ALM percentage, was most associated with physical performance. Absolute muscle mass including ALM/height^2 was not associated with physical performance. This should be accounted for when defining sarcopenia.

Introduction

Sarcopenia has been associated with self reported mobility limitations (1), cognitive decline (2), and mortality (3). The onset of age related loss of muscle mass occurs as early as 30 years of age, with a decrease of 1 to 2 percent after the age of 50 years, and results in a loss of over 50 percent by the age of 80 years (1;4). During the last two decades, several diagnostic criteria for sarcopenia have been proposed, which can be categorized into measures of relative muscle mass (defined as total or appendicular lean mass (ALM) as percentage of body mass), absolute muscle mass (defined as appendicular lean mass (ALM) corrected for height (ALM/height^2) or total lean mass), muscle strength, walking speed or a combination of criteria (5;6). Previously, we have shown that the prevalence of sarcopenia is highly dependent on the diagnostic criteria (7).

Evidence-based consensus on the most clinically relevant diagnostic criteria for sarcopenia requires exploration of its association with muscle-related clinical outcome, such as physical performance. Relative muscle mass (lean mass percentage or ALM percentage) has been consistently associated with physical performance (8-10). However, expressing muscle mass in a different way, such as the absolute muscle mass (ALM/height^2), has led to conflicting results with some studies showing an association with self-reported mobility limitations and physical performance (1;10), and others finding no significant relationship between absolute muscle mass and physical performance (11-13). There are also mixed reports from studies relating muscle strength with physical performance. For instance, muscle strength was associated with self-reported mobility limitation (9;14), and physical performance (9;12), but this is not a consistent finding (13). There are no studies available that have explored these different indices of muscle mass and strength, with measurements of physical performance, in the same cohort.

We compared the association of different diagnostic criteria for sarcopenia (absolute and relative muscle mass, muscle strength) with physical performance, consisting of walking speed, Timed Up and Go test (TUG), and physical fitness as estimated with the Astrand fitness test in a group of young and old men and women participating in the MYOAGE study.

Methods

Study design

MYOAGE is a cross-sectional European multicenter study of young (aged 18 to

30 years) and relatively healthy old participants (aged 69 to 81 years). A detailed description of the study design has been reported elsewhere (McPhee et al., submitted). Participants were recruited by focused advertisement in newspapers, third generation university, association of emeriti and universities, hereby selecting cognitively active individuals. In total, 461 participants were included: 110 recruited in Leiden, the Netherlands, 105 in Jyvaskyla, Finland, 100 in Tartu, Estonia, 62 in Paris, France and 84 in Manchester, United Kingdom.

Exclusion criteria were aimed to ensure selection of healthy participants and minimize the confounding effect of comorbidity on sarcopenia. In short, exclusion criteria were: dependent living situation, inability to walk a distance of 250 m, presence of morbidity (neurologic disorders, metabolic diseases, rheumatic diseases, recent malignancy, heart failure, severe chronic obstructive pulmonary disease (COPD), haemocoagulative syndromes), use of medication (immunosuppressive drugs, insulin), immobilization for 1 week during the last 3 months, and orthopedic surgery during the last two years or still causing pain or functional limitation.

Measurements were performed according to unified standard operating procedures during visits to the local study centers. The local medical ethical committees of the respective institutions approved the study. Written informed consent was obtained from all participants.

Diagnostic criteria for sarcopenia

Muscle mass

A whole body scan was performed using Dual-energy X-ray absorptiometry (DXA) (Netherlands: Hologic QDR 4500, version 12.4, Hologic Inc., Bedford, USA; Finland: Lunar Prodigy, version EnCore 9.30; Estonia: Lunar Prodigy Advanced, version EnCore 10.51.006; France: Lunar Prodigy, version EnCore 12.30; United Kingdom: Lunar Prodigy Advance, version EnCore 10.50.086). Participants wore a light cotton shirt to reduce measurement errors due to clothing absorption. A trained technician performed the dual-energy X-ray absorptiometry. From the DXA, total and compartmental lean mass and fat mass were measured. Lean mass was used as an estimation of muscle mass.

To obtain relative muscle mass, lean mass percentage was calculated as lean mass divided by body mass in percentage (8), and appendicular lean mass (ALM) percentage as the sum of lean mass of both arms and legs divided by body mass in percentage (12).

To obtain absolute muscle mass, ALM/height^2 was calculated as ALM divided by height squared (1), and total lean mass was directly derived from DXA in kilograms.

Muscle strength

Isometric knee extension torque was measured with a knee extension dynamometer chair (Netherlands: Forcelink B.V., Culemborg, the Netherlands; Finland: custom made; Estonia: custom made; France: Biodex system 3 Pro isokinetic dynamometer, Biodex Medical Systems, Shirley, New York, USA; UK: custom made). The participants were positioned in an upright position, with straps to fix the hips to the chair and the ankle to a force or torque transducer at the knee angle of 90 degrees. Lever arm length was recorded as the distance between the knee axis of rotation and the centre of the force transducer located at the point of force application above the malleoli. After three warm up trials at 50 % and 90 % of self-perceived maximal strength, three trials were conducted to measure maximal voluntary contraction (MVC) force of the knee extensor muscles. For each attempt, maximal force or torque was recorded. Each trial was separated by one minute of rest. Knee extension torque was obtained either directly or by multiplying recorded peak force with the lever arm length (in m). The trial with the highest torque output was selected for analyses. Handgrip strength was measured using the Jamar handgrip dynamometer (Sammons Preston Inc, Bolingbrook, IL, USA). The width of the dynamometer was adjusted for each participant separately for optimal fit. Participants were instructed to stand upright with the dynamometer beside but not against their body. Measurements were performed three times for each side. The best of all attempts was used for further analysis.

Physical performance

Walking speed was measured as the average speed during a six-minute walking test. Participants were instructed to walk around cones placed 20 meters apart (or 25 meters in France). In Finland, Estonia, France, and UK participants were instructed to walk as fast as possible; in the Netherlands the instruction was to walk at their usual pace.

Time needed to complete the Timed Up and Go test (TUG) was measured. Participants were instructed to rise from a chair without use of arms, walk around a cone placed three meters from the chair and return to the original sitting position. Further instructions were to complete the test as quickly as possible, while taking care not to run and to remain safe. Participants were allowed three trials; the fastest attempt was used for analyses.

In the Netherlands, additional measurements included a physical fitness test, by estimating maximal oxygen uptake (VO_2 max) according to the Astrand fitness test (15). This method has been shown to be a valid test in elderly participants (aged 60 to

Table 1: Participant characteristics, stratified by age (n=461).

	Young (n=180)	Old (n=281)
Age (years)	23.4 (2.9)	74.4 (3.3)
Females, n (%)	94 (52.2)	144 (48.8)
Living with partner	40 (22.2)	148 (52.7)
Highly educated, n (%)[a]	132 (73.3)	96 (34.2)
Anthropometry		
Height (m)	1.73 (0.09)	1.67 (0.09)
Body mass (kg)	68.8 (12.3)	71.5 (12.8)
Body mass index (kg/m2)	22.8 (3.0)	25.5 (3.4)
Lifestyle		
Excessive alcohol use, n (%)[b]	44 (24.4)	36 (12.8)
Current smoking, n (%)	23 (12.8)	13 (4.6)
Comorbidities		
Number of diseases, median (IQR)	0 (0-0)	1 (0-1)
Number of medications, median (IQR)	0 (0-1)	1 (0-3)
Mental state		
MMSE score (points), median (IQR)	30 (29-30)	29 (28-30)
GDS score (points), median (IQR)	0 (0-1)	1 (0-2)
Diagnostic criteria for sarcopenia		
Lean mass percentage (%)[c]	72.9 (9.1)	67.1 (8.3)
ALM percentage (%)[d]	33.1 (4.7)	28.7 (4.1)
ALM/height^2 (kg/m^2)	7.5 (1.3)	7.2 (1.1)
Total lean mass (kg)	50.2 (11.3)	47.7 (9.9)
Knee extension torque (Nm)	197.5 (69.5)	124.3 (44.1)
Handgrip strength (kg)	42.4 (12.2)	32.9 (9.4)
Physical performance		
TUG (s)[e]	4.86 (0.91)	6.37 (1.16)
Walking speed (m/s)[f]	1.85 (0.30)	1.46 (0.22)
Physical fitness (ml/kg/min)[g]	37.9 (9.0)	25.7 (6.4)

Variables are presented as mean and standard deviation, unless indicated otherwise. [a]Data available in n=344. [b]Excessive alcohol used defined as for males > 21 units/week and females > 14 units/week. [c]Total lean mass as percentage of total body mass. [d]ALM as percentage of total body mass. [e]Data available in n= 457. [f]Data available in n=450. [g]Expressed as the estimate of maximal oxygen uptake as derived from the Astrand fitness test, data available in a subgroup of n=108. MMSE: mini mental state examination. GDS: geriatric depression scale. TUG: Timed Up and Go test. ALM: appendicular lean mass.

70 years) (16). Participants pedalled at a cadence of 60 cycles per minutes (rpm) on a cycle ergometer at a selected workload (50, 75, 100 or 150 Watt) during six minutes. The workload was selected by asking subjects about their daily activity level and training status, and by taking age and gender into account. The workload was aimed to be at the highest tolerated intensity to ensure a heart rate of 110 beats per minute (bpm) after six minutes. Heart rate was measured continuously during the test using a polar heart rate monitor (Polar RS800CX, polar pro trainer 5). After a four minute warming up at a lower workload, the six minute Astrand fitness test was performed at the selected workload. If mean steady state heart rate (submaximal heart rate) at the end of the test was over 110 bpm, the test was ended. If the submaximal heart rate was below 110 bpm, the workload was increased and the test continued for another six minutes, if tolerated by the participant (17). The Astrand nomogram was used to calculate physical fitness (ml/kg/min) from submaximal heart rate, workload, body mass and gender (15).

Participant characteristics and health status

Standing height was measured to the nearest millimeter. Information about lifestyle factors such as smoking, alcohol use, living status, and education were self-reported using a questionnaire. Excessive alcohol use was defined as more than 21 units per week for men, or more than 14 units per week for women. Diseases were registered and categorized into cardiovascular disease (including cardiovascular events, arterial surgery, and hypertension), non insulin dependent diabetes mellitus, mild COPD, thyroid disease, and osteoarthritis. The sum score of diseases was calculated. The use of medication was registered and a sum score of all oral and inhaled medication was calculated as measure of disease severity. Cognitive function was measured by use of the Mini Mental State Examination (MMSE) and depressive symptoms were measured by using the Geriatric Depression Scale (GDS).

Statistical analysis

Continuous variables with Gaussian distribution are presented as mean (standard deviation) and those with non-Gaussian distribution as median (interquartile range (IQR)).

Results from the different countries were first analyzed separately, and subsequently pooled if the effect sizes were comparable. In pooled analyses, all described diagnostic criteria for sarcopenia and physical performance parameters were standardized into country specific z-scores, to minimize possible effects due to differences in equipment and to allow comparison of effect sizes of diagnostic criteria for sarcopenia in their

association with physical performance.
Linear regression analyses were used to identify associations between diagnostic criteria for sarcopenia and physical performance, and to calculate adjusted means and standard errors of the means. Adjusted means, and standard errors of the means were calculated for sex and country specific tertiles of the muscle characteristics. Three different adjustment models were used, stratified by age category. In model 1 analyses were adjusted for age (for residual confounding for age), sex, and country. In model 2 further adjustments were made for body mass or body fat, and additionally for height in model 3. Lean mass percentage and ALM percentage were adjusted for body mass since higher body mass is associated with physical performance and with lower relative muscle mass. As relative muscle mass is not associated with height, height was not included in the adjustment model. Lean mass and ALM/height^2 were adjusted for fat mass, since these measures do not take fat mass into account. These measures were not adjusted for height as ALM/height^2 already includes height. Knee extension torque and handgrip strength were adjusted for body mass and height. Adjustment models for the association between diagnostic criteria for sarcopenia and physical fitness did not include body mass or fat mass, as the estimation of physical fitness is already adjusted for body mass.
Results of the regression analyses with standardized variables can be interpreted as follows: 1 standard deviation (SD) increase of diagnostic criteria for sarcopenia is related to the effect size (β)*SD change in physical performance.
SPSS 20 for Windows was used for all analyses. P-values < 0.05 were considered statistically significant.

Results

Participant characteristics and health status

Baseline characteristics of the study participants are shown in Table 1, stratified for age category. Overall, values for diagnostic criteria for sarcopenia and for physical performance were lower in old participants as compared to young participants.

Diagnostic criteria for sarcopenia and physical performance

Muscle mass

Table 2 shows the association between relative and absolute muscle mass and walking speed and duration of TUG. Old participants with a higher relative muscle mass (lean mass percentage and ALM percentage) had a faster walking speed and shorter duration of TUG. Additional adjustments for body mass affected the results only

Table 2: Association between diagnostic criteria for sarcopenia and performance in 6 minute walk and Timed Up and Go test.

		Walking speed (SD in m/sec)						Timed Up and Go test (SD in sec)					
		Young (n=176)			Old (n=274)			Young (n=178)			Old (n=278)		
		β	SE	p	β	SE	p	β	SE	p	β	SE	p
Relative muscle mass	Lean mass percentage (% in SD)[a]												
	Model 1: age, sex and country	0.10	0.07	0.15	0.31	0.06	**<0.001**	0.01	0.06	0.82	-0.29	0.07	**<0.001**
	Model 2: as 1 and body mass	0.16	0.09	0.06	0.36	0.09	**<0.001**	0.02	0.07	0.70	-0.25	0.10	**0.012**
	ALM percentage (% in SD)[b]												
	Model 1: age, sex and country	0.11	0.08	0.19	0.42	0.07	**<0.001**	-0.05	0.07	0.45	-0.33	0.08	**<0.001**
	Model 2: as 1 and body mass	0.14	0.09	0.12	0.45	0.08	**<0.001**	-0.06	0.08	0.44	-0.28	0.10	**0.004**
Absolute muscle mass	ALM/height² (kg/m² in SD)												
	Model 1: age, sex and country	-0.00	0.07	0.97	0.09	0.08	0.28	-0.06	0.06	0.27	-0.05	0.09	0.61
	Model 2: as 1 and fat mass	-0.02	0.07	0.77	0.21	0.08	**0.007**	-0.07	0.06	0.24	-0.17	0.09	0.06
	Total lean mass (kg in SD)												
	Model 1: age, sex and country	0.10	0.09	0.26	0.01	0.10	0.89	0.01	0.07	0.90	0.06	0.11	0.59
	Model 2: as 1 and fat mass	0.14	0.09	0.13	0.23	0.10	**0.023**	0.01	0.07	0.92	-0.15	0.11	0.18
Muscle strength	Knee extension torque (Nm in SD)												
	Model 1: age, sex and country	0.12	0.08	0.13	0.33	0.09	**0.001**	-0.08	0.06	0.18	-0.37	0.10	**0.001**
	Model 2: as 1 and body mass	0.15	0.09	0.09	0.50	0.10	**<0.001**	-0.12	0.07	0.10	-0.55	0.11	**<0.001**
	Model 3: as 2 and height	0.18	0.09	0.05	0.46	0.10	**<0.001**	-0.12	0.07	0.09	-0.54	0.11	**<0.001**
	Handgrip strength (kg in SD)												
	Model 1: age, sex and country	0.07	0.08	0.37	0.25	0.08	**0.003**	-0.08	0.06	0.18	-0.14	0.09	0.13
	Model 2: as 1 and body mass	0.08	0.08	0.36	0.39	0.09	**<0.001**	-0.11	0.07	0.12	-0.26	0.10	**0.008**
	Model 3: as 2 and height	0.05	0.09	0.57	0.34	0.09	**<0.001**	-0.11	0.07	0.12	-0.22	0.10	**0.015**

All diagnostic criteria for sarcopenia, walking speed and Timed Up and Go test were standardized into country specific z-scores. [a]Lean mass as percentage of total body mass; [b]ALM as percentage of total body mass. ALM: appendicular lean mass. All p-values are assessed with linear regression and adjustments in separate models. Bold indicates significance (p<0.05).

Table 3: Association between diagnostic criteria for sarcopenia and physical performance (physical fitness) expressed as the estimate of maximal oxygen uptake as derived from the Astrand fitness test.

		Physical fitness (ml/kg/min)[a]					
		Young (n=34)			Old (n=74)		
		β	SE	p	β	SE	p
Relative muscle mass	Lean mass (% in SD)[b]						
	Model 1: age, sex	0.91	0.19	<0.001	0.59	0.11	<0.001
	ALM (% in SD)c						
	Model 1: age, sex	1.00	0.25	<0.001	0.57	0.11	<0.001
Absolute muscle mass	ALM/height² (kg/m² in SD)						
	Model 1: age, sex	-0.10	0.21	0.64	-0.05	0.11	0.65
	Total lean mass (kg in SD)						
	Model 1: age, sex	-0.10	0.29	0.74	-0.25	0.14	0.09
Muscle strength	Knee extension torque (Nm in SD)						
	Model 1: age, sex	-0.10	0.32	0.76	0.07	0.16	0.65
	Model 2: as 1 and height	-0.09	0.34	0.80	0.07	0.16	0.65
	Handgrip strength (kg in SD)						
	Model 1: age, sex	0.03	0.24	0.90	-0.09	0.13	0.48
	Model 2: as 1 and height	0.04	0.25	0.88	-0.07	0.13	0.57

All diagnostic criteria for sarcopenia and physical fitness were standardized into z-scores. [a]Expressed as the estimate of maximal oxygen uptake as derived from the Astrand fitness test; [b]Lean mass as percentage of total body mass; [c]ALM as percentage of total body mass. ALM: appendicular lean mass. All p-values are assessed with linear regression and adjustments in separate models. Bold indicates significance (p<0.05).

slightly. There were no associations between absolute muscle mass (ALM/height^2 and total lean mass) and walking speed or TUG. Only when additional adjustment for fat mass was applied, ALM/height^2 and lean mass were associated with faster walking speed, but not with TUG. There were no associations between relative or absolute muscle mass and walking speed or TUG in young participants. Results did not change after excluding participants from the Netherlands who were instructed to walk at their usual pace during the 6 minute walking test.

Table 3 shows the association between relative and absolute muscle mass and physical fitness. Relative muscle mass was positively associated with physical fitness in young and old participants. Absolute muscle mass was not associated with physical fitness.

Muscle strength

Table 2 shows the association of muscle strength with walking speed and TUG.

Old participants with higher knee extension torque had a faster walking speed and shorter duration of TUG. After additional adjustments for body mass and height, the associations remained significant. Old participants with higher handgrip strength had a faster walking speed in all adjusted models. Higher handgrip strength was only associated with TUG after adjustment for body mass. There were no associations between knee extension torque or handgrip strength and walking speed or TUG in young participants.

As shown in Table 3, no associations between knee extension torque or handgrip

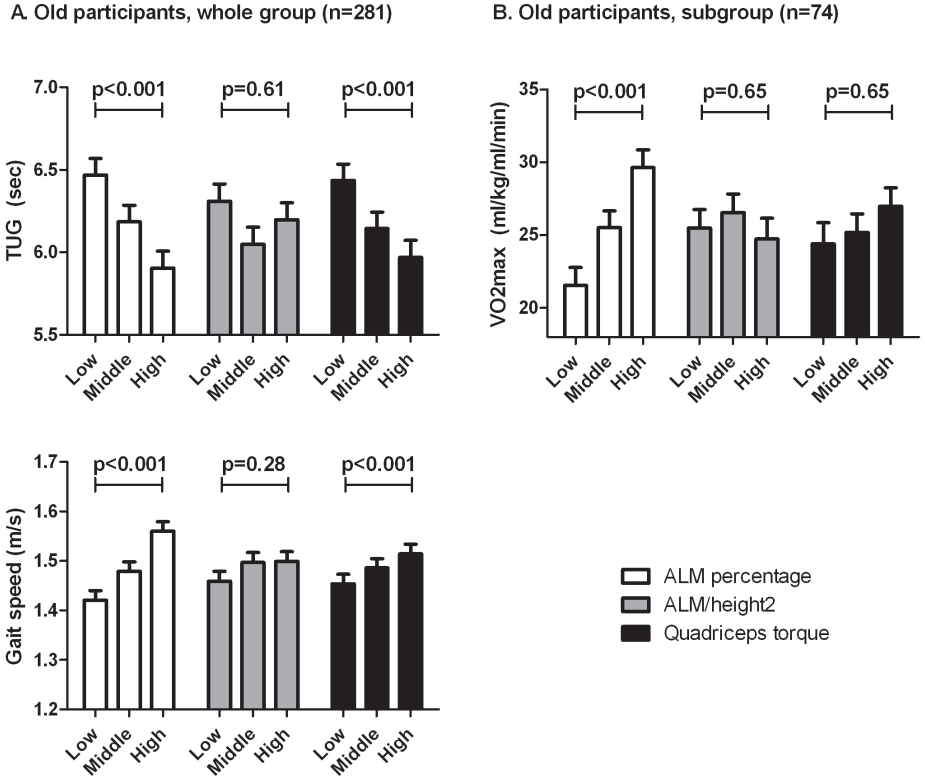

Figure: *Representation of the association between sex and country specific tertiles of different diagnostic criteria for sarcopenia and physical performance in old participants. Physical performance in A: Timed Up and Go test (TUG) and walking speed derived from 6 minutes walking test; in B: Physical fitness expressed as the estimate of maximal oxygen uptake as derived from Astrand fitness test. Muscle characteristics are ALM as percentage of body mass, ALM divided by height squared (ALM/height2) and knee extension torque. Bars indicate adjusted means and standard errors. All p-values are assessed with linear regression analyses including adjustments for gender and age (and country in A). ALM: appendicular lean mass.*

strength and physical fitness in young and old participants were found.

Comparison of diagnostic criteria for sarcopenia
To determine the strongest association of different diagnostic criteria for sarcopenia with physical performance, effect sizes (β) for these associations given in Table 2 and Table 3 were compared. In Table 2 including all participants, effect sizes (β) were strongest for relative muscle mass and muscle strength in the association with walking speed and TUG in old participants. In Table 3 including a subgroup of participants, effect sizes (β) were strongest for relative muscle mass in the association with physical fitness in young and old participants .
Figure 1 visualizes the association between tertiles of diagnostic criteria for sarcopenia and physical performance in old participants. Relative muscle mass is represented by ALM percentage, absolute muscle mass by ALM/height^2 and muscle strength by knee extension torque. Relative muscle mass was the only diagnostic criterion for sarcopenia associated with all tested parameters of physical performance: walking speed, TUG, and physical fitness.

Discussion

In this cross-sectional study, relative muscle mass expressed as lean mass percentage or ALM percentage was most associated with physical performance in old participants. Absolute muscle mass, expressed as ALM/height^2 and total lean mass, was only associated with TUG after adjustment for fat mass, and not associated with walking speed and physical fitness. This indicates that diagnostic criteria for sarcopenia based on unadjusted ALM/height^2 are not useful to predict physical performance. Greater muscle strength was associated with faster TUG and faster walking speed, but not with physical fitness. In young participants, diagnostic criteria for sarcopenia were not associated with TUG or walking speed, but there was a positive association between relative muscle mass and physical fitness.
Relative muscle mass expressed as ALM percentage or lean mass percentage was also a predictor for physical performance in other studies (8-10;12). Although the formula ALM/height^2 proposed by Baumgartner et al. (1) is the most commonly used diagnostic criterion for sarcopenia, we found no association between ALM/height^2 and physical performance without adjusting for fat mass. Studies reporting significant associations between ALM/height^2 and physical performance included adjustment models for fat percentage (1) or fat mass (10), which is in line with the present study, although we assessed ALM/height^2 on a continuous scale. Without

adjustments for fat mass, absence of an association between ALM/height^2 and physical performance or self-reported physical limitation is confirmed by other studies (11-13;18-20). In addition, no association was observed between total lean mass in kilograms and self-reported mobility limitation (14).

Differences between relative and absolute muscle mass can be explained by the role of fat mass. Most obese people have an increased muscle mass in addition to high fat mass, but may still have a low muscle mass relative to their body mass. Underweight elderly participants may have a high proportion of muscle mass in relation to their total body mass (9;21). With increasing chronological age, significant changes in body composition occur, including a decrease in bone and muscle mass and an increase in the proportion of fat mass, even when the body mass remains the same (19;22). The formula ALM/height^2 underestimates sarcopenia in obese elderly and overestimates sarcopenia in underweight elderly participants (19;21;23). Therefore, it is important to take muscle mass relative to body mass or fat mass into account when defining sarcopenia (18;21;24).

In this study, muscle strength, in particular knee extension torque, was associated with the TUG test and walking speed in old participants, but not with physical fitness. Muscle strength has been associated with self-reported mobility limitation or physical performance (9;12;14;25), but not in all studies (13). Recently it has been advocated to use an index of muscle strength relative to body mass, which appeared to be strongly related to physical performance (25). It has been suggested that muscle strength in the elderly is associated with physical performance rather than muscle mass (25-27). However, in these studies, muscle mass was not adjusted for fat mass or body mass, indicating possible misclassification of low muscle mass (23). The loss of muscle mass is closely related to the loss of muscle strength, although not at the same rate (26). Using muscle strength to define sarcopenia has several limitations. To generate strength, other factors such as cardiovascular function, joint function and neural control are involved (28-30). Furthermore, muscle strength can be underestimated due to pain (4;23).

In young participants, no association was found for diagnostic criteria for saropenia with TUG and walking speed. However, relative muscle mass was associated with physical fitness. This may be explained by the degree of challenge of these tests. For young participants, the TUG and the six minute walking tests were submaximal and did not require the full recruitment of muscle mass and strength. The differences between young participants in these tests may arise from differences in motivation, stride length and cardiorespiratory fitness. The Astrand fitness test is an individual challenging test. Under these circumstances even in young participants there are

differences in physical fitness which may be explained by their relative muscle mass. It should be noted that the Astrand nomogram already takes body mass into account to estimate oxygen uptake per kg body mass (but not muscle mass).
The strength of this study was the comparison of the associations of relative muscle mass, absolute muscle mass, and muscle strength with physical performance, both in young and old participants. The inclusion of a large group of cognitively active and healthy participants across Europe minimizes the influence of diseases and cognitive impairment, although results cannot be generalized for the entire elderly population. Even though old participants were healthy and not likely to suffer from sarcopenia, age differences between young and old participants on diagnostic criteria for sarcopenia were clearly present. Results were analyzed using continuous data rather than dichotomizing on cut-off values. Therefore we cannot conclude on the use of cut-off values in sarcopenia. A weakness of this study is the cross-sectional design, which makes causal inference impossible .
In conclusion, when comparing different diagnostic criteria for sarcopenia, relative muscle mass was associated most consistently with physical performance, while ALM/height^2 was only associated with physical performance after adjustments for fat mass were applied. This understanding is essential for the medical and scientific community to develop clinically applicable diagnostic criteria for sarcopenia.

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Chapter 6

Diagnostic criteria for sarcopenia relate differently to insulin resistance

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Abstract

Skeletal muscle is important in insulin-stimulated glucose uptake. Sarcopenia is therefore a possible risk factor for insulin resistance. Currently, different diagnostic criteria for sarcopenia include low muscle mass, muscle strength, and walking speed. We assessed these muscle characteristics in relation to insulin resistance in non-diabetics. This cross-sectional study included 301 non-diabetics, mean age 65.9 years. Area under curve (AUC) calculations of insulin and glucose from a 2-hours oral glucose tolerance test and homeostasis model assessment of insulin resistance (HOMA-IR) were used as measures of insulin resistance. Muscle characteristics were relative muscle mass (total or appendicular lean mass (ALM) as percentage of body mass), absolute muscle mass (ALM/height^2 and total lean mass), handgrip strength, and walking speed. All muscle characteristics were standardized and analyzed in linear regression models, stratified by gender. For both males and females, relative muscle mass was inversely associated with AUC insulin, AUC glucose, and HOMA-IR (ALM percentage all $p \leq 0.004$). Absolute muscle mass was positively associated with AUC insulin and HOMA-IR (ALM/height^2 all $p < 0.001$), but not with AUC glucose. Adjustments for fat mass attenuated aforementioned associations. There were no associations between handgrip strength and insulin resistance. Walking speed was inversely associated with AUC insulin in males ($p = 0.032$). The association between muscle characteristics and insulin resistance was strongest for relative muscle mass. Diagnostic criteria for sarcopenia relate differently to insulin resistance. The role of muscle tissue as an internal glucose regulating organ is better reflected by relative muscle mass than by absolute muscle mass, muscle strength or walking speed.

Introduction

The term sarcopenia was introduced as a term to describe low muscle mass at older age (1;2), but has also been used to describe low muscle strength (3) or a low walking speed or muscle strength combined with low muscle mass (4;5). Although the clinical importance of low muscle mass is underscored by its associated increased risk of mortality (6), physical disability (2;7), and cognitive decline (8), no consensus on the definition of sarcopenia has been reached yet (4;5). Various quantification methods of muscle characteristics and correction factors have been proposed (2;3;7;9;10), which are mainly based on associations with disability in elders.

Little attention has been paid so far to the role of various diagnostic criteria for sarcopenia in the association with insulin resistance. Insulin resistance has mainly been associated with higher body mass index (BMI)(11;12) and higher (visceral) fat percentage (13). Since skeletal muscle is accounting for approximately 75% of whole-body insulin-stimulated glucose uptake (14), it is important to understand which diagnostic criteria for sarcopenia relate to glucose handling expressed as insulin resistance. Only few studies have investigated this association, with conflicting results. It was shown that a lower lean mass as percentage of body mass associated with insulin resistance (15). Other cross-sectional studies showed an association between a higher total lean mass (16) or quadriceps mass with insulin resistance, not taking possible confounders into account (17). After adjustment for weight or BMI, higher quadriceps mass and higher muscle strength were associated with a lower level of insulin resistance (17-19). These results indicate that important differences exist depending on which diagnostic criteria for sarcopenia are used, which is further complicated by the use of different adjustment models.

We hypothesized that a higher amount of muscle mass will generate a higher capacity for insulin-stimulated glucose uptake and will therefore be associated with a lower level of insulin resistance. We expect that this association is influenced by fat mass, which is positively associated with insulin resistance (20). Since there is little overlap in the prevalence of sarcopenia when different definitions are applied in the same study population (21), we expect that not all diagnostic criteria for sarcopenia are suitable to reflect muscle tissue as an internal glucose regulating organ. We expect that muscle mass will show a stronger association with insulin resistance than muscle strength and walking speed. To test these hypotheses, we examined the association between different diagnostic criteria for sarcopenia and valid measures of insulin resistance derived from an oral glucose tolerance test (OGTT) (22) in non-diabetic middle aged and older adults stratified by sex.

Methods

Study design

Analyses were performed on a total of 301 middle aged and older adults including participants of the MYOAGE study and the Leiden Longevity Study (LLS).

The MYOAGE study comprises 35 young (aged 18 to 30 years) and 75 relatively healthy and cognitively active older participants (aged 69 to 81 years), recruited in 2010 and 2011 in Leiden, the Netherlands, as part of a European cohort study. The group of elderly participants was recruited based on their activity levels (high or relatively low). Application of exclusion criteria was aimed to select healthy participants, minimizing the confounding effect of disease on muscle mass, i.e. dependent living situation, unable to walk a distance of 250 m, presence of comorbidity (neurologic disorders; metabolic diseases; rheumatic diseases; recent malignancy; heart failure; severe chronic obstructive pulmonary disease (COPD); haemocoagulative syndromes), use of specified medication (immunosuppressive drugs, insulin, anticoagulation), immobilization for one week during the last three months, and orthopedic surgery during the last two years or still causing pain or functional limitation. For the present analyses, only the subgroup of older adults was selected; four participants were excluded due to previous history of diabetes mellitus, and one participant due to missing data on body composition, and the remaining 70 participants were included for analyses.

The LLS consists of long-living Caucasian siblings of 420 families together with their middle aged offspring, and the partners of the offspring as controls (23). The study included 674 participants of the middle aged to older offspring and their partners, who were assessed in the period from 2006 to 2008 (23). There were no selection criteria on health or demographic characteristics (24). A subgroup of 380 middle-aged participants living in close proximity to the research center were invited to come to the research center in a fasting state; 274 of these participants agreed to participate. For the present analysis, 24 participants were excluded because of previous history of diabetes mellitus, 15 because of unreliable OGTT, one because of nonadherence to the fasting state, and three were excluded due to missing data on body composition (25), and the remaining 231 were included for analyses.

The Medical Ethics Committee of the Leiden University Medical Centre approved both studies, and written informed consent was obtained from all participants.

Oral glucose tolerance test

After 12 hours of fasting, glucose tolerance as a measure of insulin resistance was

assessed according to 2-hours OGTT, conducted with a standard loading dose of 75 g of glucose in 0.3 L of water. Venous blood samples were drawn at time points 0, 30, 60 and 120 minutes in both studies, and additionally at 15 and 90 minutes in the MYOAGE study cohort. All serum measurements were performed using fully automated equipment. For insulin levels, the Immulite 2,500 from DPC (Los Angeles, CA) and for glucose, the Hitachi Modular P800 from Roche (Almere, The Netherlands) was used.

Assessment of body composition

In the MYOAGE study, body composition was measured by Dual-energy X-ray absorptiometry (DXA) (Hologic QDR 4500, Hologic Inc., Bedford, USA). Measurements were performed with dual-energy X-ray beams at 60 and 140 KeV, operated by a trained technologist. Single rectilinear scanning mode was used on a 148 x 330 pixel matrix in a 196 x 80 cm window. Standard regions were drawn and adapted manually when necessary.

In the LLS, body composition was measured using Direct Segmental Multi-frequency Bioelectrical Impedance Analysis (BIA) (In-Body (720) body composition analyzer, Biospace Co., Ltd, Seoul, Korea). We have previously shown this technique to be a valid tool for the assessment of whole body composition and segmental lean mass measurements in our sample of middle aged people (26). Excellent agreements were observed between BIA and DXA in total lean mass (intraclass correlation coefficient (ICC) female=0.95, $p<0.001$, ICC male=0.96, $p<0.001$) and fat mass (ICC female 0.97 $p<0.001$, ICC male 0.93 $p<0.001$) (26).

Diagnostic criteria for sarcopenia

As described previously, muscle mass was grouped into relative and absolute measures (27). Relative muscle mass corrects muscle mass for body mass and was defined as lean mass divided by body mass in percentage,(7) or appendicular lean mass (ALM, the sum of lean mass of both arms and legs) divided by body mass in percentage (27). Absolute muscle mass was defined as ALM divided by height squared ($ALM/height^2$) (2), or total lean mass in kilograms (28).

Handgrip strength was measured with a Jamar dynamometer (Sammons Preston Inc, Bolingbrook, IL). All participants were asked to stand upright and hold the dynamometer in the hand with the arm parallel to the body without squeezing the arm against the body. The width of the handle was adjusted to the size of the hand. The participant was allowed to perform three trials with both the right and the left hand and the best score was used for analyses.

Walking speed was measured during a 4 meter walking test from a standing start. Participants were instructed to walk at normal pace to the end of the corridor to prevent slowing down before the 4 meter line (29). Duration of the 4 meter walking test was recorded using a sensor unit containing accelerometers and gyroscopes (DynaPort Hybrid, McRoberts, The Netherlands), attached with a waist strap.

Participant characteristics

Height and body mass were collected for all participants. Comorbidity was defined as a sum score of diseases including myocardial infarction, stroke, hypertension, arthritis, chronic obstructive pulmonary disease, and malignancy. Smoking was defined as current smoking or past smoking with more than ten pack years. The presence of sarcopenia was assessed according to cut-off values for ALM/height^2 (for males below 7.26 kg/m^2 and for females below 5.5 kg/m^2 (2)), and with a walking speed below 0.8 m/sec, or grip strength below cut-off (30 kg for males and 20 kg for females) (4).

Statistical analyses

Continuous variables with Gaussian distribution are presented as mean (standard deviation) and those with non-Gaussian distribution as median (interquartile range (IQR)). Variables with non-Gaussian distribution were logarithmically transformed and used in all calculations. OGTT derived area under the curves (AUCs) were calculated using the trapezoid rule (22); the homeostasis model assessment for insulin resistance (HOMA-IR) was calculated by dividing the product of fasting glucose level (in millimol per L) and fasting insulin level (in milliunit per liter) by 22.5 (30).

All muscle characteristics were standardized in Z scores in order to compare effect estimates. The associations between muscle characteristics and insulin resistance were assessed using linear regression models, stratified by sex. In the first model, analysis was adjusted for age, gender and cohort. In the second model, further adjustments for fat mass were applied. For combined analyses of males and females, sex-specific tertiles of ALM percentage and ALM/height^2 were calculated. In this combined analyses, regression analyses were adjusted for age, cohort, and sex. Differences between muscle characteristics for the association with OGTT derived measures of insulin resistance were tested for significance, without taking covariance into account, using Z values calculated with the formula $((b1 - b2)/\sqrt{(se^2+se^2)})$ and p values derived from the standard normal distribution table. SPSS 17.0 for Windows was used for all analyses. P-values <0.05 were considered statistically significant.

Table 1: Characteristics of study participants.

	Male (N=146)	Female (N=155)
Age (y)	67.4 (7.1)	64.4 (7.7)
Females, n (%)		
Height (m)	1.78 (0.06)	1.66 (0.06)
Total body mass (kg)	83.9 (11.2)	71.9 (11.2)
BMI (kg/m2)	26.4 (3.3)	26.0 (4.1)
Total number of diseases, median, (IQR)[a]	0 (0-1)	0 (0-1)
Smoking, n (%)[b]	95 (66.0)	67 (43.2)
Diagnostic criteria for sarcopenia		
Lean mass percentage (%)[c]	71.5 (6.6)	62.0 (7.2)
ALM percentage (%)[d]	31.8 (3.1)	26.9 (3.0)
ALM/height^2 (kg/m^2)[e]	8.3 (0.7)	6.9 (0.7)
Total lean mass (kg)	59.6 (6.7)	44.1 (4.9)
Handgrip strength (kg)	43.8 (7.9)	28.8 (5.0)
Walking speed (m/s)[f]	1.1 (0.2)	1.2 (0.2)
OGTT derived measures of insulin resistance		
Fasting glucose (mmol/L)	5.2 (0.6)	5.1 (0.5)
Fasting insulin, median, (IQR) (mU/L)	6.0 (4-10)	6.0 (3-9)
AUC insulin (median, IQR)	93.7 (62.2-139.0)	89.1 (65.8-139.3)
AUC glucose	14.6 (3.6)	14.3 (3.7)
HOMA-IR, median (IQR)	1.48 (0.81-2.22)	1.20 (0.65-2.10)

All values are expressed as mean (standard deviation), unless indicated otherwise. [a]Sum score of total number of diseases (myocardial infarction, stroke, hypertension, arthritis, chronic obstructive pulmonary disease, malignancy). [b]Smoking was defined as current smoking or more than 10 pack years. [c]Lean mass as percentage of total body mass. [d]ALM as percentage of total body mass. [e]ALM divided by squared height. [f]Data available in a subgroup of N=159. BMI=body mass index; IQR=interquartile range; ALM=appendicular lean mass; OGTT=oral glucose tolerance test; AUC= area under curve measured during 120 minutes oral glucose tolerance test.

Results

Characteristics of the study participants are shown in table 1. The mean age of participants of the MYOAGE study was 74.1 years and 63.3 years of the LLS. Equal numbers of males and females were included in both cohorts. According to cut-off values for sarcopenia, 16 (5.3%) participants had low ALM/height^2, of which 4 (1.7%) participants simultaneously had a low walking speed or grip strength.

Table 2 shows the results of the association between different standardized diagnostic criteria for sarcopenia and OGTT derived measures of insulin resistance. Overall,

associations were comparable in males and in females. Relative muscle mass, expressed as lean mass percentage and ALM percentage, was inversely associated with ln AUC insulin, AUC glucose, and ln HOMA-IR when adjusting for age and cohort (table 2). When adjusting for fat mass, the statistically significant inverse associations attenuated. Absolute muscle mass, expressed as ALM/height^2 and total lean mass, was positively associated with AUC insulin and HOMA-IR, but not with AUC for glucose (table 2). When adjusting for fat mass, the positive associations with ln AUC insulin disappeared. The positive association between absolute muscle mass and ln HOMA-IR also disappeared in females after adjustments for fat mass, but remained statistically significant in males. There was no association between handgrip strength and the AUC for insulin, glucose and HOMA-IR in both models. In females, walking speed was not associated with the AUC for insulin, glucose and HOMA-IR. In males, walking speed was inversely associated with ln AUC insulin, but not with AUC glucose or ln HOMA-IR.

Relative muscle mass expressed as lean mass percentage and ALM percentage was most strongly inversely associated with AUC insulin, AUC glucose, and HOMA-IR. When comparing the effect estimates of lean mass percentage and ALM percentage given in table 2 (model 1), these were not statistically significantly different in their association with insulin resistance. In contrast, the effect estimates of lean mass percentage and ALM percentage were significantly different from the effect estimates of absolute muscle mass (ALM/height^2 and total lean mass)(all $p<0.001$). Walking speed was inversely associated with AUC insulin in males, but with a lower effect estimate as compared to relative muscle mass ($p<0.001$).

Combined analyses for males and females are presented in figure 1. This figure visualizes the inverse association for relative muscle mass, and the positive association for absolute muscle mass with OGTT derived measures for insulin resistance.

Discussion

In middle aged and older non-diabetic adults diagnostic criteria for sarcopenia relate differently to insulin resistance. Relative muscle mass, expressed as lean mass percentage and ALM percentage, was inversely associated with OGTT derived measures of insulin resistance. After adjustment for fat mass this association attenuated. Absolute muscle mass, expressed as ALM/height^2 and total lean mass, was positively associated with AUC insulin and HOMA-IR, and not associated with AUC glucose. After adjustment for fat mass, the association attenuated but remained significant for HOMA-IR in males. Handgrip strength was not associated with

Table 2: Association between measures of insulin resistance and standardized diagnostic criteria for sarcopenia (n=301).

		OGTT derived measures for insulin resistance							
		Adjusted for age, cohort				Further adjusted for fat mass			
		Male		Female		Male		Female	
		Beta (95% CI)	P	Beta (95% CI)	P	Beta (95% CI)	P	Beta (95% CI)	P
Ln Insulin AUC	Z Total lean mass (%)[a]	-0.56 (-0.70, -0.43)	**<0.001**	-0.29 (-0.39, -0.19)	**<0.001**	-0.33 (-0.68, 0.02)	0.067	-0.16 (-0.41, 0.09)	0.20
	Z ALM (%)[b]	-0.47 (-0.60, -0.34)	**<0.001**	-0.30 (-0.41, -0.19)	**<0.001**	-0.18 (-0.38, 0.02)	0.071	-0.15 (-0.32, 0.33)	0.11
	Z ALM/height2 (kg/m2)	0.16 (0.02, 0.30)	**0.026**	0.19 (0.07, 0.32)	**0.003**	-0.05 (-0.17, -0.08)	0.48	0.01 (-0.14, 0.15)	0.96
	Z Lean mass (kg)	0.14 (-0.01, 0.30)	0.07	0.15 (-0.03, 0.33)	0.095	-0.04 (-0.18, 0.10)	0.58	-0.03 (-0.20, 0.15)	0.77
	Z Handgrip strength (kg)	0.04 (-0.11, 0.19)	0.64	-0.06 (-0.24, 0.12)	0.52	0.02 (-0.11, 0.14)	0.76	-0.07 (-0.23, 0.10)	0.41
	Z Walking speed (m/s)[c]	-0.15 (-0.28, -0.13)	**0.032**	0.02 (-0.10, 0.14)	0.75	-0.12 (-0.23, -0.01)	**0.039**	0.03 (-0.08, 0.14)	0.57
Glucose AUC	Z Total lean mass (%)[a]	-0.81 (-1.68, 0.07)	0.069	-1.32 (-1.99, -0.65)	**<0.001**	-0.74 (-3.04, 1.57)	0.53	-0.89 (-2.51, 0.73)	0.28
	Z ALM (%)[b]	-1.17 (-2.0, -0.39)	**0.004**	-1.51 (-2.23, -0.80)	**<0.001**	-1.63 (-2.89, -0.36)	**0.012**	-1.12 (-2.28, 0.05)	0.060
	Z ALM/height2 (kg/m2)	0.10 (-0.66, 0.86)	0.79	0.78 (-0.03, 1.59)	0.059	-0.20 (-1.03, 0.63)	0.63	-0.08 (-1.03, 0.87)	0.89
	Z Lean mass (kg)	0.18 (-0.67, 1.03)	0.68	0.46 (-0.66, 1.58)	0.42	-0.07 (-0.97, 0.82)	0.87	-0.36 (-1.52, 0.80)	0.54
	Z Handgrip strength (kg)	0.34 (-0.47, 1.15)	0.40	-0.25 (-1.37, 0.87)	0.66	0.32 (-0.48, 1.12)	0.43	-0.29 (-1.37, 0.78)	0.59
	Z Walking speed (m/s)[c]	-0.50 (-1.32, 0.33)	0.23	-0.34 (-1.13, 0.45)	0.40	-0.46 (-1.29, 0.37)	0.27	-0.29 (-1.07, 0.48)	0.45
Ln HOMA-IR	Z Total lean mass (%)[a]	-0.58 (-0.76, -0.40)	**<0.001**	-0.42 (-0.56, -0.27)	**<0.001**	0.08 (-0.39, 0.54)	0.74	-0.02 (-0.37, 0.33)	0.93
	Z ALM (%)[b]	-0.45 (-0.62, -0.27)	**<0.001**	-0.37 (-0.53, -0.20)	**<0.001**	0.04 (-0.22, 0.30)	0.76	0.06 (-0.20, 0.31)	0.65
	Z ALM/height2 (kg/m2)	0.38 (0.21, 0.54)	**<0.001**	0.43 (0.25, 0.60)	**<0.001**	0.18 (0.02, 0.34)	**0.030**	0.19 (-0.01, 0.39)	0.07
	Z Lean mass (kg)	0.37 (0.18, 0.56)	**<0.001**	0.44 (0.19, 0.69)	**0.001**	0.19 (0.01, 0.36)	**0.040**	0.20 (-0.05, 0.44)	0.12
	Z Handgrip strength (kg)	0.16 (-0.03, 0.34)	0.10	-0.11 (0.37, 0.15)	0.40	0.14 (-0.02, 0.30)	0.09	-0.13 (-0.35, 0.11)	0.28
	Z Walking speed (m/s)[c]	-0.08 (-0.27, 0.12)	0.43	-0.09 (-0.19, 0.18)	0.93	-0.04 (-0.21, 0.13)	0.63	0.01 (-0.15, 0.18)	0.89

All muscle characteristics included in diagnostic criteria for sarcopenia were standardized and are presented in Z scores. Beta indicates the change in OGTT derived measure for insulin resistance with 1 SD increase of muscle characteristics. [a]Lean mass as a percentage of total body mass. [b]ALM as percentage of total body mass. [c]Data of walking speed only available in a subgroup of N=159. OGTT=oral glucose tolerance test; CI= confidence interval; ALM=appendicular lean mass; AUC=area under curve measured during 120 minutes oral glucose tolerance test; HOMA-IR= homeostasis model assessment for insulin resistance.

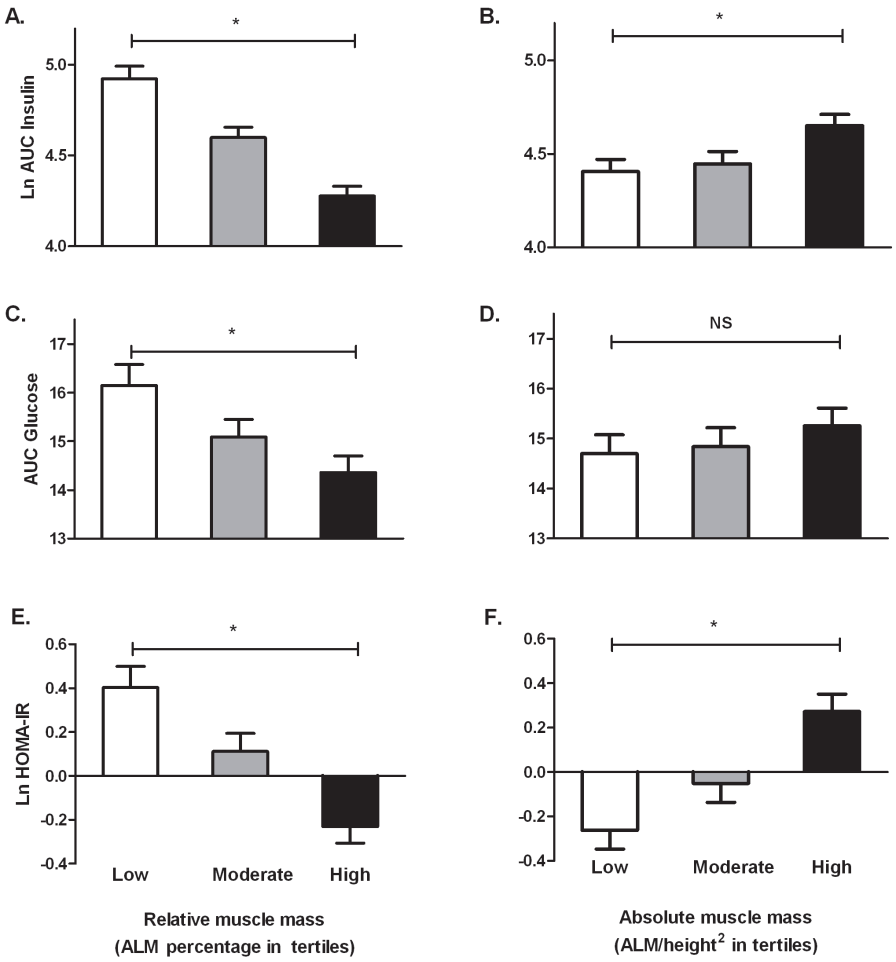

Figure 1: *Sex-specific tertiles of the relative muscle mass ALM percentage (A, C, E) and absolute muscle mass ALM/height2 (B, D, F) in relation to OGTT derived measures of insulin resistance. OGTT derived measures of insulin resistance: ln AUC insulin (A, B), AUC glucose (C,D), and ln HOMA-IR (E,F). Appendicular lean mass (ALM) percentage=ALM as percentage of total body mass; ALM/height2=ALM divided by squared height; OGTT=oral glucose tolerance test; AUC=area under curve measured during 120 minutes oral glucose tolerance test; HOMA-IR=Homeostasis model assessment for insulin resistance calculated as dividing the product of fasting glucose and insulin by 22.5. P for trend from linear regression analysis adjusted for cohort, gender, age. Bars indicate adjusted means and standard error. NS=not significant; *= P<0.001.*

OGTT derived measures of insulin resistance. Walking speed was only associated with AUC insulin in males, and with a lower effect estimate as compared to relative muscle mass. To the best of our knowledge, this is the first study comparing different muscle characteristics included in diagnostic criteria for sarcopenia in the context of insulin resistance. We conclude that diagnostic criteria for sarcopenia cannot be used interchangeably. Relative muscle mass is the best predictor of insulin resistance in middle aged to older non-diabetic participants, which strengthens the case to define sarcopenia using relative muscle mass.

This study clearly shows that relative muscle mass is strongly related to OGTT derived measures of insulin resistance. The results are in accordance with previous studies. An inverse association was observed between relative muscle mass and insulin resistance as measured with HOMA-IR (15). Midthigh cross-sectional area as measured with computed tomography (CT), standardized for body mass was inversely associated with insulin resistance in older non-diabetic adults (31). Contrarily, absolute muscle mass, unadjusted for body mass, has been found to be associated with higher insulin resistance in cross-sectional analyses (16;17;32).

In recent years some researchers preferred to define sarcopenia based on low walking speed or low muscle strength combined with low muscle mass, instead of muscle mass only (4;5). In this study we show that the role of muscle tissue as an internal glucose regulating organ is better reflected by muscle mass than by muscle strength or walking speed. This can be explained by involvement of other systems besides muscle mass in the generation of strength, such as neural control and joint function. Previous studies in older non-diabetic adults reporting on the association between muscle strength or walking speed and insulin resistance show conflicting results (17-19;33). In older adults, weight or BMI adjusted handgrip strength was inversely associated with insulin resistance (18;19). Barzilay et al. showed a trend towards a positive association between unadjusted quadriceps strength and HOMA-IR, but an inverse association with quadriceps strength divided by quadriceps mass (17). In the NHANES study no association was found between peak leg strength and HOMA-IR in men and women aged over 50 years, but there was an inverse association between insulin resistance and walking speed in men only (33). Comparing these studies is difficult since a variety of adjustment models and statistical methods were used.

The positive association between absolute muscle mass with insulin resistance can be explained by the effect of fat mass, since this association attenuated after adjustment for fat mass in this study. Adjusting muscle mass for height only, as was first suggested by Baumgartner (2), seems to be insufficient to account for the influence of fat mass. A higher lean mass at older age is often accompanied by a higher fat mass (10;27).

Fat mass is an inducer of insulin resistance by secretion of adipokines, inflammatory mediators, and growth factors, although some adipokines are associated with lower insulin resistance such as adiponectin. Tumor necrosis factor-α (TNF-α), adiponectin, and leptin are the main adipokines that appear to be involved in the cross-talk between fat mass and skeletal muscle mass (20). The secretion of inflammatory cytokines could also lead to a reduction in muscle mass, as in longitudinal studies TNF- α, interleukin-6, and C-reactive protein have been associated with loss of muscle mass (34;35). Future research is needed to further explore causal mechanisms. Another example of the interaction between muscle and fat, is that increased deposition of lipids in the myotubes leads to muscle lipoprotein lipase overexpression, which in turn is associated with insulin resistance (14). Furthermore, reduced mitochondrial function in aged muscle is associated with insulin resistance which may impair the stimulating action of insulin on mitochondrial protein synthesis and function. Through these closed loops, insulin resistance can increase the rate of loss of skeletal muscle mass and vice versa (16;32;36).

The strength of this study was the ability to compare different measures of muscle mass or muscle function in the association with insulin resistance. Furthermore, the use of OGTT is a more sensitive test for skeletal muscle insulin resistance than fasting estimates of insulin resistance such as HOMA-IR as was reported in previous studies (37;38). Fasting indices for insulin resistance such as the HOMA-IR primarily reflect hepatic insulin resistance (37;38). A clamp study would be the gold standard to differentiate between muscle insulin resistance and hepatic insulin resistance. The limitation of this study was that only cross-sectional data were available, which makes causal inference difficult. Study sample size was relatively small although this did not prevent meaningful results. Furthermore, we cannot generalize the results to older frail participants, as the study population consisted of relatively healthy middle aged and older participants.

In conclusion, diagnostic criteria for sarcopenia relate differently to insulin resistance. Lower relative muscle mass is most strongly associated with insulin resistance. ALM/height^2, the parameter most often used in literature to define sarcopenia, does not correct for body fat and is therefore an inadequate reflection of the association between muscle mass and insulin resistance. Handgrip strength and walking speed are not reflecting the role of muscle tissue as an internal glucose regulating organ. The definition of sarcopenia should include relative muscle mass hereby intrinsically adjusting for fat mass, to reflect its function as an internal organ. In future studies, assessment of relative muscle mass in larger study cohorts including the general population, could be of additional value to decide on cut-off values for a low relative

muscle mass as predictor of insulin resistance.

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Chapter 7

Diagnostic measures for sarcopenia and bone mineral density

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Abstract

Purpose: Diagnostic measures for sarcopenia utilize different measures of muscle mass, muscle strength, and physical performance. To understand differences between these measures, we determined the association with respect to whole body bone mineral density (BMD), as an example of muscle related clinical outcome.
Methods: In the European cross-sectional study MYOAGE, 178 young (18-30 years) and 274 healthy old participants (69-81 years) were recruited. Body composition and BMD were evaluated using dual-energy X-ray densitometry. Diagnostic measures for sarcopenia were composed of lean mass as percentage of body mass, appendicular lean mass (ALM) as percentage of body mass, ALM divided by height squared (ALM/height^2), knee extension torque, grip strength, walking speed, and Timed Up and Go test (TUG). Linear regression models were stratified for sex and age and adjusted for age and country, and body composition in separate models.
Results: Lean mass and ALM/height^2 were positively associated with BMD ($P<0.001$). Significance remained in all sex and age subgroups after further adjustment for fat mass except in old women. Lean mass percentage and ALM percentage were inversely associated with BMD in old women ($P<0.001$). These inverse associations disappeared after adjustment for body mass. Knee extension torque and handgrip strength were positively associated with BMD in all subgroups ($P<0.01$) except in old women. Walking speed and TUG were not related to BMD.
Conclusions: The associations between diagnostic measures of sarcopenia and BMD as an example of muscle related outcome vary widely. Differences between diagnostic measures should be taken into account when studying sarcopenia.

Introduction

Annual loss of muscle mass has been reported to be 1 to 2 percent per year after the age of 50 years (1). Sarcopenia was the term used to describe deficiency of muscle mass in old age. However, consensus on the definition of sarcopenia is lacking. Since the introduction of the term in 1988 (2), different diagnostic measures have been proposed to define sarcopenia, including muscle mass, muscle strength, and physical performance (i.e. walking speed) (3;4). Furthermore, it is unclear which correction factors for these measures should be used (5-7). Research on diagnostic measures for sarcopenia is of emerging importance, since the prevalence of sarcopenia is highly dependent on the applied diagnostic measures (8).

Evidence-based consensus on the most clinically relevant diagnostic measures for sarcopenia, requires exploration of their association with muscle related clinical outcome. It is important to note that muscle tissue is not only a force generator but also important in glucose homeostasis (9;10), drug distribution (11), and as a reserve of body proteins that can be used in extreme conditions of stress or malnutrition (12;13). Another example of muscle related clinical outcome is bone mineral density (BMD) (14-16). The main explanation for an association between muscle and BMD is mechanical loading by gravitational forces that stimulates bone formation, as was first recognized for body mass (16;17). Several diagnostic measures for sarcopenia, i.e. muscle mass (14-16), muscle strength (18;19), and gait speed (20;21) have been associated with BMD with inconsistent results. Whether differences can be explained by study design, demographic characteristics (i.e. sex, age, ethnicity), and/or correction factors (such as body mass and fat mass) remains largely unknown.

In the present study we compared the association of diagnostic criteria for sarcopenia with respect to BMD in healthy young and old men and women.

Methods

Study design

The MYOAGE study is a cross-sectional European multicenter study of young (aged 18 to 30 years) and relatively healthy old participants (aged 69 to 81 years). The group of old participants was selected based on self-reported activity levels into a physically active group and a physically less-active group. Participants were recruited by focused advertisement in newspapers, the third generation university, association of emeriti and universities, thus selecting cognitively active individuals. Third generation university is a series of lectures, courses, seminars and trips

(cultural, educational or recreational) organized by the university for older people for their further learning and to increase social activities. In total, 461 participants were included consisting of 110 recruited in Leiden, the Netherlands, 105 in Jyvaskyla, Finland, 100 in Tartu, Estonia, 62 in Paris, France, and 84 in Manchester, United Kingdom. Nine participants were excluded because of missing results on body composition from the Dual-energy X-ray absorptiometry (DXA). Thus, the total number of participants in this analysis was 452.

Exclusion criteria were aimed to ensure selection of healthy participants and minimize the confounding effect of comorbidity on sarcopenia. In short, exclusion criteria were: dependent living situation, unable to walk a distance of 250 m, presence of morbidity (neurologic disorders, metabolic diseases, rheumatic diseases, recent malignancy, heart failure, severe chronic obstructive pulmonary disease (COPD), haemocoagulative syndromes), use of medication (immunosuppressive drugs, insulin), immobilization for 1 week during last 3 months, and orthopedic surgery during the last two years or still causing pain or functional limitation.

Measurements were performed according to unified standard operating procedures during visits to the local study centers. The local medical ethical committees of the respective institutions approved the study. Written informed consent was obtained from all participants.

Dual-energy X-ray absorptiometry

A whole body scan was performed using Dual-energy X-ray absorptiometry (DXA) (Netherlands: Hologic QDR 4500, version 12.4, Hologic Inc., Bedford, USA; Finland: Lunar Prodigy, version EnCore 9.30; Estonia: Lunar Prodigy Advanced, version EnCore 10.51.006; France: Lunar Prodigy, version EnCore 12.30; United Kingdom: Lunar Prodigy Advance, version EnCore 10.50.086). Additionally bone mineral density at the hip region was scanned in 347 participants, and T scores were derived based on reference values (49). During the measurements a light cotton shirt was worn by the participants, reducing measurement errors due to clothing absorption. A trained technician performed the dual-energy X-ray absorptiometry. From the DXA, whole body BMD, and total and compartmental lean mass and fat mass were measured. Lean mass was used as an estimate of muscle mass.

Components of body mass

In this article, body mass, lean mass, and fat mass are summarized into the term ‘components of body mass’.

Diagnostic measures for sarcopenia

Diagnostic measures were divided into measures of muscle mass, muscle strength and physical performance.

Muscle mass

Lean mass percentage was calculated as lean mass divided by body mass in percentage (22b). Appendicular lean mass (ALM) percentage was calculated as the sum of lean mass of arms and legs divided by body mass in percentage (7). ALM divided by height squared (ALM/height^2) was calculated as proposed by Baumgartner (5).

Muscle strength

Isometric knee extension torque was measured with a knee extension dynamometer chair (Netherlands: Forcelink B.V., Culemborg, the Netherlands; Finland: custom made; Estonia: custom made; France: Biodex system 3 Pro isokinetic dynamometer, Biodex Medical Systems, Shirley, New York, USA; UK: custom made). The participants were positioned in an upright position, with straps to fix the hips to the chair and the ankle to a force or torque transducer at the knee angle of 90 degrees. Lever arm length was recorded as the distance between the knee axis of rotation and the middle of the pad. After three warm up trials at 50 % and 90 % of self-perceived maximal strength, three trials were conducted to measure maximal voluntary contraction (MVC) force of the knee extension muscle. For each attempt, maximal force or torque was recorded by the transducer and saved on the computer. Each trial was separated by one minute of rest. Knee extension torque was obtained either directly or by multiplying recorded peak force with the lever arm length. The trial with the highest torque output was taken for analyses.

Handgrip strength was measured using the Jamar dynamometer handle (Sammons Preston Inc, Bolingbrook, IL). The width of the dynamometer was adjusted for each participant separately for optimal fit. Participants were instructed to stand upright and with the dynamometer besides but not against their body. For both hands the strength was measured three times and recorded in kilograms. The best of all attempts was used for further analysis.

Physical performance

Walking speed was measured as the average walking speed during a six-minute walk test. Participants were instructed to walk around cones placed 20 meters apart (or 25 meters in France). In Finland, Estonia, France, and UK participants were instructed to walk as fast as possible during 6 minutes; in the Netherlands the instruction was

Table 1: Participant characteristics stratified by sex and age (n=452).

	Men		Women	
	Young (n=85)	Old (n=132)	Young (n=93)	Old (n=142)
Age (years)	23.6 (2.9)	74.9 (3.3)	23.2 (2.8)	74.2 (3.2)
Height (m)	1.80 (0.06)	1.74 (0.06)	1.67 (0.06)	1.61 (0.06)
BMI (kg/m^2)	23.3 (3.1)	25.9 (3.1)	22.4 (3.0)	25.1 (3.6)
MMSE	30 (29-30)	29 (28-29)	30 (29-30)	29 (28-30)
GDS (median, IQR)	0 (0-1)	1 (0-2)	0 (0-1)	1 (0-2)
Number of comorbidity[a] (median, IQR)	0 (0-0)	1 (0-1)	0 (0-0)	1 (0-1)
Number of medication[b] (median, IQR)	0 (0-0)	1 (0-3)	0 (0-1)	1 (0-3)
Osteoporosis medication[c] (n,%)	4 (4.7)	14 (10.6)	1 (1.1)	42 (29.6)
Current smoking (n,%)	9 (10.6)	8 (6.1)	13 (14.0)	5 (3.5)
Excessive alcohol used[d] (n,%)	25 (29.4)	23 (17.4)	19 (20.4)	13 (9.2)

Variables presented as mean and standard deviation, unless indicated otherwise. [a]Total number of comorbidity includes cardiovascular disease, osteoarthritis, thyroid disease, diabetes mellitus and other diseases. [b]Number of medication is the total number of inhaled and oral medication. [c]Number of participants using either bisphosphonates, calcium, or vitamin D. [d]Excessive alcohol use was determined as >210 g/week for men and >140 g/week for women. BMI: body mass index. GDS: Geriatric Depression Scale. MMSE: Mini Mental State Examination.

to walk at usual pace.

Time needed to complete the Timed Up and Go test (TUG) was measured. Participants were instructed to stand up from a chair without use of arms, walk around a cone placed three meters from the chair and return to the original sitting position. Further instructions were to complete the test as quickly as possible, while taking care not to run and to remain safe. Participants were allowed three trials, and the fastest attempt was used for analyses.

Participant characteristics and health status

Standing height was measured for each participant. Information about lifestyle factors such as smoking, alcohol use, living status, and education were self-reported using a questionnaire. Excessive alcohol use was defined as more than 21 units per week for men, or more than 14 units per week for women. Morbidities were registered and categorized into cardiovascular disease (including cardiovascular events, arterial surgery, and hypertension), non insulin dependent diabetes mellitus, mild COPD, thyroid disease, and osteoarthritis. Sum score of diseases including these diseases was calculated. The use of medication was registered and a sum score of all oral and inhaled medication was calculated as measure of disease severity. Use of bisphophonates, calcium and vitamin D (separately or combined) was grouped

under the term 'osteoporosis medication'. Cognitive function was measured by use of the Mini Mental State Examination (MMSE) and depressive symptoms were measured by using the Geriatric Depression Scale (GDS).

Statistics

Continuous variables with Gaussian distribution are presented as mean (standard deviation) and those with non-Gaussian distribution as median (interquartile range (IQR)).

Results from the different countries were first analyzed separately, and were pooled if the effect sizes were comparable. In pooled analyses, all described diagnostic measures for sarcopenia, components of body mass and BMD were standardized into country specific Z-scores, to minimize possible effect due to differences in equipment. The standardization allowed for comparison between effect sizes of diagnostic measures for sarcopenia and components of body mass in their association with BMD.

Students T-test was used to calculate differences between young and old participants. Linear regression analyses were used to identify associations of components of body mass and diagnostic measures for sarcopenia with BMD. Two different adjustment models were used, stratified for sex and age group. In model 1 analyses were adjusted for age (for residual confounding for age) and country. In model 2 further adjustments were made for appropriate measures of body composition. Lean mass and ALM/height^2 were adjusted for fat mass, since these measures do not take fat mass into account. Lean mass percentage and ALM percentage were adjusted for body mass since higher body mass is associated with lower lean mass percentage and with higher BMD (34;50). Lean mass and fat mass were included in the same model to assess the independent contribution in the association with BMD. Results of the regression analyses with standardized variables can be interpreted as follows: 1 standard deviation (SD) increase of diagnostic measures for sarcopenia or components of body mass, is related to the effect size (β)*SD change in BMD. SPSS 17.0 for Windows was used for all analyses. P-values < 0.05 were considered statistically significant.

Results

Participant characteristics

Participant characteristics stratified by sex and age group are presented in Table 1. All participants had a high MMSE score, low GDS score and a low number of co-

Table 2: Age differences in measures of bone mineral density, components of body mass and diagnostic measures for sarcopenia stratified by sex (n=452).

	Men			Women		
	Young (n=85)	Old (n=132)	P	Young (n=93)	Old (n=142)	P
Body BMD (g/cm²)	1.3 (0.01)	1.2 (0.01)	<0.001	1.15 (0.01)	1.04 (0.01)	<0.001
Components of body mass						
Body mass (kg)	76.0 (1.3)	78.3 (1.0)	0.15	62.2 (1.0)	64.6 (0.9)	0.07
Fat mass (kg)	13.3 (0.7)	20.5 (0.7)	<0.001	18.8 (0.7)	22.8 (0.6)	<0.001
Lean mass (kg)	59.9 (0.8)	55.6 (0.6)	<0.001	41.4 (0.6)	40.2 (0.5)	0.10
Diagnostic measures						
Muscle mass						
Lean mass (%)[a]	79.4 (0.7)	71.6 (0.6)	<0.001	67.0 (0.7)	62.9 (0.6)	<0.001
ALM (%)[b]	36.8 (0.3)	31.2 (0.3)	<0.001	29.7 (0.3)	26.3 (0.3)	<0.001
ALM/height² (kg/m²)	8.6 (0.1)	8.0 (0.7)	<0.001	6.6 (0.08)	6.5 (0.06)	0.33
Muscle strength						
Knee extension torque (Nm)	249.0 (6.5)	152.2 (3.7)	<0.001	150.3 (3.7)	97.5 (2.2)	<0.001
Handgrip strength (Kg)	52.7 (1.0)	39.6 (0.7)	<0.001	33.2 (0.5)	26.2 (0.4)	<0.001
Physical performance						
Walking speed (m/s)	1.94 (0.03)	1.48 (0.02)	<0.001	1.76 (0.03)	1.44 (0.02)	<0.001
TUG (s)	4.67 (0.10)	6.10 (0.10)	<0.001	5.02 (0.09)	6.60 (0.09)	<0.001

Variables presented as mean with s.e. of the mean. Students T-test was used to calculate the differences between young and old. [a]Lean mass in percentage is the lean mass as percentage of body mass. [b]ALM in percentage is the appendicular lean mass as percentage of body mass. BMD: whole body bone mineral density. TUG: Timed Up and Go test.

morbidities and number of medication.

Age differences in BMD, components of body mass, and diagnostic measures for sarcopenia

In Table 2, differences between young and old participants in measures of BMD, components of body mass and diagnostic measures for sarcopenia are presented for men and women separately. BMD was lower both in old men and in old women as compared to young men and women. Based on T score values below -2.5, 6 (5.6%) of old females were osteoporotic at the hip region. None of the young participants or old males were osteoporotic. Body mass did not differ between young and old participants. Compared to young participants, fat mass was higher both in old men and in old women. Old men had a lower muscle mass than young men (lean mass, lean mass percentage, ALM/height²). Old women also had lower muscle mass than

Table 3: Association of components of body mass and diagnostic measures for sarcopenia including muscle mass with whole body bone mineral density, stratified by sex and age (n=452).

	Whole body bone mineral density (g/cm² in SD)							
	Young men (n=85)		Young women (n=93)		Old men (n=132)		Old women (n=142)	
	β (se)	P	β (se)	P	β (se)	P	β (se)	P
Components of body mass								
Body mass (kg in SD)								
Model 1: age, country	0.46 (0.09)	<0.001	0.29 (0.08)	0.001	0.42 (0.08)	<0.001	0.37 (0.07)	<0.001
Fat mass (kg in SD)								
Model 1: age, country	0.22 (0.12)	0.07	0.10 (0.07)	0.16	0.24 (0.08)	0.002	0.29 (0.06)	<0.001
Model 2: as 1 and lean mass	0.02 (0.11)	0.85	-0.01 (0.07)	0.90	0.08 (0.08)	0.30	0.25 (0.07)	<0.001
Lean mass (kg in SD)								
Model 1: age, country	0.62 (0.11)	<0.001	0.77 (0.14)	<0.001	0.66 (0.12)	<0.001	0.50 (0.16)	0.002
Model 2: as 1 and fat mass	0.61 (0.12)	<0.001	0.77 (0.15)	<0.001	0.61 (0.13)	<0.001	0.23 (0.17)	0.17
Diagnostic measure – *Muscle mass*								
Lean mass (% in SD)[a]								
Model 1: age, country	-0.11 (0.14)	0.42	0.01 (0.08)	0.93	-0.20 (0.11)	0.08	-0.36 (0.08)	<0.001
Model 2: as 1 and body mass	0.34 (0.14)	0.025	0.37 (0.10)	<0.001	0.32 (0.13)	0.018	-0.16 (0.12)	0.19
ALM (% in SD)[b]								
Model 1: age, country	0.16 (0.16)	0.63	0.12 (0.10)	0.22	-0.10 (0.12)	0.39	-0.34 (0.09)	<0.001
Model 2: as 1 and body mass	0.65 (0.14)	<0.001	0.47 (0.10)	<0.001	0.30 (0.12)	0.022	-0.13 (0.11)	0.26
ALM/height² (kg/m² in SD)								
Model 1: age, country	0.55 (0.10)	<0.001	0.43 (0.10)	<0.001	0.51 (0.11)	<0.001	0.32 (0.11)	0.007
Model 2: as 1 and fat mass	0.32 (0.10)	0.001	0.43 (0.10)	0.001	0.46 (0.11)	<0.001	0.16 (0.12)	0.18

All components of body mass, diagnostic measures for sarcopenia and whole body bone mineral density were standardized into country specific z-scores. Results from regression analyses using standardized variables are displayed using different adjustment models. Interpretation: 1 standard deviation (SD) increase of diagnostic measures for sarcopenia or components of body mass, is assocated with the effect size (β)*SD higher/lower BMD. [a]Lean mass in percentage is the lean mass as percentage of body mass. [b]ALM in percentage is the ALM as percentage of body mass. ALM: appendicular lean mass.

young women for lean mass percentage, but not for lean mass in kilogram or ALM/height^2. Muscle strength (knee extension torque and handgrip strength), walking speed and performance on TUG were lower both in old men and in old women compared to young men and women.

Components of body mass and BMD

Table 3 displays the results from linear regression analyses using standardized variables for the association of components of body mass with BMD, stratified by age and sex. In all groups, body mass was associated with BMD. Fat mass was associated with BMD in old men and old women, but not in young participants. Significance was lost in old men after adjustment for lean mass. In all groups there was a highly significant positive association between lean mass and BMD. Adjustment for fat mass affected these results only slightly, except in old women; in this group significance was lost. The association between components of body mass with BMD were visualized in Fig. 1.

Diagnostic measures for sarcopenia and BMD

Muscle mass

Table 3 shows the results from linear regression analyses using standardized variables, for the association of diagnostic measures for sarcopenia with BMD, stratified by age and sex. In young men, young women, and old men, lean mass percentage and ALM percentage were significantly associated with BMD after adjustments for body mass. In old women, lean mass percentage and ALM percentage were significantly inversely associated with BMD; after adjustment for body mass significance was lost. In all groups ALM/height^2 was positively associated with BMD. After adjustment for fat mass, significance remained except in old women. The association between ALM percentage and ALM/height^2 with BMD is visualized in Fig. 2.

Muscle strength

The association of muscle strength and physical performance with BMD is shown in Table 4. Knee extension torque as well as handgrip strength were positively associated with BMD in young men, young women, and old men. This association remained significant in young men and young women with further adjustments for body mass. In old women, knee extension torque and handgrip strength were not associated with BMD. The association between knee extension torque and BMD is visualized in Fig. 2.

Table 4: Association of diagnostic criteria for sarcopenia including muscle strength and physical performance with whole body bone mineral density stratified by sex and age (n=452).

	Whole body bone mineral density (g/cm2 in SD)							
	Young men (n=85)		Young women (n=93)		Old men (n=132)		Old women (n=142)	
	β (se)	P	β (se)	P	β (se)	P	β (se)	P
Diagnostic measure - *Muscle strength*								
Knee extension torque (Nm in SD)								
Model 1: age, country	0.59 (0.10)	<0.001	0.58 (0.12)	<0.001	0.50 (0.12)	<0.001	0.25 (0.17)	0.15
Model 2: as 1 and body mass	0.44 (0.12)	<0.001	0.47 (0.13)	0.001	0.26 (0.13)	0.05	0.16 (0.16)	0.33
Handgrip strength (kg in SD)								
Model 1: age, country	0.51 (0.10)	<0.001	0.36 (0.13)	0.01	0.29 (0.11)	0.01	0.25 (0.15)	0.10
Model 2: as 1 with body mass	0.33 (0.12)	0.005	0.28 (0.13)	0.035	0.10 (0.11)	0.35	0.06 (0.14)	0.65
Diagnostic measure - *Physical performance*								
Walking speed (m/s in SD)								
Model 1: age, country	0.24 (0.14)	0.09	-0.01 (0.10)	0.93	-0.01 (0.08)	0.88	0.03 (0.10)	0.74
TUG (s in SD)								
Model 1: age, country	0.17 (0.17)	0.31	-0.21 (0.13)	0.12	-0.02 (0.09)	0.82	0.12 (0.07)	0.10

All muscle strength and physical performance variables and whole body bone mineral density were standardized into country specific z-scores. Results from regression analyses using standardized variables are displayed using different adjustment models. Interpretation: 1 standard deviation (SD) increase of diagnostic measures for sarcopenia or components of body mass, is assocated with the effect size (β)*SD higher/lower BMD. TUG: Timed Up and Go test.

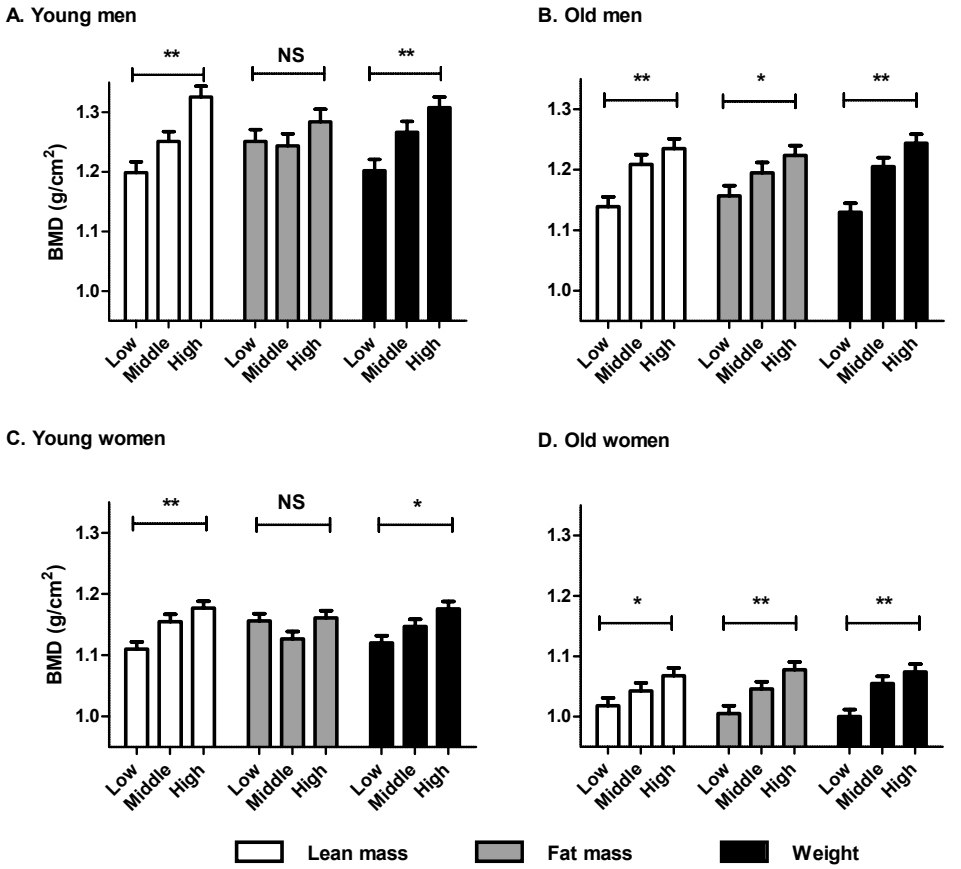

Figure 1: *The association between components of body mass and whole body bone mineral density (BMD) in young men (a), old men (b), young women (c) and old women (d). Lean mass (kg), fat mass (kg), and body mass (kg) are presented in country, sex, and age specific tertiles. Bars represent the adjusted means and s.e. P values were calculated with linear regression models for the association between components of body mass and BMD with adjustments for age and country. *=p<0.01. **=p<0.001.*

Physical performance

Walking speed and TUG were not related to BMD. Discarding data from the Netherlands, where walking speed was measured at usual pace, did not change these results. The association for walking speed and BMD is visualized in Fig. 2.

Comparison of effect sizes

To determine the strongest association with BMD, effect sizes (β) for components of body mass (Table 3) and diagnostic measures for sarcopenia (Table 3 and 4) were compared in Tables 3 and 4. The effect size indicates the SD increase in BMD

with increase of 1 SD of the diagnostic measure. Lean mass showed the strongest association with BMD in all groups in the model adjusting for age and country. The association between tertiles of lean mass, fat mass, and body mass with BMD is displayed in Fig. 1, adjusted for age and country. Diagnostic criteria for sarcopenia are visualized in Fig. 2. Since effect sizes were similar in the association with BMD for ALM percentage and lean mass percentage only ALM percentage is depicted in Fig.2. Likewise, knee extension torque is representative of handgrip strength, and walking speed is representative of TUG in Fig. 2.

Discussion

In this cross-sectional European study of young and old participants, the main objective was to compare different diagnostic measures for sarcopenia and their association with BMD as a muscle related clinical outcome. We have shown that the associations of different diagnostic measures for sarcopenia with BMD varies substantially. Therefore, different diagnostic measures cannot be compared or interpreted interchangeably. Lean mass was most strongly related with BMD and positively associated with BMD when adjusted for age and country. ALM/height^2 was positively associated with BMD in all subgroups, although in old women this association was no longer present when further adjustments for fat mass were applied. Lean mass percentage and ALM percentage were inversely associated with BMD without adjustment for body mass in old women. Fat mass was associated with whole body BMD in older women, independent of lean mass. Muscle strength was associated with whole body BMD in young participants and older men, but not in women. Walking speed and TUG were not associated with BMD.

In the present study, lean mass was found to be most strongly associated with BMD. In a previous study comparing the association between different diagnostic measures for sarcopenia with glucose regulation, lean mass percentage was most associated with glucose tolerance (10). More research comparing diagnostic measures with relevant muscle related clinical outcome is needed before reaching a final consensus for the definition of sarcopenia. Muscle mass (5;22), muscle strength (23), and physical performance (3;4) have all been suggested to be included in the definition of sarcopenia with different correction factors, but evidence is lacking to decide on the most appropriate diagnostic measures. The use of muscle strength or walking speed for defining sarcopenia implies a constant ratio between these variables and muscle mass. This is not the case, as muscle strength declines much more with age than muscle mass, while muscle strength is positively but not linearly

associated with maximum walking speed (24;25). Therefore, it has been suggested to differentiate between the terms 'sarcopenia' and 'dynapenia' (26;27). Other factors in addition to muscle mass are important to generate muscle strength and physical performance such as neural control, cognition, cardiovascular and joint function (26). To keep terminology clear, we suggest to reserve the term sarcopenia for diagnostic measures based on muscle mass only, and not for muscle strength or walking speed. Diagnostic measures for sarcopenia based on muscle mass have been described previously in the association with BMD, although not all in a comparative way. In accordance with this study, lean mass in kilograms has been reported to have a positive association with BMD in several studies (14;15;28-31). ALM/height^2 was positively associated with BMD in men without adjustment (16) and in another study after adjustments for age, fat mass, height, smoking, physical activity, and estradiol (32). In postmenopausal women with hip fracture, ALM/height^2 was not associated with whole body BMD after adjustment for body fat (33). An inverse association between lean mass percentage and BMD has been described, whereas a positive association of lean mass in kilograms and BMD was found (34). These contradictory results for muscle mass measures may be explained by the inverse asscociation between lean mass percentage and total body mass, as with lower body mass there is less weight-bearing effect on bones. We have now confirmed that differences in results between studies, describing the association for a muscle mass measure with BMD, may arise from different corrections for body composition (body mass or height), next to differences in characteristics of study populations.

In this study, muscle strength expressed as knee extension torque and handgrip strength was associated with BMD in all subgroups, except in old women. Previous studies have described an association between muscle strength and whole body BMD in postmenopausal women (18;19;35), but not all (36). This association generally disappeared after adjustment for body mass (18;35). It can be noted that these studies were of comparative size or smaller with respect to this study. In one study including 1380 women and 1265 men aged over 50 years (mean age 63.6 years), low grip strength was associated with low BMD independent of body mass in women, but not in men (37).

The association between physical performance and BMD has been studied before (20;21;38). In line with this study, some groups reported no association between gait speed and BMD (20;38). However, other studies describe a positive association between gait speed and BMD (21;38).

This study was aimed to investigate muscle ageing in healthy individuals in the absence of disease. Even though old participants were healthy, age differences

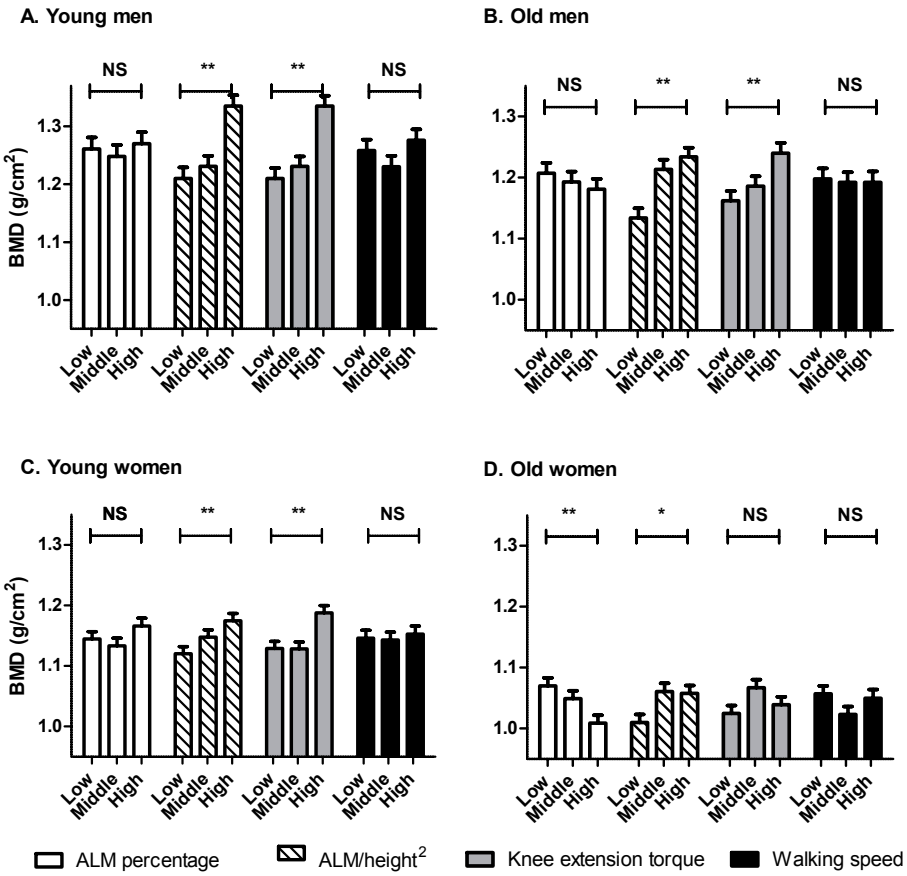

Figure 2: *The association between different diagnostic measures for sarcopenia and whole body bone mineral density (BMD) in young men (a), old men (b), young women (c) and old women (d). ALM in percentage is the appendicular lean mass as percentage of body mass. ALM percentage, ALM/height2 (kg/m2), knee extension torque (Nm) and walking speed (m/s) are presented in country, sex, and age group specific tertiles. Bars represent the adjusted means and s.e. P values for the association between diagnostic measures for sarcopenia and BMD were calculated with linear regression models with adjustments for age and country. *=p<0.01. **=p<0.001.*

in muscle measures were clearly present. In particular old women were different from young women in the association between diagnostic measures for sarcopenia and BMD. These results may not be generalized to more frail populations who are more likely to suffer from multimorbidity and decreased physical activity including increased risk of falls and fractures in frail older women (46-48). Future studies are needed to investigate the association between diagnostic measures for sarcopenia and BMD in frail populations.

Loading of bones with a subsequent induction of bone formation by stimulation of the mechano-sensing osteocyte (17), is the most obvious pathophysiological link between BMD and measures of muscle mass, muscle strength, and physical performance. Mechanical stress exerted on bones is sensed by osteocytes which become activated and subsequently stimulate osteoblasts to increase BMD at site which is under most pressure (17). Both muscle and fat tissue contribute to this mechanism since body mass is predominantly composed out of these tissues. Muscles are connected to bones by tendons and are therefore in a position to apply stress directly onto the bones. This could explain the greater effect of muscle mass compared to fat mass on BMD. Since the absolute mass of both muscle and fat are beneficial for loading on bones, lean mass as a percentage of body mass does not reflect the direct effect of body mass on bones and is therefore less relevant with respect to mechanical loading of bones. Load exerted on bones by exercising has been shown to suppress BMD decline (39). In the present study, the association between muscle strength and BMD was strongest in the young participants and was independent of body mass. We hypothesize that in the young participants muscle strength might be a reflection of exercising which could stimulate of bone formation. Whereas at old age lifestyle becomes less active and the importance of the gravitational forces of body mass on bone maintenance would increase.

Hormonal and systemic factors should also be considered as explanation for the observed associations between lean mass, fat mass and BMD (40). This may be particularly relevant for women. The positive association between fat mass and BMD could be explained by adipokines secreted by fat tissue which might be beneficial for estrogen-deficient women after menopause. Adiponectin, insulin, amylin, preptin, leptin and adipocytic estrogens are all likely to contribute positively to BMD (34). For example leptin affects both bone formation and resorption by increasing proliferation and differentiation of osteoblasts, promoting bone nodule formation, increasing chondrocyte growth, and regulating osteoclast development (41). In postmenopausal women the role of the adipocyte as an estrogen-producing cell becomes more important, as estrogen influences bone density. Insulin increases free concentrations of both androgens and estrogens, which are positively associated with bone mass (34). Since muscle tissue is responsible for approximately 75 percent of insulin-mediated uptake of glucose, crosstalk between muscle and fat is of high importance (42). Furthermore, recent evidence suggests that a factor secreted by muscles, irisin, can decrease body mass in obesity and improve glucose homeostasis (43). It has become clear that osteocalcin, which is secreted by bone tissue, also affects energy metabolism (40). Studies on the contribution of fat mass on BMD have shown

inconsistent results, with an inverse (30;44), no (28;45), or a positive association (14;29;31). This study contributes to appreciate these inconsistencies, which arise (partially) from differences in sex and age. The important role of fat mass might explain why different results are observed in old women compared to old men.

The strength of this study was the ability to discriminate between the effects of both muscle mass and fat mass on BMD stratified for sex and age. The comparison of the associations of different diagnostic measures such as muscle strength and physical performance with BMD was performed. The inclusion of a large group of cognitively active and healthy participants across Europe minimizes the influence of diseases and cognitive impairment, although results cannot be generalized for the entire elderly population. Even though old participants were healthy and not likely to suffer from sarcopenia, age differences between young and old participants on diagnostic measures for sarcopenia were clearly present. A limitation of studying relatively healthy old participants is that we were not able to dichotomize into a sarcopenic and non-sarcopenic group based on currently available definitions for sarcopenia (3;4). Therefore we cannot conclude on the use of cut-off values in sarcopenia. A limitation of the adjustment models for body composition is the co-linearity between fat and lean mass. As DXA measures areal rather than volumetric density, BMD is not completely corrected for skeletal size (34). Finally a limitation is the cross-sectional design of the study.

In conclusion, the associations between several diagnostic measures for sarcopenia and BMD vary widely. Lean mass was most strongly associated with whole body BMD, and lean mass in percentage and ALM percentage are not appropriate to describe this association without further adjustment for body mass. Gait speed and TUG do not associate with BMD. This should be accounted for when defining sarcopenia. Future investigations should focus on the associations of diagnostic measures for sarcopenia with respect to other muscle related clinical outcome.

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Chapter 8

Muscle strength rather than muscle mass is associated with standing balance in elderly outpatients

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Abstract

Objectives: Assessment of the association of muscle characteristics with standing balance is of special interest as muscles are a target for potential intervention, i.e. by strength training.
Design: Cross-sectional study
Setting: Geriatric outpatient clinic
Participants: The study included 197 community-dwelling elderly outpatients (78 males, 119 females, mean age 82 years).
Measurements: Muscle characteristics included handgrip and knee extension strength, appendicular lean mass divided by height squared (ALM/height^2), and lean mass as percentage of body mass. Two aspects of standing balance were assessed: the ability to maintain balance, and the quality of balance measured by Center of Pressure (CoP) movement during ten seconds of side-by-side, semi-tandem and tandem stance, with both eyes open and eyes closed. Logistic and linear regression models were adjusted for age, and additionally for height, body mass, cognitive function and multimorbidity.
Results: Handgrip and knee extension strength, adjusted for age, were positively related to the ability to maintain balance with eyes open in side-by-side (p=0.011; p=0.043), semi-tandem (p=0.005; p=0.021) and tandem stance (p=0.012; p=0.014), and with eyes closed in side-by-side (p=0.004; p=0.004) and semi-tandem stance (not significant; p=0.046). Additional adjustments affected the results only slightly. ALM/height^2 and lean mass percentage were not associated with the ability to maintain standing balance, except for an association between ALM/height^2 and tandem stance with eyes open (p=0.033) that disappeared after additional adjustments. Muscle characteristics were not associated with CoP movement.
Conclusion: Muscle strength rather than muscle mass was positively associated with the ability to maintain standing balance in elderly outpatients. Assessment of CoP movement was not of additional value.

Introduction

Among 37 million elderly aged over 65 years, 7 million reported impaired standing balance in the past 12 months in the National Health Interview Survey in 2008 (1). Standing balance is dependent on integrated functioning of the sensory systems (vestibular, visual, and proprioceptive system), neural control, and muscle characteristics. These systems degenerate with increasing chronological age, by cumulative tissue damage, specific diseases and medication use (2-6). Muscle characteristics are of special interest, as recent evidence suggests that strength training can improve muscle strength and muscle mass, even in elderly (7-9). To develop targeted interventions for impaired standing balance in elderly outpatients, it is important to understand the contribution of muscle strength and muscle mass to standing balance.

In healthy elderly it was shown that muscle strength is associated with the ability to maintain standing balance (10;11). Quadriceps muscle mass has also been associated with the ability to maintain standing balance in healthy elderly (12). Besides the ability to maintain standing balance, the quality of balance can be assessed additionally by measuring the Center of Pressure (CoP) movement. In healthy elderly, muscle mass (12;13) but not muscle strength has been associated with CoP movement (14-16).

It remains unknown if associations between muscle characteristics and standing balance are present in elderly outpatients, while this group is obviously of clinical interest. These outpatients are more likely to suffer from multimorbidity and deterioration in more than one system involved in standing balance (11;17;18). Only few studies describe the association between muscle characteristics and standing balance in elderly with mobility difficulties, often applying exclusion criteria for co-morbidity or severe mobility limitations (19;20). We assessed the association between muscle characteristics and two aspects of standing balance, the ability to maintain balance as well as the CoP movement, in community-dwelling elderly referred to a geriatric outpatient clinic.

Methods

Setting

This cross-sectional study included 207 community-dwelling elderly who were referred to a geriatric outpatient clinic in a middle-sized teaching hospital (Bronovo Hospital, The Hague, Netherlands) for a comprehensive geriatric assessment (CGA) between March 2011 and January 2012. CGA was performed during a two hour visit

including questionnaires and physical and cognitive measurements. All tests were performed by trained nurses or medical staff. Medical charts were retrospectively evaluated. The study was reviewed and approved by the institutional review board of the Leiden University Medical Center (Leiden, the Netherlands). Because this research is based on regular patient care, the need for individual informed consent was waived. In the present analyses, 10 elderly outpatients (4.8%) were excluded due to missing data on standing balance, leaving 197 outpatients for analyses.

Elderly outpatient characteristics

Questionnaires included information on marital status, current smoking, alcohol use and living arrangements. Anthropometric data included assessment of body mass, height and body mass index. Information on diseases and use of medication was extracted from medical records. Multimorbidity was rated as the presence of two or more diseases, including chronic obstructive pulmonary disease, heart failure, diabetes mellitus, hypertension, malignancy, myocardial infarction, Parkinson's disease, (osteo)arthritis, transient ischemic attack and stroke. The Hospital Anxiety and Depression scale (HADS) was used to detect depressive symptoms (21). A score higher than 8 out of 21 points indicated depressive symptoms. Global cognitive function was assessed using the Mini Mental State Examination (MMSE) (22). Physical functioning was self-reported in a questionnaire with questions on experienced falls during the last 12 months, walking difficulties, impaired standing balance and use of walking aids. Physical functioning was assessed with a 10 meter walking test at usual pace in steady state, and with the short physical performance battery (SPPB) (23). The SPPB comprises the ability to maintain balance in three different standing positions with eyes open, a timed four meter walk, and a timed sit-to-stand test.

Standing balance

The ability to maintain standing balance

The ability to maintain standing balance was tested in different standing conditions. Elderly outpatients, wearing non slip socks, were instructed to maintain balance for 10 seconds in each standing condition. Three different standing positions characterized by a progressive narrowing of the base of support were performed both with eyes open and eyes closed. During side-by-side stance, elderly outpatients were instructed to stand with the medial malleoli as close together as possible; during semi-tandem stance, elderly outpatients were standing with the medial side of the heel of one foot touching the big toe of the other foot; during tandem stance, elderly outpatients were standing with both feet in line while the heel of one foot

Table 1: Elderly outpatient characteristics.

	All (n=197)	Male (n=78)	Female (n=119)
Age, years	81.9 (7.1)	80.7 (6.8)	82.7 (7.2)
Widowed, n (%) [a]	80 (41.5)	17 (21.8)	63 (54.8)
Living arrangements, n (%) [a]			
Institutionalized	0 (0)	0 (0.0)	0 (0.0)
Sheltered	40 (20.6)	13 (16.9)	27 (23.1)
Independent	154 (79.4)	64 (83.1)	90 (76.9)
Current smoking, n (%) [b]	22 (16.2)	9 (16.1)	13 (16.3)
Excessive alcohol use, n (%) #	8 (4.1)	5 (6.4)	3 (2.5)
Body mass, kg	71.8 (15.5)	78.7 (12.1)	67.3 (15.8)
Height, cm	167 (10)	176 (7)	161 (6)
BMI, kg/m2	25.8 (4.5)	25.5 (3.6)	25.9 (5.0)
Multimorbidity, n (%) c, †	95 (50.3)	43 (55.1)	52 (46.8)
Number of medication, median (IQR) c	5 (3-7)	6 (3-7)	5 (2-7)
Depressive symptoms, n (%) d, ‡	28 (23.1)	17 (30.9)	11 (16.7)
MMSE, points; median (IQR)	27 (24-29)	27 (25-29)	27 (24-29)
Gait speed, m/s	0.87 (0.29)	0.93 (0.31)	0.83 (0.27)
SPPB, points; median (IQR)	7 (5-10)	8 (6-10)	7 (5-9)
Self-reported functioning, n (%)			
Fall incident previous 12 months	127 (64.5)	45 (57.7)	82 (68.9)
Walking difficulties [a]	143 (73.0)	52 (66.7)	91 (77.1)
Use of walking aid [a]	108 (55.1)	33 (42.9)	75 (63.0)
Impaired standing balance [a]			
Never	34 (17.4)	10 (12.8)	24 (20.5)
Sometimes	73 (37.4)	33 (42.3)	40 (34.2)
Regularly	57 (29.2)	24 (30.8)	33 (28.2)
Always	31 (15.9)	11 (14.1)	20 (17.1)
Handgrip strength, kg	26.1 (8.2)	33.7 (6.2)	21.1 (4.9)
Knee extension strength, N [b]	202 (96)	261 (108)	162 (60)
ALM/height², kg/m² [b]	7.14 (1.20)	7.82 (0.84)	6.63 (1.19)
Lean mass percentage, % [b]	63.8 (8.9)	69.6 (6.6)	59.6 (7.9)

All parameters are presented as mean with standard deviation unless indicated otherwise. Data available in [a] n=194/195, [b] n=132, [c] n=189 and [d] n=121. # Defined as > 14 units per week for females or > 21 per week for males. †Present in outpatients with two or more diseases, including chronic obstructive pulmonary diseases, decompensatio cordis, diabetes mellitus, hypertension, malignancy, myocardial infarction, Parkinson's disease, (osteo)arthritis, transient ischemic attack and stroke. ‡Present with a depression subscore of >8 on the Hospital Anxiety and Depression Scale. IQR: inter quartile range. MMSE: Mini Mental State Examination. SPPB: Short Physical Performance Battery. ALM: appendicular lean mass.

touched the toes of the other. Standing positions were first assessed with eyes open as part of the SPPB (23). Subsequently, all standing positions were repeated with eyes closed. The elderly outpatients were allowed three trials if standing balance was lost prematurely. When the elderly outpatients could not complete a standing position, consecutive positions were not performed. Six elderly outpatients did not attempt the standing positions with eyes closed due to lack of time or lack of motivation, leaving 191 outpatients for analyses of standing balance conditions with eyes closed.

Center of Pressure movement

All standing conditions were performed on a triangular six degrees of freedom force plate (Forcelink B.V., Culemborg, The Netherlands) to measure CoP movement. Only successful trials, i.e. completion of 10 seconds of maintaining balance without stepping out in case of loss of balance, were considered for further analyses (i.e. n=183 were able to maintain balance in side-by-side stance). Because of missing data due to technical problems (n=18) and unknown reasons (n=29), CoP movement was available in 136 elderly outpatients (in side-by-side stance eyes open). Time series of CoP movement in medio-lateral and anterior-posterior direction were used to calculate single CoP parameters (24). Direction specific CoP composite scores were calculated from standardized single CoP parameters (mean amplitude, amplitude variability, mean velocity, velocity variability and range), in anterior-posterior (AP) and medial-lateral (ML) direction (25). As age related differences in CoP movement are most pronounced in ML direction (25) analyses are shown in ML direction. Analyses in AP direction are given in supplementary tables.

Muscle characteristics

Muscle strength

Handgrip strength was measured using an isometric hand dynamometer (JAMAR hand dynamometer, Sammons Preston, Inc., Bolingbrook, IL, USA). Outpatients were instructed to maintain an upright standing position with their arms along the side, while holding the dynamometer in one hand. The width of the dynamometer's handle was adjusted to hand size such that the middle phalanx rested on the inner handle. Three trials were performed alternately for each hand. Outpatients were actively encouraged to squeeze with maximal strength. The best performance of all trials was used for analyses.

Isometric knee extension strength was measured in a seated position with hips and knees in 90 degrees by a force transducer mounted in a chair (Forcelink B.V., Culemborg, The Netherlands). Outpatients were asked to push with maximal effort

against a cuff positioned just above the talocrural joint. Holding on to the armrest of the chair or leaning backward was allowed, but not rising from the seating. This was checked by the investigator and corrected if necessary. Three trials were performed for each leg. The best performance of all trials was used for analyses. Structural measurement of knee extension strength was added to the CGA in May 2011.

Muscle mass

Body composition was measured using a direct segmental multi-frequency bioelectrical impedance analysis (BIA, InBody 720, Biospace Co., Ltd, Seoul, Korea). This technique has been shown to be a valid tool for the assessment of whole body composition and segmental lean measurements (26). The elderly outpatients wore normal indoor clothing and were instructed to stand barefoot on the machine platform holding a sensor in each hand. Two formulas were used to represent muscle mass. ALM/height^2 was calculated as the sum of lean mass in all four limbs (appendicular lean mass (ALM)) divided by the height squared (4). Lean mass percentage was calculated as total lean mass as percentage of total body mass (27).
In case of inability to stand on the machine platform without assistance for two minutes (n=5), wearing compressive stockings (n=22), having a pacemaker (n=15), or unknown reasons (n=14), BIA was not assessed. After exclusion of data due to technical problems (n=9) valid BIA data were available in 132 elderly outpatients.

Statistical analyses

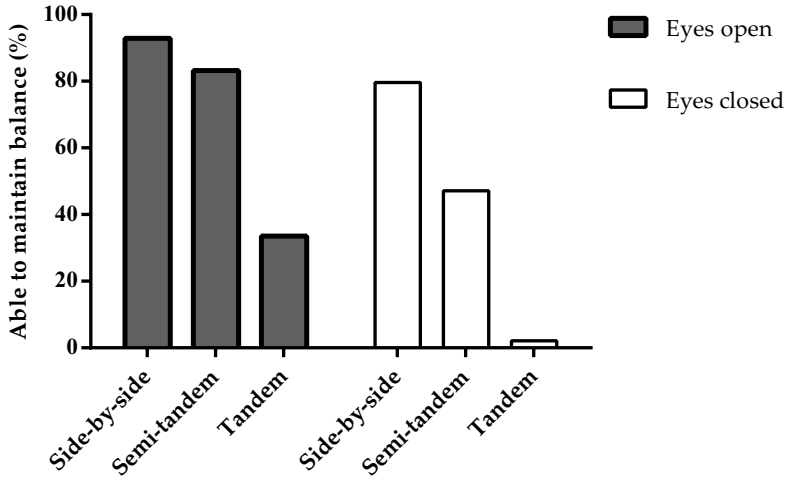

Figure 1: *Percentage of elderly outpatients able to maintain balance in the different standing positions with eyes open and eyes closed.*

Continuous variables with Gaussian distribution are presented as mean and standard deviation, otherwise as median and interquartile range or number and percentage. All muscle characteristics were standardized into sex-specific z-scores. The association between standardized muscle characteristics and the ability to maintain standing balance was analyzed using logistic regression with adjustment for age. Additional adjustment models included body mass, height, MMSE score and multimorbidity. The association between muscle characteristics and CoP movement was studied using linear regression with the same adjustment models. Statistical analyses were performed using SPSS for Windows (SPSS Inc, Chicago, USA), version 20. P values <0.05 were considered statistically significant.

Results

Elderly outpatient characteristics

The characteristics of elderly outpatients are presented in Table 1. Mean age was 81.9 years. 64.5 Percent of the elderly outpatients had at least one fall incident in the 12 months prior to the visit to the outpatient clinic.

Standing balance

Ability to maintain standing balance

The percentage of elderly outpatients able to maintain balance in different standing conditions is shown in Figure 1. In more difficult standing conditions, less elderly outpatients were able to maintain standing balance. In the standing positions with eyes open 183 elderly outpatients (92.9%) were able to maintain side-by-side stance, 164 (83.2%) semi-tandem stance and 66 (33.5%) tandem stance. In standing positions with eyes closed 152 elderly outpatients (79.6%) were able to maintain side-by-side stance, 90 (47.1%) semi-tandem stance and 4 (2.1%) tandem stance.

Center of Pressure movement

Table 2 shows the CoP movement represented by different CoP parameters used for calculating composite scores in anterior-posterior (AP) and medio-lateral (ML) direction. CoP parameters were higher in more difficult standing conditions.

Muscle characteristics and standing balance

Muscle strength

The association between muscle strength and the ability to maintain balance in different standing conditions is displayed in Table 3. Elderly outpatients with a

Table 2: CoP movement, represented by CoP parameters, within elderly outpatients able to maintain different standing positions with eyes open and eyes closed in anterior-posterior and medio-lateral direction.

	Side-by-side		Semi-tandem		Tandem	
	AP	ML	AP	ML	AP	ML
Eyes open (available)	(n=136)		(n=120)		(n=56)	
Mean amplitude (cm)	0.56 (0.02)	0.60 (0.02)	0.61 (0.04)	0.72 (0.03)	0.74 (0.04)	0.72 (0.03)
Range (cm)	3.38 (0.11)	3.51 (0.13)	3.88 (0.19)	4.25 (0.18)	4.94 (0.28)	3.92 (0.17)
Mean velocity (cm/s)	5.51 (0.10)	4.09 (0.10)	5.89 (0.13)	4.78 (0.13)	6.85 (0.22)	5.41 (0.21)
Amplitude var (cm)	0.71 (0.02)	0.75 (0.03)	0.77 (0.04)	0.91 (0.04)	0.95 (0.05)	0.88 (0.04)
Velocity var (cm/s)	7.87 (0.14)	5.70 (0.14)	8.41 (0.22)	6.76 (0.23)	9.88 (0.38)	7.55 (0.28)
Eyes closed (available)	(n=119)		(n=75)			
Mean amplitude (cm)	0.74 (0.03)	0.85 (0.03)	0.78 (0.04)	1.03 (0.04)		
Range (cm)	4.38 (0.15)	4.86 (0.17)	4.91 (0.25)	5.64 (0.23)	n.a.*	
Mean velocity (cm/s)	6.59 (0.15)	5.67 (0.14)	7.24 (0.24)	6.76 (0.26)		
Ampltiude var (cm)	0.93 (0.03)	1.06 (0.04)	0.99 (0.05)	1.27 (0.05)		
Velocity var (cm/s)	9.09 (0.20)	7.88 (0.20)	10.02 (0.34)	9.33 (0.37)		

Data are given in mean and standard error. *Not applicable, number of patients able to maintain the task is less than 5. AP = anterior-posterior direction, ML = medio-lateral direction, var=variability.

higher handgrip strength or knee extension strength were significantly more likely to be able to maintain standing balance for ten seconds in all standing conditions, except for handgrip strength and semi-tandem stance with eyes closed. Further adjustments for body mass, height, MMSE score, and multimorbidity, attenuated the associations, but overall significance remained.

Handgrip strength and knee extension strength were not associated with CoP movement in ML (Table 4) and in AP (Table 5) direction.

Muscle mass

Table 3 displays the association between muscle mass and the ability to maintain standing balance in different standing conditions. There was no association between ALM/height^2 or lean mass percentage and the ability to maintain standing balance, except for a positive association between ALM/height^2 and tandem stance with eyes open that disappeared in the fully adjusted model.

Both indices of muscle mass, ALM/height^2 as well as lean mass percentage, were not associated with the CoP movement in ML (Table 4a) and in AP (Table 4b) direction.

Table 3: Association between muscle characteristics and ability to maintain balance in different standing positions with eyes open and eyes closed.

		Side-by-side			Semi-tandem			Tandem		
		OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Eyes open	Handgrip strength									
	Model 1	2.81	1.27-6.21	0.011	1.98	1.23-3.18	0.005	1.58	1.11-2.26	0.012
	Model 2	2.17	0.89-5.33	0.09	1.78	1.07-2.95	0.026	1.59	1.09-2.31	0.016
	Model 3	2.16	0.85-5.45	0.11	1.69	1.01-2.81	0.046	1.47	1.00-2.16	0.050
	Knee extension strength									
	Model 1	3.87	1.04-14.36	0.043	2.11	1.12-3.99	0.021	1.67	1.11-2.51	0.014
	Model 2	5.33	1.14-24.96	0.034	2.38	1.21-4.68	0.012	1.78	1.16-2.74	0.008
	Model 3	5.34	1.04-27.33	0.045	2.11	1.06-4.23	0.035	1.76	1.11-2.78	0.016
	ALM/height^2									
	Model 1				0.81	0.48-1.35	0.41	1.57	1.04-2.39	0.033
	Model 2[a]				0.64	0.34-1.21	0.17	1.57	1.03-2.41	0.038
	Model 3[a]		n.a.		0.65	0.34-1.24	0.19	1.44	0.85-2.46	0.18
	Lean mass percentage									
	Model 1				1.24	0.69-2.20	0.47	0.96	0.66-1.40	0.82
	Model 2[b]				1.26	0.70-2.26	0.45	0.95	0.65-1.39	0.78
	Model 3[b]				1.69	0.87-3.30	0.12	0.90	0.60-1.36	0.62
Eyes closed	Handgrip strength									
	Model 1	1.94	1.24-3.03	0.004	1.11	0.80-1.54	0.54			
	Model 2	2.03	1.26-3.30	0.004	1.17	0.83-1.66	0.37			
	Model 3	2.00	1.22-3.27	0.006	1.19	0.83-1.71	0.34			
	Knee extension strength									
	Model 1	2.62	1.37-5.03	0.004	1.5	1.01-2.23	0.046			
	Model 2	3.33	1.61-6.89	0.001	1.72	1.13-2.63	0.012			
	Model 3	2.95	1.40-6.18	0.004	1.74	1.11-2.73	0.017			
	ALM/height^2								n.a.	
	Model 1	0.99	0.60-1.62	0.95	0.87	0.59-1.29	0.50			
	Model 2[a]	1.02	0.55-1.89	0.95	0.98	0.59-1.62	0.94			
	Model 3[a]	1.00	0.54-1.85	1.00	0.96	0.56-1.64	0.88			
	Lean mass percentage									
	Model 1	1.30	0.77-2.20	0.33	1.16	0.80-1.68	0.44			
	Model 2[b]	1.30	0.77-2.19	0.33	1.16	0.80-1.69	0.43			
	Model 3[b]	1.41	0.80-2.48	0.23	1.23	0.83-1.83	0.31			

All muscle characteristics were standardized in gender-specific Z-scores. Ability to maintain standing balance: 0=unable, 1=able. Model 1: adjusted for age, model 2: as model 1 and body mass and height, model 3: as model 2 and MMSE score and multimorbidity. [a] not adjusted for height. [b] not adjusted for body mass. n.a.: not applicable, number of elderly outpatients able or unable to maintain the standing condition is less than 5. MMSE: mini mental state examination. ALM: appendicular lean mass.

Discussion

Muscle strength is positively associated with the ability to maintain standing balance in community-dwelling elderly referred to a geriatric outpatient clinic. Muscle mass did not associate with the ability to maintain standing balance in most balance conditions, although a positive association was found between ALM/height^2 and tandem stance with eyes open. Muscle strength and muscle mass were not associated with quality of balance as measured with CoP movement. This is the first study that examines different muscle characteristics in association with the ability to maintain standing balance as well as CoP movement during standing balance in a population of elderly outpatients without any exclusion criteria.

When comparing the present study to previous studies, two aspects need to be considered. First, no exclusion criteria were applied in the present study, which contrasts other studies including healthy elderly. Elderly outpatients are more likely to have multimorbidity and deterioration in more than one system involved in standing balance (11;17;18). Second, "balance" is inconsistently defined in literature for standing (static) and dynamic balance, i.e. not as isolated standing conditions, but as the score from SPPB (23), a sum score of the three foot positions (10;20), or as different dynamic balance tests as assessed with the Timed Up and Go test, walking speed, or chair-stand test (19). It has been shown that standing balance tests are different from dynamic balance tests (28;29). Therefore we discuss our results with respect to studies that measured standing balance (also called quiet stance, or static balance).

To the best of our knowledge, there are no studies describing the association of muscle strength with both the ability to maintain standing balance and the CoP movement during standing balance in elderly. In line with this study, a positive association between muscle strength and the ability to maintain balance has been described in healthy elderly (10;11) as well as elderly with mobility difficulties (19;20) aged 65 years and older. In 985 elderly women with mobility difficulties, those with a higher knee extension strength had a higher ability to maintain balance in side-by-side, semi-tandem, and tandem stance with eyes open (20). The association between muscle strength and standing balance was not present in previous studies evaluating quality of standing balance by CoP movement in healthy elderly (14-16;28;30). This is also in line with our study, as no association was found between muscle strength and CoP movement. However, a positive association between muscle strength and CoP movement has also been reported in healthy elderly (13) and women with osteoporosis (31).

Table 4a: Association between muscle characteristics and CoP movement in medio-lateral direction in different standing positions with eyes open and eyes closed.

	Side-by-side			Semi-tandem			Tandem		
	Beta	SE	P	Beta	SE	P	Beta	SE	P
Eyes open (available)	*(n=136)*			*(n=120)*			*(n=56)*		
Handgrip strength									
Model 1	−0.08	0.08	0.33	0.02	0.09	0.86	−0.09	0.13	0.52
Model 2	−0.10	0.09	0.23	−0.03	0.09	0.78	−0.15	0.14	0.27
Model 3	-0.09	0.09	0.34	−0.03	0.10	0.78	−0.14	0.15	0.33
Knee extension strength									
Model 1	−0.02	0.08	0.77	0.03	0.07	0.64	0.04	0.14	0.78
Model 2	−0.01	0.09	0.92	0.07	0.07	0.31	0.01	0.14	0.95
Model 3	0.01	0.09	0.88	0.07	0.08	0.35	0.02	0.15	0.88
ALM/height²									
Model 1	0.06	0.09	0.54	-0.04	0.12	0.75	-0.12	0.12	0.30
Model 2[a]	0.06	0.12	0.64	-0.17	0.17	0.31	-0.25	0.16	0.14
Model 3[a]	0.10	0.12	0.42	-0.17	0.18	0.34	-0.19	0.17	0.28
Lean mass percentage									
Model 1	0.09	0.09	0.33	0.01	0.10	0.96	-0.06	0.10	0.55
Model 2[b]	0.07	0.09	0.45	-0.03	0.10	0.78	-0.09	0.11	0.41
Model 3[b]	0.10	0.10	0.31	-0.04	0.11	0.74	-0.07	0.11	0.51
Eyes closed (available)	*(n=119)*			*(n=75)*					
Handgrip strength									
Model 1	0.09	0.08	0.30	0.10	0.10	0.32			
Model 2	0.06	0.08	0.46	0.08	0.11	0.47			
Model 3	0.05	0.09	0.55	0.05	0.12	0.67			
Knee extension strength									
Model 1	0.14	0.10	0.15	0.23	0.12	0.06			
Model 2	0.17	0.10	0.08	0.27	0.13	0.033			
Model 3	0.14	0.10	0.16	0.17	0.14	0.23			
ALM/height²								n.a.	
Model 1	0.06	0.11	0.60	0.04	0.17	0.82			
Model 2[a]	-0.10	0.15	0.53	-0.04	0.25	0.88			
Model 3[a]	-0.07	0.15	0.65	0.06	0.27	0.81			
Lean mass percentage									
Model 1	-0.02	0.09	0.80	0.11	0.13	0.43			
Model 2[b]	-0.06	0.09	0.53	0.04	0.13	0.78			
Model 3[b]	-0.10	0.09	0.28	0.03	0.15	0.85			

(Table legend for Table 4a and 4b) All muscle characteristics were standardized in gender-specific Z-scores. Model 1: adjusted for age, model 2: as model 1 and body mass and height, model 3: as model 2 and Mini Mental State Examination and multimorbidity. [a]: not adjusted for height. [b]:not adjusted for body

Table 4b: Association between muscle characteristics and CoP movement in anterior-posterior direction in different standing positions with eyes open and eyes closed.

	Side-by-side			Semi-tandem			Tandem		
	Beta	SE	P	Beta	SE	P	Beta	SE	P
Eyes open (available)	*(n=136)*			*(n=120)*			*(n=56)*		
Handgrip strength									
Model 1	0.04	0.08	0.62	0.05	0.08	0.58	0.03	0.12	0.81
Model 2	0.07	0.08	0.37	0.002	0.09	0.98	−0.01	0.13	0.96
Model 3	0.07	0.08	0.37	−0.01	0.09	0.93	−0.05	0.14	0.70
Knee extension strength									
Model 1	0.05	0.08	0.48	−0.01	0.07	0.91	−0.06	0.14	0.69
Model 2	0.11	0.08	0.18	0.02	0.07	0.76	−0.08	0.15	0.63
Model 3	0.13	0.08	0.11	0.02	0.07	0.75	-0.06	0.16	0.73
ALM/height²									
Model 1	-0.18	0.09	0.04	0.03	0.11	0.80	-0.19	0.12	0.11
Model 2[a]	-0.18	0.11	0.11	-0.12	0.16	0.45	-0.23	0.17	0.18
Model 3[a]	-0.15	0.11	0.19	-0.11	0.16	0.50	-0.22	0.18	0.22
Lean mass percentage									
Model 1	0.10	0.08	0.24	0.00	0.09	0.96	-0.03	0.11	0.82
Model 2[b]	0.09	0.09	0.28	-0.02	0.10	0.80	-0.04	0.11	0.75
Model 3[b]	0.14	0.09	0.14	-0.02	0.10	0.85	-0.04	0.12	0.75
Eyes closed (available)	*(n=119)*			*(n=75)*					
Handgrip strength									
Model 1	0.06	0.08	0.45	−0.11	0.10	0.28			
Model 2	0.05	0.08	0.54	−0.14	0.10	0.17			
Model 3	0.05	0.08	0.57	-0.18	0.11	0.11			
Knee extension strength									
Model 1	0.11	0.09	0.21	0.04	0.12	0.74			
Model 2	0.17	0.09	0.06	0.07	0.13	0.57			
Model 3	0.15	0.09	0.12	0.01	0.14	0.93			
ALM/height²								n.a.*	
Model 1	-0.05	0.11	0.68	0.22	0.15	0.16			
Model 2[a]	-0.14	0.14	0.32	-0.42	0.23	0.08			
Model 3[a]	-0.08	0.15	0.61	-0.31	0.25	0.23			
Lean mass percentage									
Model 1	0.02	0.09	0.87	0.02	0.13	0.89			
Model 2[b]	-0.01	0.09	0.93	-0.04	0.13	0.76			
Model 3[b]	0.00	0.09	1.00	-0.02	0.14	0.91			

(continued from Table legend 4a) mass. n.a.: not applicable, number of elderly outpatients able to maintain the balance condition is less than 5. ALM: appendicular lean mass.

No association between measures of muscle mass and the ability to maintain standing balance was found in the present study. A limited number of studies describe the association between muscle mass and ability to maintain standing balance (12;27). A positive association has been described between quadriceps muscle mass and one-leg standing time in healthy elderly (12). Furthermore, Janssen et al. reported a positive association between lean mass percentage and the ability to maintain balance in tandem stance in males aged over 60 years (27). Previous research on the association between muscle mass and CoP movement is limited, reporting a positive association for quadriceps muscle mass (12), and no association for lean mass divided by height squared (14).

The fact that in the current study muscle strength was found to be associated with the ability to maintain standing balance rather than muscle mass, is explained by the differences between the characteristics "muscle strength" and "muscle mass". Muscle strength appears to decline more with age than muscle mass (32-35). Other factors in addition to muscle mass are important to generate muscle strength such as neural control, cognition, cardiovascular and joint function (35). Furthermore, due to pain muscle strength may be underestimated (36;37). Muscle tissue is not only a force generator, but has an important function as an internal organ, i.e. involved in glucose metabolism (38;39). Maintenance of standing balance obviously reflects the role of muscle as a strength generator (35;40). In this respect, this article provides further evidence to include assessment of muscle strength in clinical practice (41-43).

A possible explanation for the absence of an association between muscle characteristics and CoP movement could be selection of the fittest. CoP movement could only be assessed in outpatients who completed the standing balance conditions. Another explanation is large heterogeneity among elderly outpatients: the presence of multimorbidity and the deterioration of multiple systems involved in standing balance, i.e. sensory systems and neural control may interfere with the association between muscle characteristics and CoP movement (11;17;18). For instance, in patients with an intact sensory system and neural control, a higher muscle mass or strength may be associated with low CoP movement. In patients with deterioration of the sensory or neural system, high muscle strength could also be the result of repetitive use of muscles as compensatory strategy. For these patients, higher muscle mass or strength would therefore be associated with higher CoP movement. A decline of distinct systems and compensatory strategies can result in comparable CoP movement (44). In fact, lower CoP movement may not be related to better quality of standing balance, despite previously described differences in CoP movement between young and old adults (25).

The question arises whether an increase in muscle strength does improve standing balance in elderly outpatients. Physical exercise and training programmes have been shown to be beneficial in elderly, as they lead to an increase of muscle mass, muscle strength and even neuromuscular activity (45;46), although not all trials show a positive effect (47). Suppletion of hormones (48), vitamin D, or nutrients (46;49) may increase or prevent further decrease of muscle mass and strength. However, evidence is still very weak, as large scale placebo controlled intervention studies for long term effects of interventions are missing. Regarding strength training, a systematic review of randomized controlled trials including elderly showed a positive effect of resistance training to improve balance in 18 of 33 randomized controlled trials. These studies included a range of methods (static and dynamic) to measure 'balance' (50). Two of these randomized controlled trials included elderly with mobility difficulties (51;52): one trial found an improved balance after training in a small number of elderly in the intervention group (51), and one trial found no effect on balance (52).

Strength of this study was the combined analyses of both muscle strength and muscle mass with the ability to maintain standing balance and CoP movement. The population of elderly outpatients is unique as there were no exclusion criteria. By assessing the ability to maintain standing balance in elderly outpatients, results of this study will be highly relevant in clinical practice. The heterogeneity of the study population implies that larger numbers of outpatients need to be assessed to relate outcome measures to function of specific systems involved in standing balance, i.e. sensory systems and neural control. Another limitation is the cross-sectional design, which prevents assessments causal inference.

Conclusion

Muscle strength rather than muscle mass is associated with the ability to maintain standing balance in community-dwelling elderly referred to a geriatric outpatient clinic. This indicates the additional value of assessment of muscle strength in clinical practice. Improvement of muscle strength is a target for potential intervention for impaired standing balance in this population of elderly outpatients with multimorbidity.

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Chapter 9

Key findings and general discussion

Sarcopenia has been associated with a higher mortality, poor physical functioning, poor outcome of surgery and higher drug toxicity (1-4). Despite increasing knowledge on the clinical implications of sarcopenia, there is no general consensus on the definition of sarcopenia.

To diagnose sarcopenia in clinical practice a clear definition for sarcopenia is needed. Since the coining of the term 'sarcopenia' in 1989, many different diagnostic criteria have been suggested to establish a clinically applicable definition (5). The aim of the research presented in this thesis was to assess the implications of the use of different diagnostic criteria for sarcopenia, and to define the most accurate criteria for sarcopenia.

This chapter summarizes the key findings presented in this thesis, reflects on differences between diagnostic criteria for sarcopenia, and includes recommendations for the definition of sarcopenia and future research.

Diagnostic criteria for sarcopenia

Diagnostic criteria for sarcopenia that are being used in literature can be divided into criteria based on (1) low muscle mass (1;6), (2) low muscle strength (7), and (3) low walking speed (8;9). It is important to note that most of these diagnostic criteria include cut-off points based on 'low muscle mass', and not 'loss of muscle mass'. In this thesis it was shown that criteria based on low muscle mass can be further divided into relative muscle mass and absolute muscle mass. Lean mass as measured with bioimpedance analysis (BIA) or dual-energy X-ray absorptiometry (DXA) was used as an estimate of muscle mass. Absolute muscle mass was defined as the unadjusted total amount of lean mass in kilograms, or as the appendicular lean mass divided by height squared (ALM/height^2) (1). Although the formula ALM/height^2 corrects for body height, we considered ALM/height^2 to be an absolute measure of muscle mass, as results in **Chapters five to eight** show the importance of adjusting for fat mass or body mass. Relative muscle mass was defined as the amount of muscle mass as percentage of total body mass (lean mass percentage or ALM percentage) (10).

In **Chapter four** it was shown that the prevalence of sarcopenia in middle-aged to older adults from the Leiden Longevity Study (LLS) varied widely depending on which diagnostic criteria and cut-off points were used. Criteria based on low grip strength and absolute muscle mass failed to match with criteria based on relative muscle mass. Therefore, the presence of sarcopenia in participants was highly dependent on the used criteria. This indicates that the variance in prevalence of sarcopenia ranging from 7 to 40 percent between cohorts could be at least partially

explained by the use of different diagnostic criteria (11). Consequently, concerns were raised about the validity of comparison between studies using different criteria to diagnose sarcopenia.

Sarcopenia and muscle related outcome

Muscle tissue is important in the generation of force and in physical performance (1;6;12). In addition, muscle tissue is an important internal organ involved in protein storage, glucose regulation, hormonal homeostasis and cellular communication (4;13;14). Finally, muscle tissue can stimulate bone formation, by mechanical stress exerted on bones (15;16). In this thesis, diagnostic criteria for sarcopenia were compared in their association with these different aspects of muscle related clinical outcome.

Association of diagnostic criteria for sarcopenia with physical performance

In **chapter five**, we compared the predictive value of relative and absolute muscle mass and muscle strength with respect to physical performance: walking speed, Timed Up and Go test (TUG) and physical fitness as estimated with the Astrand-Rhyming test. In old participants of the MYOAGE study, relative muscle mass was the only diagnostic criterium for sarcopenia associated with all the tested parameters of physical performance: walking speed, TUG, and physical fitness. Contrarily, absolute muscle mass was not associated with physical performance. Knee extension torque and handgrip strength were associated with a faster walking speed. Knee extension torque was associated with TUG. Handgrip strength was not associated with TUG. Knee extension torque and handgrip strength were not associated with physical fitness. In young participants of the MYOAGE study, diagnostic criteria for sarcopenia were not associated with physical performance, except for a positive association between relative muscle mass and physical fitness. We concluded that relative muscle mass was most associated with physical performance, whereas absolute muscle mass was not associated with physical performance. Diagnostic criteria for sarcopenia cannot be used interchangeably in the association with physical performance.

Association of diagnostic criteria for sarcopenia with glucose regulation

In **Chapter six** we compared the association between different diagnostic criteria for sarcopenia and valid measures of insulin resistance derived from an oral glucose tolerance test (OGTT). Measures of insulin resistance were: area under the

curve (AUC) insulin, AUC glucose, and homeostasis model assessment for insulin resistance (HOMA-IR). In middle aged and older non-diabetic males and females from the MYOAGE study and LLS, relative muscle mass was inversely associated with OGTT derived measures of insulin resistance. Contrarily, absolute muscle mass was positively associated with AUC insulin and HOMA-IR, and not associated with AUC glucose. This association appeared to be influenced by the amount of fat mass. Handgrip strength was not associated with OGTT derived measures of insulin resistance. Walking speed was only associated with AUC insulin in males. We concluded that the role of muscle tissue as an internal glucose regulating organ is better reflected by relative muscle mass than by muscle strength or walking speed.

Association of diagnostic criteria for sarcopenia with bone mineral density

In **Chapter seven** we compared diagnostic criteria for sarcopenia with respect to their association with BMD in healthy young and old men and women of the MYOAGE study. Besides, we investigated whether muscle mass or fat mass as components of body mass were most strongly associated with BMD. Absolute muscle mass was most strongly positively associated with BMD in all subgroups. Relative muscle mass was inversely associated with BMD in old women, and not significantly associated with BMD in other subgroups. This association in old women appeared to be influenced by the total body mass. Muscle strength was associated with whole body BMD in young participants and older men, but not in old women. Walking speed and TUG were not associated with BMD.

Association of diagnostic criteria for sarcopenia with standing balance

In **Chapter eight** we compared muscle mass and muscle strength with respect to their association with standing balance in community-dwelling elderly referred to a geriatric outpatient clinic. Standing balance was measured with the ability to maintain balance during ten seconds in different balance conditions, and with the quality of balance during these conditions, measured as the movement of the center of pressure. Handgrip and knee extension strength were positively related to the ability to maintain balance with eyes open in side-by-side, semi-tandem, and tandem stance, and with eyes closed in side-by-side and semi-tandem stance (knee extension strength only). Relative and absolute muscle mass were not associated with the ability to maintain standing balance, except for an association between absolute muscle mass and tandem stance with eyes open that disappeared in the fully adjusted model. Muscle mass and muscle strength were not associated with quality of standing balance.

Reflection

Sarcopenia versus Dynapenia

In **Chapters four to eight**, obvious differences between muscle mass and muscle strength were observed. Previously it has been shown that muscle strength declines much more with age than absolute muscle mass (17). An explanation for differences, is that other factors in addition to muscle mass are important to generate muscle strength such as neural control, cognition, cardiovascular and joint function (18). These factors are also known to deteriorate with increasing age (19;20). It is shown that muscle strength is more predictive than muscle mass of certain outcome parameters such as disability (21) or mortality (22). Therefore, it has been suggested to differentiate between the terms 'sarcopenia' for a low muscle mass, and 'dynapenia' for a low muscle strength (18;23). Others argue against the separation of the terms sarcopenia and dynapenia due to risk of nomenclature introducing confusion (24).

This thesis underlines that sarcopenia and dynapenia have different implications in old age. It appears that the predictive value of sarcopenia and dynapenia is dependent on the muscle related outcome of interest. If neural control is involved in the muscle related outcome of interest, as is the case with standing balance, this outcome is probably better predicted by muscle strength as neural control is also needed to generate strength. If the functioning of muscle tissue as an internal organ is evaluated, as is the case with insulin resistance, the muscle related outcome is better predicted by muscle mass. On the other hand, relative muscle mass was predictive of Timed Up and Go test and walking speed which also requires neural control.

The characteristics of the study population may also affect the predictive value of sarcopenia and dynapenia. The geriatric outpatient population studied in **Chapter eight** is more frail as compared to the relatively healthy MYOAGE older adults. In the more frail elderly, muscle strength was lower and therefore more likely below the threshold needed for safe standing and walking. In the healthy older adults from the MYOAGE study it is possible that the age-related decline in muscle strength is not yet below the threshold for impact on muscle related outcome such as the ability to maintain balance. Future research is needed to explore whether relative muscle mass has the same predictive value for physical performance, glucose regulation, and bone mineral density in more frail elderly as it has in healthy older adults.

Because of the differences between muscle mass and muscle strength, it is suggested to use the term sarcopenia for low muscle mass only, and dynapenia for a low muscle strength.

Consensus groups on sarcopenia, walking speed and frailty

The need for a consensus definition for sarcopenia has been recognized before. Several consensus groups have been established to reach consensus for defining sarcopenia. Currently it is suggested to use walking speed as diagnostic criterion for sarcopenia, combined with a low muscle mass or muscle strength (8;9). Walking speed has been shown a good predictor of mortality (24), overall health and functional status (25). This is an argument to measure walking speed in clinical practice as a predictor of general health. However, reservations can be expressed about the use of walking speed to detect sarcopenia. Walking speed is not dependent on muscle tissue only, but also requires the functioning of other systems. Furthermore, walking speed has also been used in diagnostic criteria for frailty, which makes the distinction between frailty and sarcopenia less clear (26). Besides, in frail elderly who are unable to walk, walking speed cannot be measured. In this thesis, walking speed was not predictive of the multiple functions of muscle tissue, and therefore not an appropriate diagnostic criterion to define sarcopenia.

Despite the effort of consensus working groups, there is no unanimous agreement on the definition for sarcopenia, so that different definitions still co-exist in scientific literature.

Relative muscle mass versus absolute muscle mass

In **Chapters six and seven** the association between muscle mass and insulin resistance and BMD respectively, was in the opposite direction for relative muscle mass as compared to absolute muscle mass. This indicates that relative and absolute muscle mass are different characteristics. In order to visualize differences between relative and absolute muscle mass, body mass and fat mass, we combined DXA and BIA data from the MYOAGE study, the Leiden Longevity study and elderly outpatients, described in detail in this thesis. This analysis shows a poor correlation between relative and absolute muscle mass (figure 1). This poor correlation may be explained by differences between relative and absolute muscle mass in their correlation with body mass (figure 2) and fat mass (figure 3). A higher body or fat mass is correlated with a lower relative muscle mass but with a higher absolute muscle mass. Differences between relative and absolute muscle mass have been described before (10). In line with the correlations presented in figure 2 and 3, a higher body mass index was associated with a lower relative muscle mass but with a higher absolute muscle mass (10).

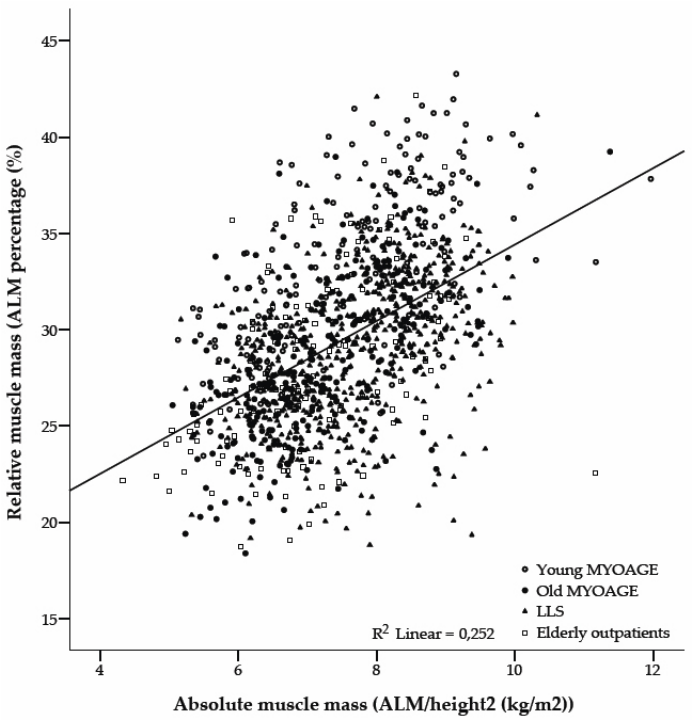

Figure 1: *Scatterplots with fit line for the correlation between absolute muscle mass (appendicular lean mass divided by height squared) and relative muscle mass (appendicular lean mass as percentage of body mass). Preliminary analyses in young and old adults from the MYOAGE study, the LLS, and elderly outpatients. Colors represent the different study cohorts and age categories.*

Role of fat mass or body mass on muscle related outcome

Studying the association between relative muscle mass with muscle related outcome such as insulin resistance, the question arises whether observed associations are caused by muscle mass or by fat mass. A change in muscle mass at older age is often associated with a change in fat mass (10;12). The inverse relation of relative muscle mass but not absolute muscle mass with insulin resistance can be explained by the effect of fat mass. The positive relation between absolute muscle mass and measures of insulin resistance attenuated after adjustment for fat mass in this study. Adjusting muscle mass for height only, as was first suggested by Baumgartner (1) seems to be insufficient to account for the influence of fat mass. Fat secreted adipokines and the recently described muscle secreted myokines appear to be involved in the cross-talk between fat mass and skeletal muscle mass (27;28).

The association between absolute muscle mass and muscle-related outcome is highly

influenced by fat mass, as is shown in **Chapters four to seven**. These examples illustrate that fat mass or body mass are important confounders when assessing the role of muscle mass.

Cut-off points and reference populations

Next to differences between relative and absolute muscle mass, the diagnosis of sarcopenia depends on reference populations and cut-off points. Ideally, the amount of muscle mass in an elderly patient is compared with the amount of muscle mass during the patient's own adult life, to measure 'loss of' muscle mass. In the absence of previous measurements of muscle mass, cut-off points for sarcopenia have been suggested for assessment of muscle mass on an individual level in clinical practice. In **chapter four** it was shown that cut-off points for sarcopenia have been based on two standard deviations below a young reference populations mean (1), the lowest percentile in an elderly population (29), or from the association with low physical functioning (7;30). Differences in reference populations may be caused by age, ethnicity, genetic background and environmental factors such as the level of physical activity. Besides deciding on which diagnostic criteria for sarcopenia to use, it is important to agree on reference populations that can be used in specific ethnic groups. Establishing reference databases generally requires a large sample size to achieve reliable results. Furthermore, it remains important to invest in longitudinal studies including the general population. Assessing the relation between muscle mass and muscle related outcome in these studies, helps to establish possible critical thresholds of muscle mass needed for muscle function.

Clinical implications

Currently the presence of sarcopenia is not always recognized in clinical practice. Results presented in this thesis contribute to understand the importance of clinical recognition of sarcopenia. We have shown that muscle mass is not only related to physical performance, but also to glucose regulation and bone mineral density. By reviewing the literature we found an association of sarcopenia with increased drug toxicity and poor outcome after surgery (**Chapter two**). This should be taken into account in clinical practice when sarcopenia is recognized.

Final implementation of the term sarcopenia is difficult in the absence of a generally accepted definition for sarcopenia, but currently used cut-off points could contribute to clinical judgement when sarcopenia is suspected (Table 1, **Chapter two**). Physical exercise and training programmes have been shown to be of benefit to elderly, as they lead to an increase of muscle mass, muscle strength and even neuromuscular activity

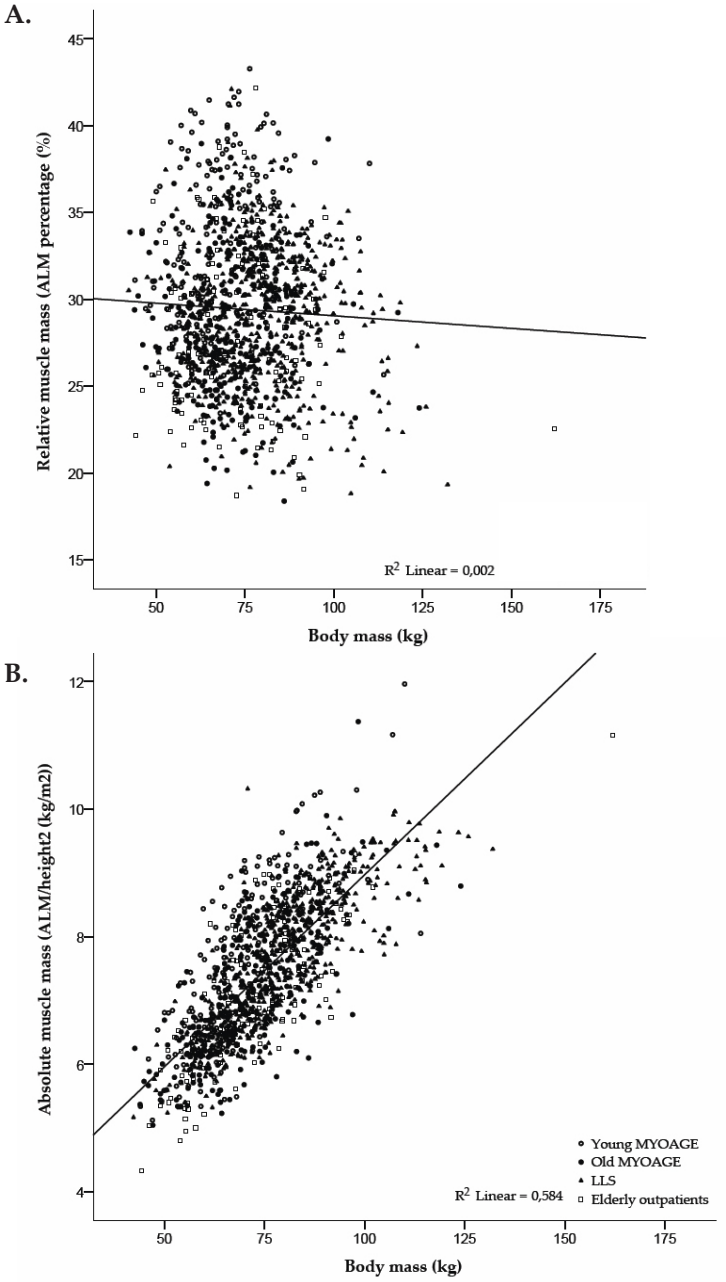

Figure 2: *Scatterplots with fit lines for the correlation between (A) relative muscle mass (appendicular lean mass as percentage of body mass) and body mass; and (B) absolute muscle mass (appendicular lean mass divided by height squared) and body mass. Symbols represent the different study cohorts: young (18-30 y) and old adults (69-81 y) from the MYOAGE study, the Leiden Longevity Study (mean age 63 y), and elderly outpatients (mean age 82 y).*

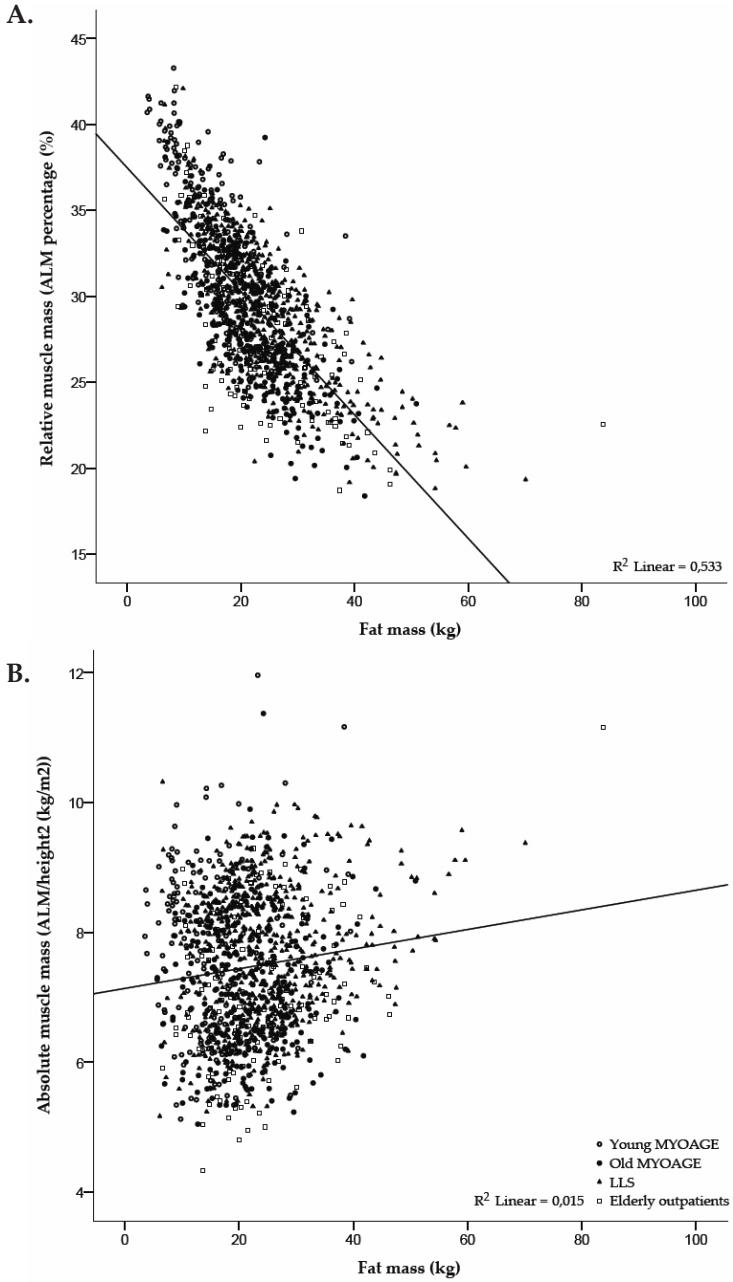

Figure 3: *Scatterplots with fit lines for the correlation between (A) relative muscle mass (appendicular lean mass as percentage of body mass) and fat mass; and (B) absolute muscle mass (appendicular lean mass divided by height squared) and fat mass. Symbols represent the different study cohorts: young (18-30 y) and old adults (69-81 y) from the MYOAGE study, the Leiden Longevity Study (mean age 63 y), and elderly outpatients (mean age 82 y).*

(19;31), although not all trials have been successful (32). Furthermore, suppletion of hormones (33), vitamin D or nutrients (31;34) may be helpful to increase or prevent further decrease of muscle mass. However, evidence is still very weak, as large scale placebo controlled intervention studies for long term effects are missing.

General conclusions and future research

The first aim of this thesis was to assess the implication of the use of different diagnostic criteria for sarcopenia. Currently used diagnostic criteria for sarcopenia consist of relative or absolute muscle mass, muscle strength, and walking speed. It is important to note that most of these diagnostic criteria include cut-off points based on 'low muscle mass', and not 'loss of muscle mass'. Results from this thesis contribute to the understanding that these diagnostic criteria cannot be used interchangeably in the definition of sarcopenia. The use of different diagnostic criteria for sarcopenia leads to confusion and poor understanding of what is described. It is impossible to compare studies on sarcopenia when different diagnostic criteria are used to define sarcopenia.

The second aim of this thesis was to define the most accurate criteria for sarcopenia. Despite the work presented in this thesis, it remains difficult to be conclusive on the most accurate criteria. However, recommendations can be given. To avoid confusion, the term sarcopenia should be reserved for a low muscle mass and dynapenia for a low muscle strength. Comparing sarcopenia and dynapenia, dynapenia is more predictive of muscle related outcome where neural control is important, i.e. for standing balance. Sarcopenia is better associated with muscle related outcome that reflects muscle tissue as an internal organ such as insulin resistance. Defining sarcopenia as 'low muscle mass' is not specific enough, as results presented in this thesis show that there is an important difference between relative muscle mass and absolute muscle mass. Absolute muscle mass defined as ALM/height^2 is highly dependent on fat mass or body mass and not a good predictor of insulin resistance or physical performance. There was a positive association between absolute muscle mass and BMD, probably because of the weight-bearing effect on bone. Relative muscle mass defined as ALM or lean mass as percentage of body mass is a good predictor of insulin resistance and physical performance, but the disadvantage is that it is difficult to conclude if associations are due to a higher relative muscle mass or due to a lower relative fat mass, even after adjustments for fat mass. Based on results presented in this thesis it is recommended to use relative muscle mass as diagnostic criterion for sarcopenia.

Future research is needed to assess if sarcopenia is simply a marker for health and underlying disease, or a cause of poor outcome. There is a need for studies aimed to improve muscle mass in a randomized controlled way, including muscle related outcome as endpoint. Furthermore, studies are needed to explore whether drug dosage based on muscle mass leads to less drug toxicity when compared to drug dosage based on body surface area in geriatric oncology.
Knowledge on clinical consequences of sarcopenia and meaningful cut-off points would help to finally settle the debate on the definition of sarcopenia.

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Chapter 10

Summary in Dutch - Nederlandse Samenvatting
Acknowlegdements - Dankwoord
List of Publications
List of Co-author Affiliations
About the Author

Introductie

Het aantal ouderen is de laatste jaren flink toegenomen en de levensverwachting stijgt nog steeds in de Westerse samenleving. In de afgelopen 40 jaar is het aantal mensen boven de 65 jaar verdubbeld, met bijna 2,6 miljoen ouderen in 2011 in Nederland (1). Met het toenemen van de leeftijd is de vraag hoe wij gezond oud kunnen worden zeer actueel. Gezond oud worden, betekent niet alleen het uitblijven van een ernstige ziekte, maar ook het zelfstandig kunnen blijven functioneren. Uit onderzoek is gebleken dat de hoeveelheid spiermassa na het 50ste levensjaar afneemt met ongeveer 1 à 2 procent per jaar (2). Verlies van spiermassa en spierkracht kan het vermogen zelfstandig te functioneren bedreigen. Ook kan de functie van de spier als intern orgaan veranderen.
In 1989 is de term sarcopenie geïntroduceerd om een gebrek aan spiermassa op oudere leeftijd te beschrijven (3). Momenteel zijn er veel verschillende diagnostische criteria voor sarcopenie die in de literatuur worden beschreven (4-9). Hierdoor is het onduidelijk welke diagnostische criteria gebruikt dienen te worden om sarcopenie in de wetenschap of in de praktijk vast te stellen.
In dit proefschrift wordt onderzocht wat de consequenties zijn van het hanteren van verschillende diagnostische criteria voor sarcopenie. Het uiteindelijke doel is het vinden van de beste definitie voor sarcopenie.

De spier als multifunctioneel orgaan

Hoofdstuk twee geeft een overzicht van de huidige literatuur over een aantal aspecten van sarcopenie. Hieruit blijkt de multifunctionaliteit van de spier als orgaan. De spier is behalve krachtsleverancier, betrokken bij eiwitopslag, glucoseregulatie, hormoonhuishouding en cellulaire communicatie (2). Een lage spiermassa is gerelateerd aan een hogere kans op sterfte, afhankelijkheid in dagelijks functioneren, bijwerkingen van chemotherapie en ouderdomssuikerziekte (4;6;10-12). Ook bij een zeer actieve leefstijl kan sarcopenie optreden door systemische, cellulaire en neuromechanische factoren.

Sarcopenie in vergelijking met osteoporose

Sarcopenie is niet het enige begrip binnen de ouderengeneeskunde met discussie over de definitie. Voor de leeftijdsgerelateerde ziekte osteoporose ('botontkalking') dateert deze discussie al van 1940, toen de eerste medische definitie voor osteoporose werd

beschreven. De term osteoporose bestond toen al ruim honderd jaar. Om te kunnen leren van deze oude discussie vergeleken wij het proces voor het tot stand komen van een definitie voor osteoporose met sarcopenie in **Hoofstuk drie**. Een aantal mijlpalen is geïdentificeerd voor het ontwikkelen van een universeel geaccepteerde definitie voor osteoporose. Voor sarcopenie zijn de eerste stappen reeds genomen, te weten het ontstaan van de term sarcopenie, het vormen van criteria om sarcopenie vast te stellen en het begrijpen van de consequenties van sarcopenie. Resterende stappen voor het vormen van een algemeen gebruikte definitie van sarcopenie zijn specifieke behandelingsmogelijkheden, interesse van de farmaceutisch industrie en publieke kenbaarheid.

Studie populaties

MYOAGE Studie Een deel van het onderzoek beschreven in dit proefschrift maakt gebruik van gegevens van deelnemers aan de MYOAGE studie. Binnen het Europese onderzoeksproject "MYOAGE" wordt onderzoek gedaan naar de mechanismen van spierveroudering. In Nederland, Engeland, Finland, Estland en Frankrijk zijn in totaal 462 deelnemers geïncludeerd, bestaande uit jongeren (18 to 30 jaar oud) en ouderen (69 tot 81 jaar oud). De ouderen werden geselecteerd op het hebben van een goede gezondheid, en onderverdeeld in twee groepen op basis van een lager of juist hoger activiteitenniveau. Deelnemers aan deze studie bezochten het studiecentrum in Leiden.
Leiden Langleven Studie In de Leiden Langleven Studie (LLS) werden 420 families geïncludeerd bestaande uit langlevende Kaukasische broers en zussen samen met de kinderen en de partners van hun kinderen. In dit proefschrift worden gegevens beschreven van de kinderen en hun partners van middelbare tot oudere leeftijd, bij wie de spiermassa is gemeten (n=654). Deelnemers aan deze studie bezochten het studiecentrum in Leiden.
Patiënten van de geriatrische polikliniek In de periode tussen maart 2011 en januari 2012 zijn 207 patiënten van de geriatrische polikliniek in het Bronovo Ziekenhuis te Den Haag onderzocht middels een standaard geriatrische analyse.

Verschillende diagnostische criteria voor sarcopenie

Sarcopenie blijft vaak onopgemerkt, omdat de afnemende spiermassa wordt opgevuld door vet en bindweefsel. Spiermassa kan worden gemeten met dual-energy X-rayabsorptiometry (DEXA) of bioimpedantie analyse (BIA)(13). Spierkracht kan

worden bepaald door het meten van de handknijpkracht als proxy voor algehele spierkracht.
Diagnostische criteria voor sarcopenie die momenteel gebruikt worden kunnen grofweg worden ingedeeld in drie categorieën: een lage spiermassa, een lage spierkracht, of een lage loopsnelheid. Uit dit proefschrift blijkt dat de spiermassa kan worden onderverdeeld in een absolute spiermassa en een relatieve spiermassa, afhankelijk van gebruikte correctiefactoren (zie **Hoofdstuk 1**, Figuur 1). Daarnaast worden verschillende afkappunten beschreven waarbij sarcopenie vastgesteld kan worden.
Het gebruik van verschillende diagnostische criteria om sarcopenie vast te stellen heeft grote gevolgen. In **Hoofdstuk vier** onderzochten wij de invloed van het gebruik van verschillende diagnostische criteria, op het vóórkomen van sarcopenie in de LLS. Het vóórkomen van sarcopenie was sterk afhankelijk van het gebruikte criterium. Dit betekent dat studies gebaseerd op verschillende criteria voor sarcopenie niet te vergelijken zijn.

Sarcopenie als voorspeller van spier-gerelateerde uitkomstmaten

Om vast te kunnen stellen welke diagnostische criteria voor sarcopenie het meest voorspellend zijn voor spier-gerelateerde uitkomstmaten, vergelijken wij deze criteria in **hoofdstuk vijf tot en met acht.**

Sarcopenie als voorspeller van fysiek functioneren

In **Hoofdstuk vijf** vergelijken wij de relatieve en absolute spiermassa en spierkracht voor wat betreft de voorspellende waarde van fysiek functioneren bij deelnemers van MYOAGE. Fysiek functioneren werd bepaald met een test voor de loopsnelheid, opstaan uit een stoel en afleggen van een parcours (TUG) en een fitness test. Bij oudere deelnemers bleek alleen een hogere relatieve spiermassa een voorspeller te zijn van beter functioneren op alle drie de testen. In tegenstelling tot relatieve spiermassa, was absolute spiermassa niet geassocieerd met de testen van fysiek functioneren. Oudere deelnemers met een hogere spierkracht hadden een hogere loopsnelheid en betere prestatie op de TUG, maar dezelfde prestatie op de fitness test in vergelijking met deelnemers met een lagere spierkracht. Uit deze resultaten hebben wij de conclusie getrokken dat relatieve spiermassa het meest voorspellend is voor fysiek functioneren.

Sarcopenie als voorspeller van insulineresistentie

In **Hoofdstuk zes** vergelijken wij de diagnostische criteria voor sarcopenie als voorspeller van insulineresistentie in deelnemers van de MYOAGE studie en de LangLeven Studie. Insuline is een hormoon dat zorgt voor de opname van suiker (glucose) in de spieren. Bij ouderdomssuikerziekte is er sprake van een verminderde gevoeligheid van de spier voor insuline (insulineresistentie). Er is dan meer insuline nodig om dezelfde hoeveelheid suiker op te nemen. Bij deelnemers met een lage relatieve spiermassa werd vaker een verminderde opname van suiker gezien, wat betekent dat er sprake is van meer insulineresistentie. Dit verband werd niet gezien bij andere diagnostische criteria voor sarcopenie. Er werd zelfs een tegengesteld effect gevonden in het verband tussen absolute spiermassa en insulineresistentie. Uit deze resultaten hebben wij de conclusie getrokken dat relatieve spiermassa het meest voorspellend is voor insulineresistentie.

Sarcopenie als voorspeller van botdichtheid

Een lage botdichtheid op oudere leeftijd (osteoporose) geeft een hogere kans op botbreuken. Op oudere leeftijd heeft een hoger lichaamsgewicht een beschermend effect op de botdichtheid. Dit komt waarschijnlijk doordat meer bot wordt aangemaakt als het bot meer belast wordt door het hogere lichaamsgewicht. In **Hoofdstuk zeven** vergelijken wij de diagnostische criteria voor sarcopenie als voorspeller voor botdichtheid in gezonde jongere en oudere mannen en vrouwen in de MYOAGE studie. Het blijkt dat vooral de absolute spiermassa een positieve voorspeller is van botdichtheid. Hoe meer absolute spiermassa, hoe sterker de botten, zowel op jonge als op oude leeftijd. Relatieve spiermassa was juist een negatieve voorspeller van botdichtheid in oudere vrouwen. Jonge mannen en vrouwen en oudere mannen met een hogere spierkracht hadden ook een hogere botdichtheid; dit effect was niet aanwezig in vrouwen. Loopsnelheid en TUG waren geen voorspellers van botdichtheid. Wij concluderen hieruit dat de mechanische invloed van spieren op bot het best voorspeld worden door de absolute spiermassa.

Sarcopenie als voorspeller van balans

In **Hoofdstuk acht** vergelijken wij de diagnostische criteria voor sarcopenie als voorspeller van positionele balans in patiënten van een geriatrische polikliniek. Oudere polipatiënten met een hogere spierkracht hadden een betere positionele balans dan patiënten met een lagere spierkracht. Spiermassa was een minder goede voorspeller van positionele balans.

Reflectie

In **Hoofdstuk negen** wordt een reflectie gegeven op de belangrijkste bevindingen van dit proefschrift. Uit dit proefschrift blijkt dat het van belang is onderscheid te maken tussen een lage spiermassa en een lage spierkracht op oudere leeftijd. De term sarcopenie kan het beste gebruikt worden voor een lage spiermassa, en voor een lage spierkracht het woord 'dynapenie' gebruikt.
Kritische kanttekeningen kunnen worden geplaatst bij het gebruik van loopsnelheid in de definitie van sarcopenie, zoals door verschillende werkgroepen voor sarcopenie is voorgesteld (in combinatie met een lage spiermassa of spierkracht) (8;9). Loopsnelheid is geen goede voorspeller voor de vele functies van de spier.
Daarnaast is het van belang relatieve en absolute spiermassa van elkaar te onderscheiden. Het verschil tussen deze maten is uit te leggen aan de hand van de relaties met vetmassa en totaal lichaamsgewicht. Een hoger lichaamsgewicht gaat samen met een lagere relatieve spiermassa maar een hogere absolute spiermassa (Figuur 2, Hoofdstuk negen)(14). Vetmassa kan de relatie tussen spiermassa en spier-gerelateerde uitkomstmaten beïnvloeden, hiermee dient rekening gehouden te worden bij het definiëren van sarcopenie.
Een ander punt van aandacht bij het definiëren van sarcopenie is het kiezen van de juiste referentiepopulatie om afkappunten te bepalen waarbij sprake is van sarcopenie. Deze afkappunten moeten voorspellend zijn voor uitkomstmaten. Een aantal afkappunten wordt momenteel al gebruikt in de literatuur voor het stellen van de diagnose sarcopenie (Tabel 1 van Hoofdstuk 2).
In de klinische praktijk kan het stellen van de diagnose sarcopenie relevant zijn. Bijvoorbeeld kan het aanleiding zijn voor training of aanpassing van voeding. Trainingsprogramma's blijken in staat om de spiermassa en spierkracht bij ouderen te vergroten, hoewel niet alle studies succesvol zijn. Tevens zijn er aanwijzingen dat suppletie van hormonen of voedingssupplementen kunnen bijdragen aan een hogere spiermassa. Grotere studies zijn noodzakelijk om hier meer zekerheid over te krijgen. Ook kan het meten van de spiermassa inzicht geven in de vitaliteit van de patiënt.

Conclusies en toekomstig onderzoek

Het eerste doel van dit proefschrift was om de consequenties van het hanteren van verschillende diagnostische criteria voor sarcopenie te onderzoeken. Dit proefschrift laat zien dat de criteria voor sarcopenie niet door elkaar gebruikt kunnen worden

in de definitie van sarcopenie. Studies gebaseerd op verschillende diagnostische criteria kunnen niet met elkaar worden vergeleken.

Het uiteindelijke doel van dit proefschrift was het vinden van de beste diagnostische criteria om sarcopenie te definiëren. Er kunnen aanbevelingen worden gedaan. De term sarcopenie dient te worden gereserveerd voor het beschrijven van een lage spiermassa. Voor het beschrijven van een lage spierkracht kan de term 'dynapenie' worden gebruikt. Het is afhankelijk van de gebruikte spier-gerelateerde uitkomstmaat welke maat het meest voorspellend is. Sarcopenie is een betere voorspeller voor de rol van de spier als intern orgaan, terwijl dynapenie mogelijk beter is om uitkomstmaten te voorspellen waarbij de aansturing van de spier door het zenuwstelsel van belang is zoals bij de positionele balans.

Dit proefschrift toont aan dat er een belangrijk verschil is tussen relatieve spiermassa en absolute spiermassa. Gebaseerd op resultaten in dit proefschrift is het aan te raden om relatieve spiermassa te gebruiken als diagnostisch criterium voor sarcopenie.

Toekomstig onderzoek is nodig om te bepalen of er ook een oorzakelijk verband is tussen sarcopenie en spier-gerelateerde uitkomstmaten. Verder is het nodig om in grote studies te onderzoeken of het verhogen van de spiermassa ook een verbetering geeft van uitkomstmaten op korte en op lange termijn. Op gebied van de geriatrische oncologie zijn studies nodig om te onderzoeken of het doseren van chemotherapie op basis van spiermassa te verkiezen is boven de huidige strategie om chemotherapie te doseren op basis van lichaamsoppervlakte. Kennis over betekenisvolle afkappunten voor het vaststellen van sarcopenie in de praktijk is nodig om het debat over de beste definitie van sarcopenie te beslissen.

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About the author

Astrid Yvonne Bijlsma was born on the 10th of August 1983 in Rotterdam, the Netherlands. In 2001 she graduated from high school at the Stedelijk Gymnasium in Nijmegen. She studied Medicine from 2001 till 2008 at the University of Groningen. Before obtaining her medical degree in 2008, she completed her final internship in Tropical Medicine in Nguludi Mission Hospital, Malawi. In 2008, she worked as a resident (ANIOS) in Obstetrics at the University Hospital in Utrecht. In September 2008 she started to work as a resident (ANIOS) in Internal Medicine, Pulmonary Medicine and Cardiology at the Groene Hart Hospital, Gouda, the Netherlands. During her time in Gouda she developed a great interest in Internal Medicine. In 2010 she was offered a position as a PhD Student at the Department of Gerontology and Geriatrics at the Leiden University Medical Center. She became involved in the European multi-center study MYOAGE. In Leiden she participated in the study design, recruitment and analyses of data obtained from participants, and database management. From 2012 onwards she co-worked at the VU University Medical Center, Amsterdam, finishing her PhD thesis.
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The definition of sarcopenia

Astrid Y. Bijlsma