Chapter 1
General introduction
Chapter 1

General introduction
In hospital, clinicians often face older patients in need of complex healthcare and at risk of adverse clinical outcomes. Older patients account for 35–40% of all hospitalizations\textsuperscript{1-3}, of whom an increasing proportion is diagnosed with multimorbidity\textsuperscript{4}, using a high number of medications\textsuperscript{5}. As a result, clinicians are challenged to adopt a total-body approach rather than focus on a single organ. Hospitalization induces deconditioning at any age, but particularly impacts older patients of whom a third suffers from hospital-associated deconditioning\textsuperscript{6-8}. The deconditioning-induced risk of functional impairments before, during and after hospitalization may be mediated by loss of muscle tissue due to catabolism\textsuperscript{9}. In this thesis, we use “muscle status” as an encompassing term describing the condition of muscle. Muscle status is operationalized by muscle mass, muscle strength, and physical performance. Poor muscle status can result in a disease state below clinical cut-off points termed sarcopenia\textsuperscript{10}, which is highly prevalent in hospitalized older adults and may lead to adverse outcomes during hospitalization and thereafter\textsuperscript{11}. This thesis aimed to obtain insights and raise awareness among clinicians, researchers and the general public about diagnostics, determinants and consequences of poor muscle status in older adults during hospitalization.

Hospitalization in older adults: impactful on muscle status
Hospitalization in older adults is often either a result from or initiates deconditioning. Older patients who are acutely admitted to the hospital are a selected group at risk of complications due to prolonged unstable disease, suffering from a higher number of morbidities\textsuperscript{12}. In 29–46% of these patients a (further) decline in activities of daily living (ADL) is seen during hospitalization\textsuperscript{6,7,13-15}. Two-thirds of these patients show an ADL decline in the acute illness period prior to hospitalization and one-third between admission and discharge\textsuperscript{7}. One-year follow-up after hospitalization showed that these patients poorly recover from this newly-acquired deconditioning impairment and are at high risk of remaining dependent upon care\textsuperscript{16,17}. A large part of this acquired impairment is assumed to be preventable\textsuperscript{18,19}. Although patients are informed about risks of illness or surgery, the risks of deconditioning and associated functional impairments are often not anticipated and come as an unpleasant surprise after hospital discharge\textsuperscript{20}. Poor muscle status may mediate the deconditioning effect of hospitalization (see Figure 1).

Decreases in external loading and neural activation due to inactivity, increases in cytokines and glucocorticoids due to disease, patient characteristics such as multimorbidity and polypharmacy, along with (protein) malnutrition may all contribute to poor muscle status before, during and after hospitalization\textsuperscript{13}; over 80% of a patient’s time in hospital is spent lying in bed and, on average only 43–66 minutes per day are spent standing up or walking\textsuperscript{21-24}. These inactivity levels are only partly due to disease, yet may also be attributable to fear of falling, culture of bed rest during illness, poor hospital management, and hospital design (e.g. poor lighting, noise, or isolation)\textsuperscript{25,26}. Malnutrition is also a frequently reported problem in over one-third of hospitalized older adults\textsuperscript{27-30}. Protein malnutrition is especially prevalent among those at older age, alongside decreased absorption of protein from food due to anabolic resistance\textsuperscript{31,32}. Duration of hospitalization in older adults is becoming increasingly
shorter\textsuperscript{1,3,33} — in 2016, the average length of stay was 5.2 days in the United States\textsuperscript{1}, 7.5 days in Europe\textsuperscript{33}, and 5.9 days in the Netherlands\textsuperscript{3}. While shortening of hospitalization is a worthwhile endeavor for reducing the risk of hospital–associated adverse events\textsuperscript{34}, it poses a challenge for healthcare after discharge, resulting in admission to nursing homes, geriatric rehabilitation and home care being increasingly responsible for older adults with more severe illness and impairments\textsuperscript{35-37}. Preventing poor muscle status during (any stage of) hospitalization could reduce this burden.

**Pathophysiology of poor muscle status during hospitalization: a catabolic state**

The factors described above that induce poor muscle status collectively contribute to a catabolic state. Catabolism is a state of proteolysis rates exceeding synthesis rates, resulting in a net loss of protein. This is exerted through different pathways. Skeletal muscle proteolysis is mainly stimulated by ubiquitin-proteasome system activation, via expression of transcription factor Forkhead box O3 (FoxO3) and Nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), and subsequent activation of atrogin-1/Muscle atrophy F-box (MAFbx) and Muscle

![Diagram](image-url)

**Figure 1.** Mediating effect of poor muscle status and influencing factors on the relation between hospitalization and functional impairment.
ring finger protein-1 (MURF-1)\textsuperscript{9,38,39}. Simultaneously, inactivity induces a decline in basal protein synthesis\textsuperscript{32,40}, resulting in downregulation of the anabolic pathways. Under normal circumstances stimulated by insulin and insulin-like growth factor 1 (IGF-1), inactivity inhibits phosphatidylinositol 3 kinase/protein kinase B (P13K/AKT) pathways that stimulate protein synthesis through glycogen synthase kinase-3 (GSK-3) and mechanistic target of rapamycin (mTOR)\textsuperscript{41-43}. During catabolic events, resting energy expenditure increases, subsequently increasing amino acid release from proteolysis. However, amino acids provide low efficiency of energy production and cause release of waste nitrogen, resulting in increased muscle tissue breakdown, creating a negative cycle of proteolysis and muscle deterioration\textsuperscript{38}. The catabolic response may not just be confined to the period of acute illness and hospitalization, but is expected to extend months after hospitalization\textsuperscript{44}.

**Poor muscle status especially impacts older adults**

Even though poor muscle status can occur in younger adults\textsuperscript{9}, the impact of hospitalization on muscle status is much more extensive in older adults as they possess lower physical reserves (see Figure 2). As beautifully put in writing by López-Otín and colleagues, ageing cells show nine different hallmarks\textsuperscript{45}, impacting muscle tissue with advancing age. Neuron denervation leads to atrophy of muscle fibers\textsuperscript{46}, mainly fast type II fibers\textsuperscript{47}, leading to morphological changes and fiber type switching in conjunction with the muscle tissue becoming fibrotic and infiltrated with adipose cells\textsuperscript{48}. Impaired satellite cell function prevents regeneration of muscle tissue\textsuperscript{49}. Additionally, older adults show higher postprandial anabolic resistance\textsuperscript{32}, higher levels of immunosenescence\textsuperscript{50}, and slower rehabilitation of explosive muscle strength\textsuperscript{51,52}. These factors combined characterize degradation of muscle tissue with age: From the 3rd decade of life onwards, people lose muscle mass at a rate of 3–5% per decade\textsuperscript{53-55}, accompanied by a 2–5 times more rapid loss of muscle strength\textsuperscript{55}. After the age of 60, muscle mass and muscle strength continue to decline at a faster rate\textsuperscript{53-55}. Decline in physical performance is observed somewhat later, from the 5th–6th decade onwards\textsuperscript{56}. Lower physical reserves may make older inpatients more vulnerable to the impact of hospitalization and may serve as a tipping point for crossing the threshold beyond which they become dependent on others\textsuperscript{7,13,14}.

Healthy older adults lose on average 3.2% of muscle mass and 15.6% of muscle strength during 10 days of bed rest\textsuperscript{57,58}. Below sex-specific clinical cut-off points, poor muscle status is termed sarcopenia (combined low muscle mass, muscle strength and physical performance\textsuperscript{10}). Sarcopenia has been recognized as a disease since September 2016, with the assignment of an International Classification of Disease Clinical Modification code (ICD-10-CM-code)\textsuperscript{59}. Still, healthcare professionals hardly seem to recognize sarcopenia let alone diagnose it\textsuperscript{60,61}. Sarcopenia affects 10–26% of older inpatients\textsuperscript{11,62} and, as expected, is more prevalent in hospitalized compared to community-dwelling older adults\textsuperscript{63}. Suffering from sarcopenia imposes an increased risk of (re)admission to the hospital\textsuperscript{64} and a longer duration of hospital stay\textsuperscript{65}. Hospitalization may further affect muscle status, creating a negative cycle (see Figure 3). Therefore, early recognition and timely intervention to prevent the deterioration of muscle status seems vital.
Importance of healthy muscle status

Studies on physical and nutritional “pre-habilitation” in patients with cancer, cardiac and orthopedic surgery before elective hospitalization have shown that the better the muscle status before hospitalization, the better the clinical outcomes during and after hospitalization. Healthy muscle status enables early mobilization and helps to maintain ADL independence, which prevents further complications during hospitalization. Muscles form the largest bodily storage of glycogen and amino acids, which are main energy sources. During severe fasting or catabolic events demanding high energy levels like hospitalization, when glycogen stores from the liver and kidneys become depleted, proteolysis mobilizes muscle-stored amino acids for gluconeogenesis, providing energy for the whole body. Additionally, muscle cells secrete myokines (cytokines and growth factors such as interleukin (IL) 6, IL8, IL15, IGF-1, brain–derived neurotrophic factor, myostatin and leukemia inhibitory factor) that exert autocrine, paracrine, and endocrine functions influencing body metabolism and homeostasis throughout hospitalization.

Figure 2. Difference between younger and older patients exposed to hospital-associated deconditioning likely resulting from poor muscle status.
Diagnostics of muscle status: public knowledge, use of new definitions and measurements

Currently, awareness of the relevance of poor muscle status is low among healthcare professionals. Knowledge about sarcopenia among the general public has not been investigated. New definitions to diagnose sarcopenia arise, yet consensus on the criteria has not been reached while clinical impact of changing the definition may be substantial. Various technologies to assess poor muscle status are created at a high rate, yet are rarely applied in clinical practice to support diagnosis. This lack of implementation is mostly due to uncertainty about the benefits of the measurements: Measuring muscle status, especially physical performance like gait speed, has proven challenging in acute care setting. Administration of technology in the clinical field is potentially a solution to these challenges. Examples are the use of inertial sensors such as accelerometers for the use of instrumented physical performance tests to address quality characteristics of gait or movement patterns during functional task performance. These could be applied instead of the standard clinical tests measuring speed or duration using a stopwatch. Applying these technology based measurements could support identification of early signs of poor muscle status, allowing timely prevention and targeted interventions in high risk populations. However, the potential added benefits of instrumented measurements require further investigation.

Figure 3. Negative cycle of poor muscle status and hospitalization.
Determinants of poor muscle status
The influence of hospitalization and its associated determinants on muscle status is unclear. Change in muscle mass and muscle strength from admission to discharge has not yet been quantified in older patients, creating uncertainty about the short term impact of hospitalization on muscle status. Cognition and inflammation at admission are among the determinants experienced during hospitalization that predisposes patients to functional impairments and mortality. The relations with cognition and inflammation may be mediated by poor muscle status, yet this has not been investigated. Predictors could help identify at risk patients in need of interventions. One such a high risk population that needs early identification of warning signs are those with high blood pressure, trichlycerides, waist circumference, glucose and low high-density lipoprotein, collectively termed metabolic syndrome. Metabolic syndrome is also known as a pre-disease state, diagnosed in still well-functioning adults with a high risk of developing poor muscle status, functional impairments and morbidity. Identifying predictors of metabolic syndrome has so far not been investigated in older adults.

Consequences of poor muscle status during hospitalization
The contribution of poor muscle status during hospitalization to adverse clinical outcomes after discharge is largely unknown in older patients. Poor muscle status is associated with higher infection rate and prolonged mechanical ventilation during hospitalization, longer duration of hospitalization, and higher rates of readmission and rehabilitation after hospitalization. Sense of urgency for identifying of and/or intervening on poor muscle status may be strengthened by further addressing muscle status related clinical outcomes including geriatric syndromes, falls, independent living and mortality after hospitalization.
Chapter 1

**Aims of this thesis**
This thesis aims to elaborate and raise awareness among clinicians, researchers and the general public on diagnostics, determinants and consequences of poor muscle status during hospitalization. Specifically this thesis aims to address the following questions:

1. What gaps in current diagnostics of poor muscle status exist regarding public knowledge, use of new definitions and innovative measurements?
2. What are determinants of poor muscle mass, muscle strength and physical performance in various populations of older adults?
3. What are short-term and long-term consequences of poor muscle status in hospitalized older adults?

**Outline of this thesis**
The coherence of the different parts of this thesis, and their relation to poor muscle status is shown in Figure 4.

Part 1 of this thesis, chapters 2–5, provides new insights on diagnostics for muscle status. To facilitate diagnostics, we investigated the current knowledge about sarcopenia, utilization of definitions and measurements of muscle status. Chapter 2 presents the knowledge about sarcopenia in a cohort of healthy adults. Chapter 3 compares two commonly-used definitions of sarcopenia, the 2010 and 2018 European Working Group on Sarcopenia in Older People (EWG-SOP) definitions. We explored the clinical consequences of changing the applied criteria and cut-off points in identifying patients with sarcopenia. In chapter 4, we compared two measurements of gait speed in community-dwelling adults: standardized gait speed assessments, often applied in clinical practice, and daily-life gait speed measured with accelerometry. In chapter 5, we compared standard clinical measurements with instrumented measurements of two physical performance tests. The discriminative ability of the measurements was investigated to distinguish between high and low levels of functioning in older adults.

Part 2, chapters 6–10, presents determinants of low muscle mass, muscle strength and physical performance. Chapter 6 describes a systematic review of the literature on the influence of hospitalization on muscle mass and muscle strength in cohorts of older adults and summarizes the results in a meta-analysis. Chapter 7 presents the association between cognitive status and muscle mass and muscle strength in hospitalized older adults. Chapter 8 and chapter 9 re-
port the association between inflammatory markers, activities of daily living and muscle mass, muscle strength and physical performance. Chapter 8 describes the cross-sectional relation in geriatric outpatients, and chapter 9 describes the longitudinal association between inflammation status during acute hospitalization and muscle measures immediately after acute hospitalization. In chapter 10, predictors of metabolic syndrome (MetS) are investigated in community-dwelling older adults.

Part 3, chapters 11–13, presents the consequences associated with low muscle mass, muscle strength and physical performance. In chapter 11, the change in muscle mass and muscle strength during hospitalization is analyzed in relation to four geriatric conditions: malnutrition, falls, ADL disability and delirium. Chapter 12 explicates the association between muscle mass and muscle strength with falls before and three months after hospitalization. Lastly, chapter 13 reports on muscle mass, muscle strength, physical performance, and nutritional status upon hospital admission as predictors of mortality and living independently three months after discharge.

Finally, in Chapter 14 we combine the findings from part 1-3 of this thesis and discuss the results as well as the clinical and scientific implications.