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**Gaining insight in factors associated with successful ageing: body composition, nutrition, and cognition**

Nijholt, Willemke

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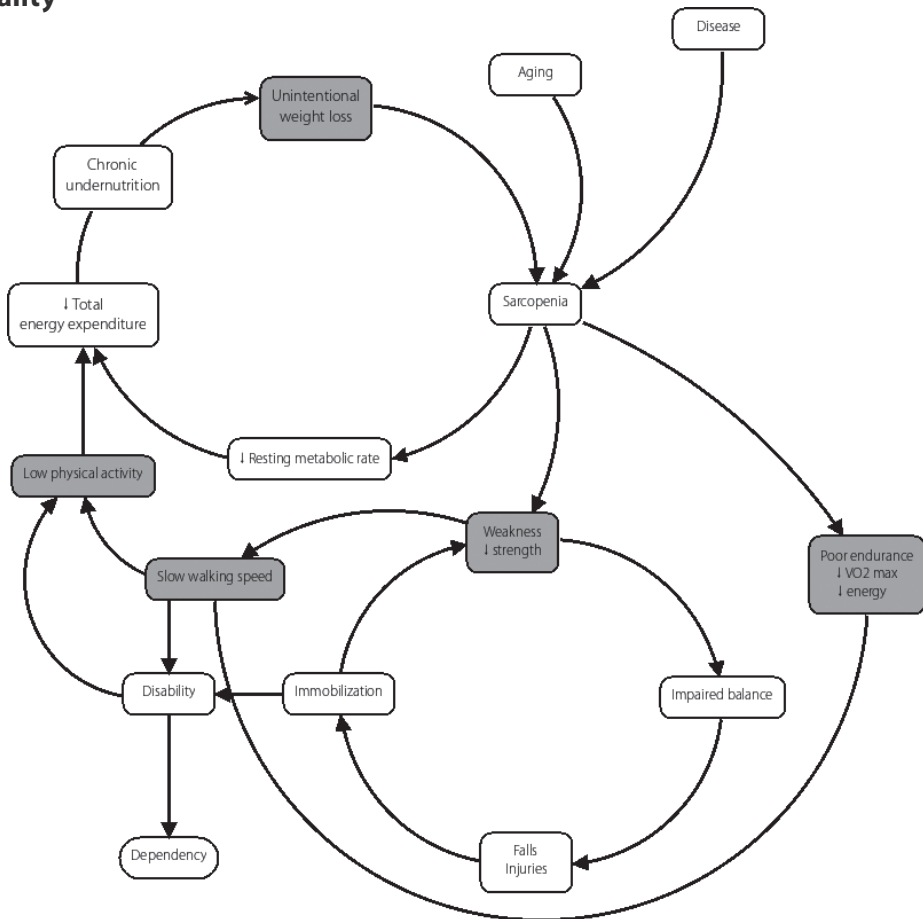
# 1

## General introduction

Mrs. Willems is a **healthy**, 97 year old woman. Ever since her husband passed away five years ago, she **lives independently** in an apartment located at her so called 'safe haven'. For her, this is a safe haven, because 40 years ago, her husband and she had a farm on the same location. In the years that they owned the farm, Mrs. Willems was always busy working at the farm, and she took care of the children. Besides her obligations on the farm and as a mother, she **was an active member of** the 'Nederlandse Bond van Plattelandsvrouwen', which is an organization aimed at promoting the cultural, social, educational, and economic conditions of women living in rural areas. Mrs. Willems was, and still is, not only socially active, she is also very much engaged in **physical activities**. During her (working) life, she has been **eager to learn and is determined** to stay informed of the latest (technical) developments. After their retirement, she and her husband decided to move to a smaller house. When the opportunity to move to apartment located at their 'safe haven' presented itself, they decided to move back there. Mrs. Willems was determined that an apartment suited their (possible) future needs: she is future-oriented. Despite the fact that she has a **poor appetite and swallowing problems**, and had pneumonia a few months ago, Mrs. Willems is still **socially and physically active**. *"Why would you take the elevator if there is a staircase?"*.

The case of Mrs. Willems illustrates the concept of successful ageing. Independent, positive, active, positive mentality, health, and solidarity are important aspects of her life. Although, currently a clear consensus definition of the concept of successful ageing is lacking, it is considered to be a complex, multi-dimensional concept.<sup>1</sup> Already in 1997, Rowe and Kahn developed a model to conceptualize successful ageing and defined it as a combination of three components: (1) low probability of disease and disease-related disability; (2) high cognitive and physical functional capacity, and (3) active engagement in life.<sup>2</sup> Of course, these three components are interrelated and, according to Rowe and Kahn, it is especially the combination of these three components that best describes successful ageing. The model of Rowe and Kahn provides a framework to conceptualize successful ageing. However, to date, no operational definition is available to evaluate the degree to which a person meets the concept of successful ageing. Nevertheless, it is well known that a decline in physical, psychological or social functioning all have a negative impact on the chance of successful ageing.<sup>1</sup> This decline is referred to as frailty. This first chapter defines the concept of frailty and introduces the main topics and the outline of the thesis.

## Frailty



**Figure 1.** Cycle of frailty. Figure based on Fried and Walston, original copyright 2001<sup>3</sup>

According to the frequently cited definition of Fried et al., frailty is a clinical syndrome in which three or more of the following five criteria are present: unintentional weight loss, weakness, poor self-reported endurance, slow walking speed, and low self-reported physical activity.<sup>3</sup> As indicated in Figure 1, this definition mainly focuses on the physical domain. Nevertheless, this frailty phenotype is associated with an increased risk of falls, disability in activities of daily living, hospitalization and mortality.<sup>3</sup> Physical frailty is strongly linked to a decline in physical performance, muscle strength, and muscle mass. Furthermore, it is considered to be a nutrition-related disorder, like other geriatric conditions such as sarcopenia.<sup>4</sup> Sarcopenia has been defined as the combination of impaired muscle function and low muscle mass.<sup>5</sup> Sarcopenia is considered a key component of physical frailty, as both sarcopenia and frailty are characterized by a loss of strength and decreased physical performance.<sup>6,7</sup>

Previous studies showed that the risk of sarcopenia is higher for frail adults, compared to older adults who are not frail.<sup>8,9</sup> Another nutrition-related disorder that is frequently present in older adults is malnutrition which is defined by the European Society for Clinical Nutrition and Metabolism (ESPEN) as “a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat-free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease”.<sup>4</sup> Also malnutrition and physical frailty share common characteristics, e.g., weight loss and diminished physical performance.

## **Sarcopenia**

Despite the fact that already in the 1980s, Rosenberg introduced the term sarcopenia to describe the loss of muscle mass there is still no uniform operational definition of it.<sup>10</sup> During the past years, different diagnostic criteria including measures and cut-off points were proposed.<sup>5,11-15</sup> Some of these definitions are based solely on the presence of low muscle mass,<sup>13-15</sup> while others use a combination of muscle mass, muscle strength, and physical performance.<sup>5,11,12</sup> Also, the diagnostic measures and cut-off points vary across the different definitions. As a result, the prevalence of sarcopenia varies from 0% to 15% in community-dwelling older adults.<sup>16</sup> Although there is a large variation in prevalence rates, it is clear that sarcopenia should be seen as a multifactorial condition in which physical performance, strength, and muscle mass are important constructs.<sup>5</sup> These constructs are not isolated: low muscle mass is associated with low strength and impaired physical performance, but low muscle strength and impaired physical performance cannot be solely attributed to low muscle mass. Furthermore, the decline in muscle strength with ageing is steeper than the decline in muscle mass.<sup>17-19</sup> Also, other factors are associated with muscle strength. For example, muscle quality, i.e., muscle strength or power per unit of muscle mass, is also closely related to muscle strength.<sup>20</sup> Therefore, muscle strength, physical performance, and mass are important constructs of sarcopenia and should be assessed in daily practice in order to identify and treat sarcopenia at an early stage.

Muscle strength can be assessed in various ways using different measurement instruments. In daily practice, handgrip strength is commonly assessed as a proxy for total muscle strength.<sup>21</sup> Also, physical performance is being measured in daily practice with the 10-meter walk test (gait speed) or the short physical performance battery, in which balance and lower extremity strength are also being assessed in addition to gait speed.<sup>22,23</sup> Both gait speed and the short physical performance battery are valid and reliable in older adults and associated with survival.<sup>22-24</sup> In brief, for the evaluation of muscle strength and physical performance in daily practice, different reliable and valid measurement instruments are available. In contrast, fewer tools are available for the assessment of muscle mass in daily practice.

Bioelectrical impedance analysis (BIA) is most frequently used for the assessment of muscle mass and is shown to be a reliable method for older adults. However, the validity on an individual level is limited.<sup>25,26</sup> A promising alternative for assessing muscle mass in daily practice is ultrasound. Ultrasound can be used to both quantify the size of (peripheral) muscles,<sup>27,28</sup> and, based on these measurements, estimate total muscle mass using prediction equations.<sup>29,30</sup> Furthermore, it can be used to qualify muscles by assessing echo intensity since an increase in echo intensity might be a result of, for example, intramuscular fat.<sup>31,32</sup> Although it is clear that ultrasound has the potential to evaluate muscles, studies on the validity and reliability of ultrasound are limited.

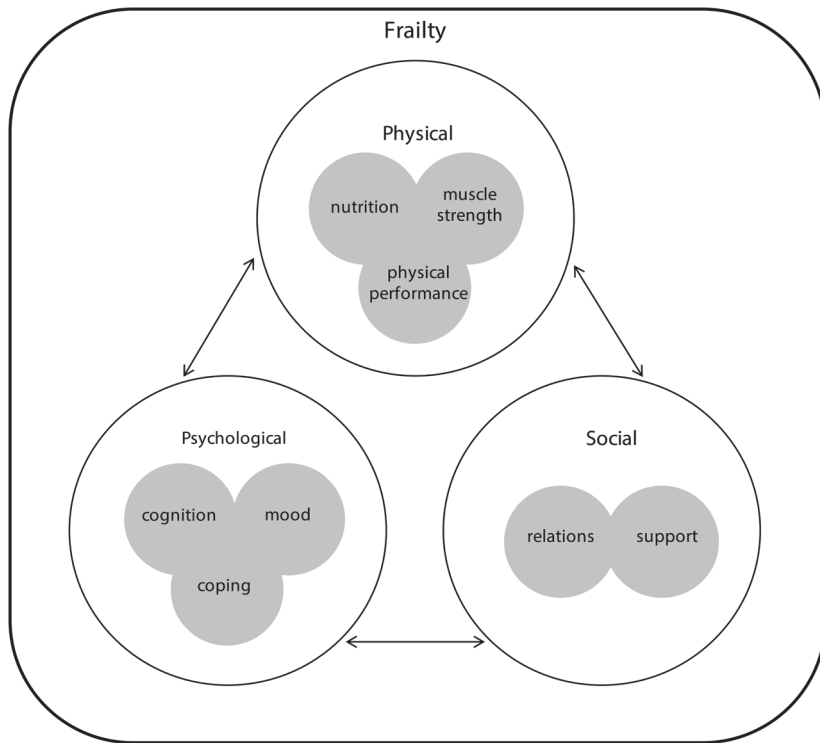
## Malnutrition

Older adults may be at risk for malnutrition, as a consequence of inadequate intake of protein and energy, which may be related to old age, disease, or both.<sup>33</sup> Also, in the case of Mrs. Willems, nutrition impact symptoms, i.e., (mostly) treatable symptoms (e.g., nausea, vomiting, loss of appetite) leading to barriers for sufficient dietary intake,<sup>34</sup> are present, evidenced by her poor appetite and swallowing problems. Various tools are being used to assess malnutrition, of which the Mini Nutritional Assessment (MNA) is widely used in older adults.<sup>35</sup> It remains unclear to what extent these tools adequately cover all dimensions of the conceptual definition of malnutrition.

As indicated previously, malnutrition and physical frailty are both nutrition-related conditions, and items in screening tools for malnutrition and physical frailty may overlap, such as weight loss and impaired physical function.<sup>35,36</sup> However, the etiology of the two nutrition-related conditions is different.

Whereas malnutrition is caused by an imbalance between nutritional intake and requirements,<sup>4</sup> physical frailty is primarily caused by decreased physical strength.<sup>37</sup> Despite the different etiology, interventions to prevent, reverse, or slow down the progression of malnutrition and physical frailty are quite similar. Resistance exercise in combination with nutritional interventions including a high protein diet seem to be the best intervention against malnutrition and physical frailty.<sup>38,39</sup> Protein intake plays an important role in the maintenance of muscle mass. It is well known that dietary protein stimulates muscle protein synthesis and inhibits breakdown, which results in a positive protein balance and, subsequently, in the gain of muscle mass.<sup>40</sup> Over the last few years, several recommendations for optimal dietary protein intake for older adults have been proposed, varying from 0.8 g protein/kg body weight per day,<sup>41,42</sup> to 30 grams protein per meal, three times a day.<sup>43</sup> Thus far, limited data are available on the prevalence of low protein intake and the association between low protein intake and physical function and muscle mass in older adults.

## Frailty as a multidimensional concept



**Figure 2.** Schematic representation of the different domains of frailty. Figure based on Gobbens, Luijckx, Wijnen-Sponselee and Schols, original copyright 2010.<sup>44</sup>

Over the years, different approaches for frailty have been proposed. These approaches can be roughly categorized into two groups. Firstly, the unidimensional approach such as the Fried criteria,<sup>3</sup> mainly addresses the physical and biological components of the definition of frailty. Secondly, in the multidimensional approach, which is characterized by the interplay between the three (i.e., physical, psychological and social) domains of frailty (Figure 2), frailty is defined as 'a dynamic state affecting an individual who experiences losses in one or more domains of human functioning (physical, psychological, social) that are caused by the influence of a range of variables and which increases the risk of adverse outcomes'.<sup>45</sup> These conflicting views on the concept of frailty have led to different assessment instruments and subsequently to differences in prevalence rates.

For example, a previous study compared the unidimensional and multidimensional approach in community-dwelling older adults and found that the prevalence rates vary from 12.7% for the unidimensional to 44.6% for the multidimensional approach of frailty.

This study also showed that both approaches are associated with disability, although the sensitivity was better for the multidimensional approach.<sup>46</sup> Within the multidimensional approach, the individual is considered as a whole, and this integrative approach fits well into the definition of successful ageing. Also, within the definition of successful ageing, the complex interplay between physical and cognitive functioning rather than the distinct components are important.

## Cognition

As shown in Figure 2, the concept of psychological frailty encompasses both cognitive, mood, and motivational components.<sup>47</sup> Although a clear definition for psychological frailty is missing, cognitive frailty (which can be considered as a subtype of psychological frailty) is defined as a “heterogeneous clinical manifestation characterized by the simultaneous presence of both physical frailty and cognitive impairment”.<sup>48</sup> There is a bidirectional association between physical frailty and cognitive frailty.

For example, depression has been linked to impaired cognitive function,<sup>49</sup> may eventually lead to physical frailty, and in turn, physical frailty might worsen depression.<sup>50</sup> It is well known that being physically active and adhering to a healthy diet are both associated with a decreased risk of poor cognitive functioning.<sup>51-54</sup> However, it remains unclear whether these two lifestyle factors act synergistically in the prevention of poor cognitive functioning. From a public health point of view, this information is very important to know, since individuals who are physically active often have a higher educational socio-economic status. It is therefore of great interest to explore the magnitude of such potential synergistic associations between being physically active and adhering to a healthy diet and cognitive functioning.

## Aims and outline of this thesis

This thesis focuses on both the physical and the psychological domain of frailty. In this introduction, the three main topics herein have been presented, namely (1) sarcopenia; (2) malnutrition; and (3) cognition. Before the first two topics (i.e., sarcopenia and malnutrition) can be evaluated in daily practice, tools for screening on, and diagnosis of sarcopenia and malnutrition need to be validated. Therefore, the purpose of **Chapters 2 and 3** is to examine the validity and reliability of ultrasound to quantify muscles. **Chapter 4** aims to determine the association between ultrasound measured muscle size and muscle mass and function in patients with COPD. The aim of **Chapter 5** is to identify tools that are used for the assessment of malnutrition, and determine their content validity with the ESPEN and ASPEN malnutrition definitions. In **Chapters 6 and 7**, the impact of diet and physical activity in relation to components of physical or psychosocial frailty will be determined.

More specifically, in **Chapter 6**, the prevalence of low protein intake in community-dwelling older adults will be assessed. An additional aim of this chapter is to study the associations between sufficient protein intake, physical function and muscle mass. **Chapter 7** aims to determine the synergistic association between diet, physical activity, and cognition in older adults.

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