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).

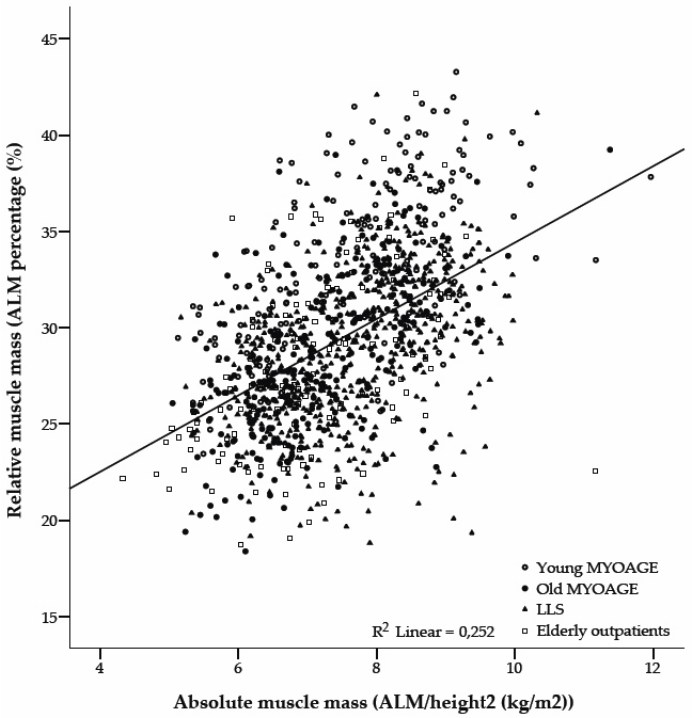

Figure 1: *Scatterplots with fit line for the correlation between absolute muscle mass (appendicular lean mass divided by height squared) and relative muscle mass (appendicular lean mass as percentage of body mass). Preliminary analyses in young and old adults from the MYOAGE study, the LLS, and elderly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

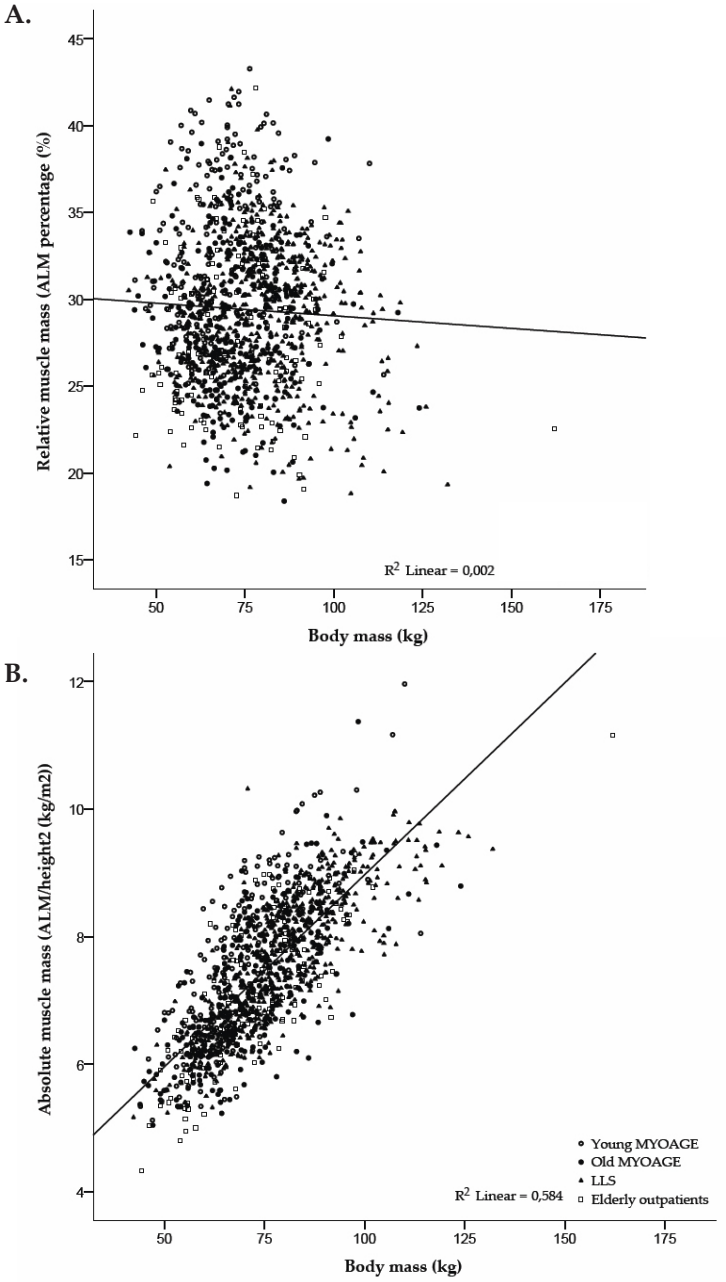

Figure 2: *Scatterplots with fit lines for the correlation between (A) relative muscle mass (appendicular lean mass as percentage of body mass) and body mass; and (B) absolute muscle mass (appendicular lean mass divided by height squared) and body mass. Symbols represent the different study cohorts: 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).*

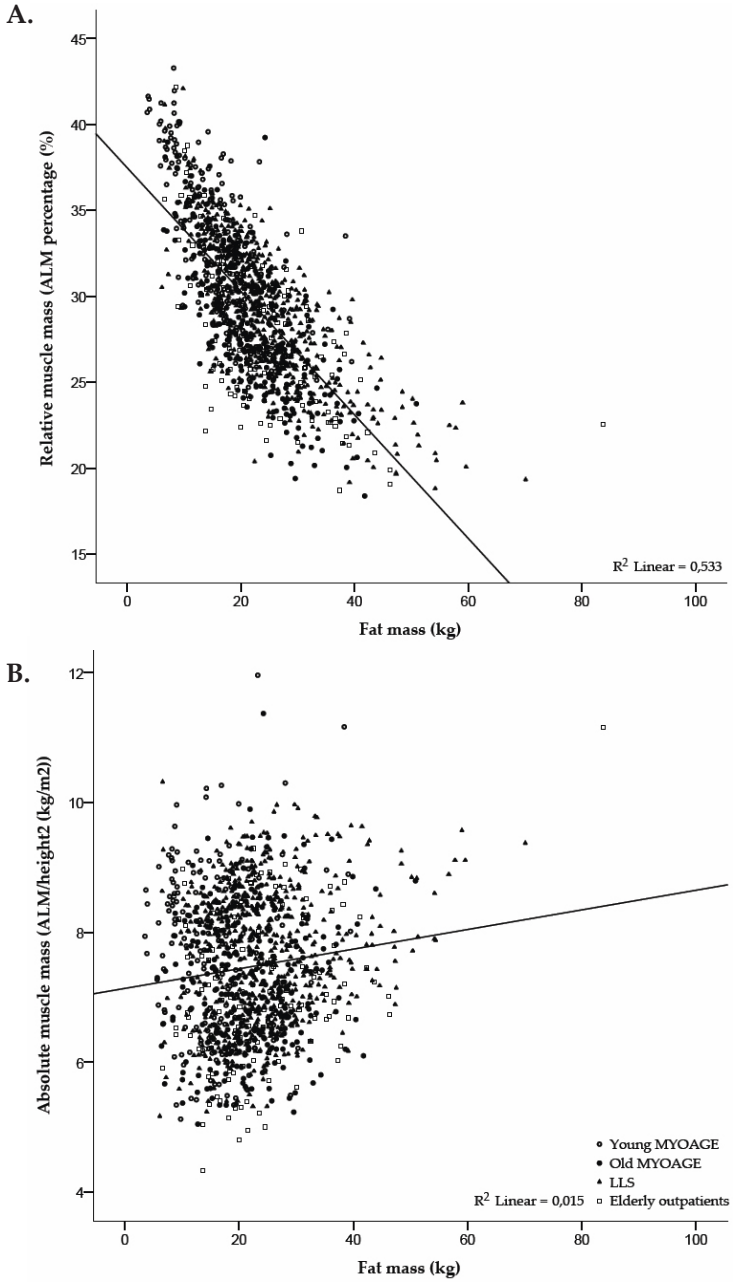

Figure 3: *Scatterplots with fit lines for the correlation between (A) relative muscle mass (appendicular lean mass as percentage of body mass) and fat mass; and (B) absolute muscle mass (appendicular lean mass divided by height squared) and fat mass. Symbols represent the different study cohorts: young (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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