Nutrition, exercise and body composition in community-dwelling older adults

Effects on function, wellbeing and mortality

ÅSA VON BERENS
Abstract

Background: The demographic shift in society with more people reaching a high age provides new challenges for both society and the healthcare system.

Aim: The overall aim of this thesis was to examine the impact of nutrition, exercise and body composition on function, wellbeing and mortality in community-dwelling older adults.

The thesis is based on 1) data from the Vitality, Independence and Vigor in the Elderly 2 study (VIVE2) (Papers I-III), i.e. 149 community-dwelling participants >70 years who took part in an exercise program, and were randomized to take either a protein- and vitamin D-rich supplement or a placebo for 6 months and 2) three cohorts from two Swedish population studies on older adults (Paper IV). Quantitative (Papers I, II and IV) and qualitative methods (Paper III) were used.

Results: Paper I reports cross-sectional data showing that there was no clear association between serum levels of serum 25(OH)D and physical performance in mobility-limited adults. In Paper II, the results of the VIVE2 study indicated positive effects on mental health from exercise but no additional effect from supplementation was detected. In Paper III, the qualitative interview investigation indicated that the VIVE2 intervention had positive effects, both psychologically and physically. Another finding was that weight loss was a main reason for participants wanting to take part in the study, whereas the aim of the study was to improve muscle function.

Paper IV shows from prospective observational data that 75-year-old women with sarcopenic obesity had an increased mortality risk within 10 years, while a similar result could not be found among 75-year-old or 88-year-old men.

Conclusion: The exercise intervention improved the mental status of the participants based on both quantitative and qualitative studies. No effect could be attributed to the protein- and vitamin D-rich nutritional supplement, a finding that needs to be evaluated in light of the participants’ good nutritional status. No clear association was revealed between physical function and serum 25(OH)D. Sarcopenic obesity may be associated with mortality but such associations may depend on age and gender.

Keywords: Older adults, function, nutrition, wellbeing, mortality, exercise, sarcopenic obesity


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ISSN 1651-6206
ISBN 978-91-513-0584-4
urn:nbn:se:uu:diva-377873 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-377873)
Nemo nascitur artifex
To my family
This thesis is based on the following papers, which are referred to in the text by their roman numerals and/or short title.

Short title in thesis: Physical performance and serum 25(OH)D status in older adults

Short title in thesis: Effect of exercise and nutritional supplementation on health-related quality of life and mood

Short title in thesis: Feeling more self-confident, cheerful and safe

Short title in thesis: Mortality associations for sarcopenic obesity in old age.

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Related papers

(not included in the thesis)


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<tr>
<td>25(OH)D</td>
<td>25-Hydroxy Vitamin D</td>
</tr>
<tr>
<td>ASMI</td>
<td>Appendicular Skeletal Muscle Index</td>
</tr>
<tr>
<td>BIS</td>
<td>Bioimpedans Spectroscopy</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>CES-D</td>
<td>Center for Epidemiologic Studies Depression scale</td>
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<tr>
<td>CLIA</td>
<td>Chemiluminescence</td>
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<tr>
<td>DXA</td>
<td>Dual-energy X-ray Absorptiometry</td>
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<tr>
<td>EWGSOP</td>
<td>European Working Group of Sarcopenia in older people</td>
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<tr>
<td>H70</td>
<td>Gerontological and Geriatric Population Studies in Gothenburg</td>
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<tr>
<td>HRQoL</td>
<td>Health-Related Quality of Life</td>
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<td>ICFSR</td>
<td>International Conference on Sarcopenia and Frailty Research task force</td>
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<tr>
<td>IOM</td>
<td>Institute of Medicine</td>
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<td>ITT</td>
<td>Intention to treat</td>
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<td>IWGS</td>
<td>International Working Group on Sarcopenia</td>
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<td>MCS</td>
<td>Mental Component Summary</td>
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<td>MMSE</td>
<td>Mini Mental State Examination</td>
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<tr>
<td>NCD</td>
<td>Non-Communicable Disease</td>
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<td>PCS</td>
<td>Physical Component Summary</td>
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<tr>
<td>PP</td>
<td>Per Protocol</td>
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<tr>
<td>PPSW</td>
<td>Prospective Population Study of Women in Gothenburg</td>
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<td>PRO</td>
<td>Patient-reported outcomes</td>
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<tr>
<td>RIA</td>
<td>Radioimmunoassay</td>
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<td>SF-36</td>
<td>Medical Outcomes Study 36-item Short Form Health Survey</td>
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<tr>
<td>SMM</td>
<td>Skeletal Muscle Mass</td>
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<tr>
<td>SMI</td>
<td>Skeletal Muscle Index</td>
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<td>SO</td>
<td>Sarcopenic obesity</td>
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<tr>
<td>SPPB</td>
<td>Short Physical Performance Battery</td>
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<tr>
<td>ULSAM</td>
<td>Uppsala Longitudinal Study of Adult Men</td>
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<tr>
<td>VIVE2</td>
<td>Vitality and Vigor in the Elderly 2 study</td>
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In my work as a primary care dietitian, I met many older persons who had become inactive as the years had passed. The reasons for their becoming inactive had, of course, been varied and included illness or disease, their spouse’s disease, loneliness or other socially-related reasons, to name but a few. Many had also been surprised to hear that our nutritional requirements change as we age, and that loss of function and muscle mass can, to some extent, be prevented and treated. When meeting these people and helping them with their nutritional needs, I was often struck by the thought that I was a bit too late, and that they should have seen a dietitian (and in the best of worlds, a dietitian in a team with a physiotherapist) several years ago. Working with physiotherapists for several years led me to understand that teamwork is essential, and that combining good nutrition with physical activity could be one vital key to adding life to years. When I was given the opportunity to be involved in the VIVE2 study, which then led to my becoming a PhD student, it was an opportunity I could not refuse.

This thesis investigates potential contributors to a healthy and active ageing and examines the impact of nutrition, exercise and body composition on function, wellbeing and mortality in community-dwelling older adults.
Introduction

Demography and ageing
The world’s population is ageing and the number of people aged 65 years and older is expected to double by the year 2050 (1). A longer life provides important opportunities for older adults, their families and societies, opportunities that very much rely on the factor of health. Healthy ageing is defined by the World Report on Ageing and Health as “the process of developing and maintaining the functional ability that enables well-being in older age”. This definition does not automatically include a disease-free life but instead functional ability, which involves the health-related features that allow people to do the things that they value (2). The growing ageing population and the pursuit of healthy ageing also means new challenges for health-care professionals in the management of geriatric syndromes, for example sarcopenia, i.e. age-related loss of muscle mass and function, and sarcopenic obesity, i.e., sarcopenia in combination with obesity. In this thesis, the term “older adults” includes adults over the age of 65 years.

Sarcopenia
Sarcopenia is a geriatric condition defined as age-, disease- and nutrition-related involuntary loss of muscle mass and function, a term first introduced by Irwin Rosenberg in 1988 (3). Studies have shown associations between sarcopenia and several negative outcomes, such as an increased risk of falls and fractures, dependency, lower quality of life, mortality and increased health costs (4-7). Sarcopenia is also a main contributor to limitations in mobility in older adults which is also associated with a reduced quality of life (8, 9). Furthermore, inadequate physical activity and low protein intake are factors associated with sarcopenia (4, 10).

Although the term sarcopenia has attracted attention in research since 1988, there is still no formal consensus regarding its clinical definition. The European Working Group on Sarcopenia in Older People (EWGSOP) developed a clinical definition and diagnostic criteria for sarcopenia in 2010. The group recommended that sarcopenia is diagnosed based on the combination of low muscle mass and low muscle function (strength and performance), and also
suggested different measurements and cut-offs for use in both research and clinical practice (11). In 2018, EWGSOP presented a new consensus for the definition of sarcopenia, EWGSOP2 (12). This consensus stresses that sarcopenia is a muscle disease and includes a change in focus, emphasizing low muscle strength as the key characteristic of sarcopenia and low muscle mass as confirmation of the diagnosis. The EWGSOP2 focuses more on the clinical utilization of the diagnoses, promoting earlier detection and treatment of the condition by providing clear cut-offs for the diagnosis of sarcopenia. There are also other proposed definitions and diagnostic criteria for sarcopenia, for example those by the International Working Group of Sarcopenia (IWGS), which recommends that sarcopenia is diagnosed based on low muscle mass in combination with poor muscle function identified as gait speed less than 1 meter/second (13), and by The Foundation for the National Institutes of Health (FNIH) Sarcopenia Project, which proposes other cut-offs for clinically relevant muscle weakness and low muscle mass using hand grip strength and muscle loss (as appendicular lean mass adjusted for BMI, kg/m²)(14).

The various definitions and diagnostic criteria for sarcopenia that have been used during the past decades make comparisons between studies concerning, for example, adverse effects challenging. Guidelines concerning the definition of, screening for, diagnosis of, and interventions for sarcopenia have been proposed by a task force from the International Conference on Sarcopenia and Frailty Research (ICSFR), including eight recommendations based on available evidence (15). One recommendation, although based on low certainty of evidence, is that screening for sarcopenia should be performed annually on all older adults (over the age of 65 years) or after the occurrence of a major health event and that diagnosis is based on the definitions proposed by EWGSOP, IWGS or the FNIH.

Sarcopenia, as a serious geriatric condition, is the focus throughout this thesis. The intervention VIVE2 (on which Papers I-III are based) had the primary aim of investigating if a combination of exercise and a specific nutritional supplement high in protein and vitamin D could enhance physical function measured by gait speed (16). Since sarcopenia definitions include loss of physical function and muscle mass, and gait speed is recommended by the international, multidisciplinary guideline development task force from the International Conference on Sarcopenia and Frailty Research (ICSFR) as a suitable screening tool for sarcopenia, VIVE2 was, to some extent, designed to try to find an efficient intervention for preventing of or delaying the development of this condition. Sarcopenia is also the focus in Paper IV, since the aims of the study were to describe the prevalence of sarcopenic obesity (sarcopenia in combination with obesity) in cohorts of older Swedish men
and women and to compare the risk of mortality associated with different body composition phenotypes.

**Obesity in older adults**

The proportion of overweight and obese persons in the adult population is increasing and a growing number reaching older age are overweight or obese. The worldwide prevalence of obesity tripled between 1975 and 2016, and in Sweden in 2016, 19% of the adult population between 45 and 84 years of age were obese (17, 18).

Ageing is per se associated with a loss of muscle mass, a relative increase in fat mass and changes in body fat distribution (visceral abdominal fat increases and subcutaneous abdominal fat decreases) (19, 20). These are changes that occur in weight-stable ageing individuals. However, while the risks associated with overweight and obesity are well established for the adult population in general, there is an ongoing discussion concerning the health consequences of obesity for older individuals and whether excessive weight could actually be protective (21-24).

**Definitions of obesity**

A common way of defining obesity is using the Body Mass Index (BMI), weight in kilograms divided by height in meters$^2$ (kg/m$^2$). The WHO proposes cut-offs for BMI in adults as follows: BMI >25 kg/m$^2$ defines overweight and >30 kg/m$^2$ defines obesity. The report from WHO “Obesity: preventing and managing the global epidemic” emphasizes that there is a need for more research concerning BMI standards for older adults (21).

Central obesity is often measured and defined as a waist circumference over a certain cut-off, measured midway between the lowest rib and the iliac crest. The WHO gives the cut-offs by Lean et al. 1995, that is >102 cm for men and 88 cm for women as an example of cut-offs indicating central obesity and increased risk of cardiovascular diseases, but WHO also emphasizes the need for cut-offs for waist-circumference specific to population and sex (21, 25). Moreover, lower cut-offs for waist circumference are proposed by the Obesity Management Taskforce (European Guidelines): >94 cm for men and >80 cm for women (26). Alternatively, Heim et al. suggest that the optimal waist circumference for older adults should be higher: below 100-106 cm for older men and below 99 cm for older women (27).

The use of body composition measures is another way of defining obesity and, as for BMI and waist circumference, different cut-offs for defining an
excessive amount of total body fat mass, i.e. obesity, are suggested in the literature. For example, Gallagher et al proposes cut-offs of >30% for men and >42% for women while the cut-offs often referred to in the literature are >35% for women and >25% for men, which are those originally proposed by the WHO (28, 29).

The obesity paradox

The obesity paradox is a phenomenon which means that, contrary to expectations, excessive weight is associated with beneficial outcomes and is usually observed in those who are older and chronically ill (30). The paradox is described in the context of some diseases, for example cancer and heart failure, but also in ageing, implying that the relationship between obesity and obesity-related morbidities weakens with age (22, 23, 31). The mechanisms explaining this obesity paradox are not clear, but hypotheses include that obesity is often accompanied by a greater amount of muscle mass and that the excessive weight might, therefore, have a protective effect (31).

However, the obesity-paradox is questioned for a number of reasons. One important aspect is that BMI might not be an optimal measure for older adults (32, 33). BMI does not account for age-related loss of height, changes in fat distribution or changes in body composition (32, 34). Furthermore, several studies showing the protective effects of excessive weight do not discriminate between intentional and unintentional weight loss, and a low BMI could be associated with end-stage illness and excessive fat mass may reflect a state of health, i.e. the absence of disease, rather than it being of benefit to health (31, 33). Some researchers also suggest that the risks of obesity in older age are, in fact, underestimated. They state that central body fat are more important than BMI in determining health risks, and suggest that the risks for obesity-related mortality actually increase with age and results in this domain showing the opposite might be due to confounders or selection biases (35, 36).

Studies have shown that obesity in older age is associated with increased disability and that obesity leads to frailty by reducing a person’s ability to exercise (37, 38). Furthermore, studies have shown that obesity-related limitations and disabilities have a major impact on HRQoL in older adults (38, 39).

Sarcopenic obesity

Sarcopenic obesity (SO), a condition that has received increasing attention, is the loss of muscle mass and strength in combination with obesity (40). SO is described as a condition in older adults that is increasing and is suggested
to have an extensive effect on disability, morbidity and mortality (19, 41). There is no clear consensus regarding the definition of sarcopenic obesity, due to the fact that there are several definitions for both the term sarcopenia and the measurement and definition of obesity. This lack of consensus makes comparisons of results between studies problematic and there is a need for more research concerning the consequences of and strategies for battling sarcopenic obesity (40, 42).

Nutrition and physical function

Optimal nutrition upholds both functional health status and mental well-being. However, older adults are at increased risk of developing nutritional problems due to multiple factors, including changes in smell and taste, loss of appetite, limitations in mobility affecting access to food, comorbidities and dental problems (43, 44). These difficulties can lead to problems meeting nutritional needs, such as adequate intakes of energy and specific important nutrients, including protein and vitamin D. For older adults, an inadequate intake of energy and nutrients contributes to the progression of several diseases and to loss of function (45, 46).

Protein

Protein is a prerequisite for retaining and preserving muscle mass. It has been, and still is, the focus of interventions aiming at the prevention and management of sarcopenia. Studies have shown that a short-fall in protein intake may accelerate the development of sarcopenia (46) and, in older adults, a high protein intake has been associated with a lower loss of lean body mass when compared to low protein intakes (47).

Skeletal muscle protein is the largest reservoir of amino acids in the body, which can be utilized during fasting or stress, and an insufficient intake of protein leads to a negative protein balance and skeletal muscle atrophy and functional decline (48). The European Society for Clinical Nutrition and Metabolism (ESPEN) recommends a total protein intake during the day of at least 1.0 g/kg bodyweight/day for healthy older adults, an amount that should be adjusted in relation to level of physical activity, nutritional status and disease status (45). The Nordic Nutrition Recommendations (NNR) recommends that 15-20 % of an older persons total energy intake during the day should come from protein, which corresponds to approximately 1.1-1.3 g/kg bodyweight/day (49). Older adults have a higher need for protein than younger individuals for a number of reasons, including a reduced ability to use available protein (anabolic resistance) and age-related diseases (50-52). Several studies have reported that age-related anabolic resistance, which
could contribute to a negative muscle protein balance if muscle protein synthesis does not exceed the rate of breakdown, could be overcome with a higher protein intake, and results suggest amounts of 25-30 grams (in one meal) for maximal stimulation of muscle protein synthesis (53, 54).

Despite the fact that the intake of protein is essential for skeletal muscle protein synthesis and function, results from studies concerning supplements to older adults with sarcopenia are inconsistent. A meta-analysis examining the effect of supplementation of protein or amino acids (no exercise interventions were included) on lean body mass, leg strength or handgrip strength failed to show any significant effect in older adults (55). This result could be explained by the heterogeneity of the included studies, differences in study durations, and variations in health status and habitual protein intake among the subjects included. Looking at the collective evidence, which the ICFSR (International Clinical Practice Guidelines for Sarcopenia) task force have done, there is not enough available evidence to recommend supplementation of protein or a high intake of protein for individuals with sarcopenia, however, the ICFSR conditionally recommends care-givers to discuss the impact of an adequate protein intake with older adults with sarcopenia (15).

Whey protein is rich in the amino acid leucine and has been shown to stimulate protein synthesis to a greater extent than other proteins (56). Studies investigating the effect of supplementation of the essential amino acid leucine in older adults indicate that it can increase protein synthesis and body weight, and it is suggested as being an alternative in the management of age-related loss of muscle mass, although more research is necessary (57, 58). It is also suggested that it is β-hydroxy β-methylbuvrate (HMB), a downstream metabolite of leucine that has been shown to reduce protein degradation and up-regulate protein synthesis, which could be the reason for leucine stimulating muscle-synthesis, although more studies are needed to confirm if and how HMB could be effective in treating sarcopenia (59, 60).

**Vitamin D**

It has been suggested that Vitamin D deficiency plays a role in physical function in older age and in the development of sarcopenia (61, 62). Vitamin D is assumed to directly affect muscle function through mechanisms such as calcium uptake and the transport of phosphate through the cell membrane (63). The Endocrine Society clinical practice guidelines identify deficient and insufficient status as 25(OH)D serum concentrations of <50 nmol/L or 50-75 nmol/L, respectively (64). The Institute of Medicine, (IOM) defines 25 (OH) D concentrations of <30 nmol/L as deficient and 30-50 nmol/L as inadequate (65). The recommendation for vitamin D intake from the diet in the Nordic countries is 20 µg/day for adults >75 years, and younger adults
with no or limited sun exposure, and 10 µg/day for other adults (49). Difficulties obtaining an adequate amount of vitamin D from the diet and the risks involved with excessive sun exposure are factors contributing to the risks of vitamin D deficiency (66). Advancing age is also a risk factor for vitamin D deficiency due to factors such as reduced skin synthesis, low dietary intake, and a reduced amount of time spent outdoors (67, 68).

Research concerning the effect of vitamin D on age-related outcomes and the association between vitamin D intake, serum concentrations of 25(OH)D and physical function in older persons provides inconsistent results (69-71). Several studies, cross-sectional and longitudinal, demonstrate a positive association between level of 25(OH)D and physical performance, however other studies do not support these conclusions. Several intervention studies in older adults have failed to show improvements in function from vitamin D supplementation (70, 72-79). Factors that can complicate comparisons of studies regarding level of 25(OH)D and physical function include the use of different 25(OH)D assay methods, heterogeneity of study samples and differences in follow-up time and choice of confounding variables (70, 80). The latest guidelines from the ICFSR do not consider the evidence to be strong enough to recommend supplementation of vitamin D with the aim of treating sarcopenia, although in cases of deficiency or other conditions where this is beneficial, supplementation may be relevant (15).

It has also been suggested that Vitamin D affects non-skeletal disorders, including depression. Results from observational studies have confirmed a linear inverse relationship of 25(OH)D and depression, although in a recent study using Mendelian randomization, results showed no association between level of 25(OH)D and major depression (81, 82).

**Physical activity for older adults**

**Concepts related to physical activity in this thesis**

The studies in this thesis partly concern concepts linked to physical activity, physical function and exercise. Physical activity is used as an umbrella term defined as “any bodily movement produced by skeletal muscles that results in energy expenditure”, and exercise is a sub-category of physical activity that is structured, planned and repetitive with the aim of improving or preserving physical fitness (83, 84). The terms physical activity and exercise have, to some extent, been used interchangeably in this thesis.
Physical function

The concept physical function is also used in this thesis as an umbrella term for assessments that include measures of both performance and strength, for example gait speed, repeated chair stands and hand grip strength. The terms physical limitations, limitations in mobility and functional limitations are also used interchangeably. In the VIVE2 study (Papers I-III), “mobility limitations” were defined as a score of 9 or below on the Short Physical Performance Battery (SPPB)(85)(explained later in the methods section).

Physical activity recommendations for older adults

Limitations in physical function are associated with dependency and low quality of life in older adults (86-88). Furthermore, there is strong evidence, according to the Physical Activity Guidelines Advisory Committees Scientific report, that physical activity improves physical function and reduces age-related loss of function in the general older adult population (84). The World Health Organization recommends that older adults do at least 150 minutes of moderate-intensity aerobic physical activity or at least 75 minutes of vigorous-intensity aerobic physical activity per week to improve cardiorespiratory and muscular fitness, functional health and bone health and to reduce the risk of non-communicable diseases (NCD), depression and cognitive decline (89). Older adults with limitations in mobility are recommended to perform physical activity at least three days per week to improve balance and prevent falls (89).

Preventive interventions to maintain physical function

There is evidence that, for community dwelling older adults, supervised aerobic and/or resistance physical activity interventions are able to significantly improve physical function (90). A prominent study in this field is the Lifestyle Interventions and Independence for Elders (LIFE) study, which included an intervention that lasted for 2.6 years (91). In the LIFE study the effect of a structured physical exercise program was compared to that of an educational program. Participants in the study were home-dwelling men and women, 70-89 years of age, with a sedentary lifestyle and some limitations in mobility, and the physical exercise intervention included exercise sessions at a center twice a week and home training that included a goal of 150 minutes of walking per week. The educational program included workshops on topics relevant for older adults. The results showed that the exercise program was significantly more effective in improving gait speed and physical function (measured by the Short Physical Performance Battery, (SPPB)(85)) than the educational program. The individuals who benefitted most from the
exercise intervention were those with a lower physical function at base-line (SPPB <8) (92).

The combination of nutrition and exercise

Since low physical activity levels and inadequate dietary intake are two aspects contributing to the decline in function and muscle mass associated with ageing, and therefore major risk factors for sarcopenia, they are important factors to consider in the design of interventions aimed at preventing and treating loss of function and sarcopenia (11, 93). There are theories that nutritional supplementation in combination with exercise could have synergetic effects in older adults, although results from studies investigating these theories suggested that the effects are not consistent and seem to vary with, for example, the health status of the individuals included. In a meta-analysis including studies on both relatively healthy and frail older adults, results showed that protein supplements did not have any significant additional impact on the effect of resistance exercise on body composition, muscle strength, muscle size or functional ability in older adults (94). Denison et al. carried out a systematic review including studies conducted up until 2013 that investigated the effect of the combination of supplementation, not just protein supplements, and exercise on muscle mass, strength and physical performance in mostly healthy older individuals. They concluded that beneficial effects had been shown in some studies, although the findings were inconsistent and the heterogeneity among the studies included made it difficult to draw any conclusions (95). This review was updated in 2017 by Beaudart et al. who concluded that, based on the available evidence, the interactive effect of nutritional supplementation and exercise on muscle function, appears to be modest (96).

However, in a meta-analysis that only included studies on frail older adults (where frailty was defined by frailty indices from Fried’s frailty criteria (97)), the results showed that protein supplementation in combination with exercise significantly improved frailty status, muscle mass and strength (98). In another meta-analysis, where all the subjects studied were older and either overweight or obese, results showed that the combination of protein supplementation and exercise was effective in stimulating gains in muscle volume, leg strength and lean body mass (99).

Due to the low grade of evidence, the ICFSR task force guidelines only conditionally recommend that nutritional supplementation be combined with a physical activity intervention as treatment for older adults with sarcopenia (100).
It is important to take into consideration that studies in this field of nutrition can be challenging to perform and interpret due to the difficulties in modulating dietary intake, differences in baseline nutritional status of participants, and variations in protocols, for example in the type and dose of protein supplementation (59).

Results from the Vitality Independence and Vigor in the Elderly study (VIVE2)

Three of the papers included in this thesis (Papers I-III) are based on data from the VIVE2 study, an intervention trial designed to compare the effects of a protein-rich nutritional supplement and a placebo when combined with regular exercise in older adults. For a detailed description of the design of the VIVE2 study, see the methods section in this thesis and also the design and methods article by Kirn et al. (16). The primary outcome analyzed in the VIVE2 study was gait speed, assessed by the 400-meters walking test (which is not part of this thesis). The analyses showed that after the 6-month intervention, all participants, irrespective of whether they received the supplement or the placebo drink, improved their gait speed, with no significant difference between the two groups (101). Subgroup-analyses based on baseline measures of serum 25(OH)D, SPPB score or prevalent sarcopenia (defined as low appendicular lean mass (ALM)) did not show any variation in effect (101).

Analyses of secondary outcomes from the VIVE2 study showed that the intervention resulted in improvements in body composition and strength in both groups, but that the group receiving the supplement had significantly lower amounts of intermuscular fat at the end of the trial compared to the group receiving the placebo (102). This result is interesting since high levels of intermuscular adipose tissue (IMAT) are associated with muscular dysfunction (103, 104). However, the improvement in performance and strength could not be attributed to the nutritional supplementation in the VIVE2 study, a result that could be explained by the 6-month time course of the intervention possibly being too short, and that the magnitude of change in intermuscular fat might be too small to have an effect on other outcomes (102).

Wellbeing

In the title of this thesis the term wellbeing is used as a collective term incorporating health-related quality of life, positive emotions and mood, joy, the absence of depression, and physical wellbeing. Although it is a frequently
used term, there is no consensus in the literature regarding the definition of
the term well-being (105). WHO defines health as “a state of complete phys-
ical, mental and social wellbeing,” and states that “wellbeing offers an inte-
grated model of health – one that does not separate the mind from the body”
and that well-being exists in two dimensions: subjective and objective (106).
Wellbeing is also part of the concept of healthy ageing, which is defined by
the World Report on Ageing and Health as “the process of developing and
maintaining the functional ability that enables well-being in older age (2).

Health related quality of life (HRQoL)

Health-related quality of life (HRQoL) is a multidimensional concept con-
centrating on how treatment and health status affect quality of life, and cov-
ering aspects of physical and mental health, and emotional and social well-
being (107). There is no consensus on the definition of quality of life, and
although we (in the western world) often intuitively know what it means as a
concept, quality of life could mean different things to different people in
different contexts. This is a fact also recognized by Aristotoles (as described
in the book Quality of Life by PM Fayers, 2015) “What constitutes happi-
ness is a matter of dispute... some say one thing and some another, indeed
very often the same man says different things at different times...”(108).

Reports on HRQoL use so-called patient-reported outcomes (PRO), also
referred to as person-reported outcomes (108, 109). The effectiveness of any
intervention has many dimensions and PROs are reports that come directly
from the individuals participating in an intervention. PROs capture the pa-
tient’s own opinions concerning the impact of their condition, disease and
treatment on their life, and PROs are used in both research and clinical prac-
tice (109, 110). There are several types of instruments used to measure
HRQoL, generic instruments and disease-specific instruments. Generic in-
struments can be used in healthy individuals, despite underlying disease and
health status, and are often used to compare outcomes at group level (110).
The disease-specific instruments focus on single patient groups or disease
states and are more sensitive to changes within individuals (107, 110).

There are studies showing that engagement in physical activity is associated
with increases in some domains of quality of life, including general quality
of life, mental health and functional capacity in older adults (111). In the
adult population, cross-sectional studies have shown a positive association
between self-reported physical activity level and HRQoL (112). Further-
more, studies show that functional limitations and sarcopenia are associated
with lower quality of life, and that physical activity interventions could slow
down the decline of, and even enhance, HRQoL (113, 114). When examin-
ing the association between quality of diet, physical activity level and HRQoL in a recent study, Xu et al., found that higher levels of physical activity and a healthier diet were associated with higher HRQoL in older adults (115). However, due to the cross-sectional design, conclusions about the causality and possible reciprocal relationship between the variables cannot be drawn.

Interventions combining exercise with nutritional supplementation have, in some studies, been shown to improve HRQoL in older individuals with sarcopenia (116), while other studies have failed to show any additional effects on HRQoL of protein supplements combined with exercise in older adults (117). Moreover, malnutrition has been shown to be associated with a lower quality of life and interventions aimed at treating malnutrition have also been shown to improve HRQoL, although there is great heterogeneity among the methods used in studies in this field and more research is warranted (118). However, when evaluating the effects of different interventions, measures of HRQoL provide a comprehensive assessment of the effect when compared to only using biological markers or physical assessments and are therefore important complements to clinical endpoints (110).

Self-efficacy
Self-efficacy is defined as a person’s belief in their ability to perform a task, for example physical activity, and it is a key concept encompassed in the Social Cognitive Theory by Albert Bandura (119). This theory has often been used when discussing older people’s engagement in physical activity and to understand certain health behaviors and how psychological barriers for physical activity can be overcome (120, 121). The theory advocates that the stronger the individual’s self-efficacy and expectations regarding the outcome, the more likely it is that she or he will initiate and continue with an activity (119). Self-efficacy is also described as an important mediator in the relationship between physical activity and quality of life for older adults, i.e. just participating in physical activity might not enhance quality of life, but if the activity plays a role in affecting the individual’s belief in their own abilities then the activity might influence their quality of life (122-124).

A qualitative approach
When designing interventions, an important aspect to consider is the experiences of the individuals who take part in the intervention study; an aspect that might be seen as obvious but which is not always emphasized in the research context. By adding a qualitative inquiry when evaluating an inter-
vention study, new knowledge and understandings can be acquired that are not captured by quantitative methods (125). The qualitative approach provides an opportunity for the participants to express experiences and opinions, and can thereby provide valuable insights (126, 127).

There are a limited number of studies with interventions combining exercise with a nutritional supplement or component for older adults that have been evaluated using qualitative methods. Although it does not include nutritional supplementation, one example is a study by Herrema et al. (2018) where older participants from an intervention combining exercise (resistance exercise in a group setting) with a high intake of protein-rich dairy products were interviewed with the aim of obtaining insights about drivers and barriers for compliance in such an intervention (128). The results showed that drivers for compliance in the dietary part of the intervention included products that tasted good and knowledge about the health benefits, and that important drivers for participating in the exercise program were social contact and customized support (128). The importance of support and social interaction has also been emphasized in several other qualitative studies of physical activity interventions for older adults (129-132). The barriers expressed by the participants in the study by Herrema et al included the risk of the intervention “disturbing” the participant’s habitual consumption patterns, and that barriers to continuing with exercise after the intervention could be high costs and a lack of the customized settings (128).

Qualitative studies investigating facilitators and barriers for physical activity in older age have pointed out the importance of focusing on physical activity as being fun and enjoyable, sociable, and including relevant short-term benefits (133). Another review concluded that, besides enjoyment, one important predictor of physical activity for older adults is the degree of self-efficacy (134).
Aims

The overall aim of this thesis was to examine the impact of nutrition, exercise and body composition on function, wellbeing and mortality in community-dwelling older adults. The specific aims are described for each manuscript.

Paper I - To examine the potential association between serum 25(OH)D and performance on the Short Physical Performance Battery (SPPB) including the sub-components: five repeated chair stands test (chair stand), four meters walk test (gait speed) and balance in a sample of older inactive community-dwelling men and women.

Paper II - To analyze the effects of a 6-months physical activity program in combination with protein supplementation on HRQoL and depressive symptoms in community-dwelling, mobility-limited older adults.

Paper III - To explore older persons’ experiences of an intervention designed to prevent sarcopenia, with the aim of capturing the participants’ thoughts and opinions.

Paper IV - To describe the prevalence of sarcopenic obesity using the recently launched EWGSOP2 definition of sarcopenia in combination with various definitions of obesity in three Swedish cohorts of older adults. A further objective was to examine how the risk of mortality was associated with different body composition phenotypes, including sarcopenic obesity.
Materials and methods

Study designs

Paper I in this thesis use a cross-sectional design on a sample of individuals screened for potential participation in the Vitality Independence and Vigor in the Elderly 2 study (VIVE2). Papers II and III are based on results from the VIVE2; Paper II has a quantitative design and Paper III a qualitative design. Paper IV has a longitudinal design based on cohorts of Swedish older adults.

Vitality Independence and Vigor in the Elderly study (VIVE2) (Paper I-III)

VIVE2 was a randomized controlled trial designed to compare the effect of a daily nutritional supplement to that of a placebo in combination with a 6-months structured exercise program. The study was conducted at two study-centers, one in Uppsala/Stockholm, Sweden and one in Boston, USA. The primary outcome for the VIVE2 study was the time taken to walk 400 meters. Data was obtained from a sample of 149 older adults.

The participants eligible for VIVE2 were men and women >70 years, community-dwelling, inactive in their daily life but able to complete a 400-meters walk in 15 minutes, and with low vitamin D status (serum 25(OH)D of 22.5-60 nmol/L). The inclusion criteria also included a score of 24 or more on the Mini Mental State Examination (MMSE, 0-30), a score of 9 or below on the Short Physical Performance Battery (SPPB, 0-12), a BMI ≤35 kg/m², a willingness to be randomized to a group and to participate for six months, and that an informed consent had been obtained. Exclusion criteria included cognitive impairment (defined as Mini Mental State Examination (MMSE) score ≤24), severe illness, current use of a vitamin D supplement or high protein oral supplement, myocardial infarction in the previous six months, upper or lower extremity fracture in the previous six months and severe visual impairment. For a full list of the inclusion and exclusion criteria, see Appendix 1.

The recruitment strategies for VIVE2 included an advertisement in local papers, direct mailing and posters and brochures distributed to local senior centers, primary health-care centers and senior living facilities. Potential
participants were interviewed by study staff over the telephone to assess eligibility. Those qualifying for enrollment were asked to attend an orientation screening visit. At the screening visit, the potential participants received a presentation of the background and main objective of the study. Those who decided to participate performed the SPPB with assistance from the study staff. If eligible, i.e. had a SPPB score ≤9, a blood sample was obtained to measure serum 25(OH)D level.

Informed consent was collected before each screening visit. The participants were provided with a copy of the informed consent to read at home prior to the visits. All subjects eligible for randomization also signed the study informed consent form before randomization. A separate tissue banking informed consent, to allow biological samples to be retained for future unspecified use, was also obtained.

The randomization of subjects (to the nutritional supplement or placebo) was stratified for gender and applied as a separate blocked randomization schedule for men and women. A block size of 10 was employed (allocating 5 subjects of each sex to the supplement group and five subjects of each sex to the placebo group). An electronical randomization procedure determined the order in which the supplements were allocated in each block. This was a double-blind study and the study staff, including the staff conducting the intervention and outcome measurements, and the Principal Investigators were all blinded to the treatment group (supplement and placebo). The participants entered the intervention on a rolling basis, starting in early spring 2012 with the last participant entering in May 2014.

The intervention
When enrolled, all participants were asked to attend an exercise program consisting of three supervised exercise sessions per week for six months. The exercise program was similar to the program in the LIFE study (91). The sessions were group based with up to 15 participants per group. The sessions took place at a research study center in Boston, MA, USA and at Aleris rehab, Stockholm, Sweden. The exercise sessions lasted approximately 60 minutes, and included walking, strength exercises (mainly for lower extremities), balance, flexibility and periods of rest between the different exercises. The Borg scale was used and the participants were asked to walk at a pace that they would rate as 13-14, (activity perception “somewhat hard”) and perform the strength exercises at 15-17 (“hard”-“very hard”) on the scale (135). Due to the participants’ limitations in mobility at enrollment, they were introduced to all the activities in a structured way, starting with a lighter intensity and with gradual increase in intensity during the first 2-3 weeks of the intervention. The exercise sessions were supervised by trained
instructors, at the Swedish site experienced physiotherapists, who were present at all times to give the participants instruction, support and help.

Furthermore, the participants were also encouraged to carry out physical activity outside of the exercise sessions. The goal was for participants to complete at least 150 minutes per week of moderate physical activity. Each participant completed and handed in a log of their weekly physical activity.

The participants each received an oral nutritional supplement, which was a drink of 119 ml or a placebo. The drinks were delivered to their home and they were instructed to take one every day, immediately after each exercise session. Each participant completed and handed in a weekly log of their supplement/placebo intake. The supplement consisted of (per serving) 150 kcal, 20 grams of whey protein, 7.2 grams of carbohydrates, 4.7 grams of fat, 800 IU of vitamin D, 350 mg of calcium and other vitamins and minerals. The composition of the nutritional supplement is described in detail in Appendix 2 in this thesis. The placebo drink was a non-nutritive sweetened drink (30 kcal per serving). Both products were developed and manufactured by Nestlé Health Science, Switzerland.

**Adherence**

The participants in VIVE2 were considered adherent if they attended 60% or more of the exercise sessions and consumed at least 60% of the supplement/placebo.

The design and methods used in VIVE2 are also described in detail in the study protocol publication “The Vitality, Independence, and Vigor in the Elderly 2 Study (VIVE2): Design and methods” published in 2015 (16).

**Participants in Papers I-III**

**Paper I. Physical performance and serum 25(OH)D status in older adults**

The participants (n=610) in the study described in Paper I were recruited between October 2011 and January 2014 from subjects who had been investigated for potential inclusion in the VIVE2 study. Those who met the eligibility criteria (assessed during the telephone interview) and were still interested were asked to attend a screening visit at each study site. At the screening visit SPPB was performed and if the person was eligible, i.e. SPPB score ≤9, a blood sample was obtained to measure serum 25(OH)D. For a flow chart over subjects included in Paper I, see Figure 1.
Paper II. Effect of exercise and nutritional supplementation on health-related quality of life and mood
Participants in the study described in Paper II were those who had completed the VIVE2 intervention, and for whom data on SF-36 (n=128) and CES-D (n=133) were available. See Figure I.

Paper III. Feeling more self-confident, cheerful and safe
The participants in the study described in Paper III were a subsample of the individuals completing the VIVE2 study and were recruited through purposeful sampling. Individuals who participated in the VIVE2 intervention at the Swedish site were asked by mail, from March to May 2014, to participate in focus group interviews. In total, 23 individuals completed the intervention during this period and 22 of them were invited to take part in the focus groups. In addition to having completed the entire intervention, inclusion criteria were: a willingness to participate and the ability to speak Swedish fluently. Two potential participants rejected participation, one for health reasons and another for unknown reasons. One was not invited to participate due to not speaking Swedish fluently. See Figure 1.
Figure 1. Flowchart of the inclusion and randomization process for the VIVE2 study. Sample size and point in time for Papers I, II and III.
Participants in the study described in Paper IV. Mortality associations for sarcopenic obesity in old age

The fourth paper in this thesis is based on data from two Swedish population studies: the H70 Study from Gothenburg, and the Uppsala Longitudinal Study of Adult Men (ULSAM). Two cohorts of older individuals came from the H70 Study: the Gothenburg H70 Birth Cohort Studies, including both women and men (136), and the Prospective Population Study of Women in Gothenburg (PPSW)(137). The third cohort came from the ULSAM study. (138).

Participants in H70 and PPSW were all born in 1930 and data from a total of 521 individuals, 202 men and 319 women, mean age 75.6 years (±0.3), were collected in 2005. Data from 516 of these individuals (excluding 5 with sarcopenia as described later in the methods section) were used in the analyses in Paper IV. The population study of older people in Gothenburg (H70) started in 1971/72, with the aim of making a survey of the medical and social conditions of 70 year olds living in Gothenburg and to contribute to the knowledge of the normal ageing process. A representative sample of approximately 1000 70- year olds was included at the study start. Since then several age cohorts have been included in the study, including the one with individuals born in 1930 used in Paper IV in this thesis (136).

The Prospective Population Study of Women in Gothenburg (PPSW) started in 1968-1969 with examinations of a random sample of women living in Gothenburg. In total 1462 women aged 38, 46, 50, 54 or 60 years participated in the first examinations (137). In Paper IV women from both the H70 cohort and the PPSW are included in the analyses and referred to as H70 women.

The ULSAM study is a longitudinal study focusing on identification of cardiovascular risk factors and based on all available men born between 1920 and 1924 residing in Uppsala County. The men were investigated for the first time in 1970-1973, at the age of 50 years (n=2322 out of n=2841 potential participants), and again at the age of 60, 70, 77, 82, 88 and 93 years (138, 139). Paper IV used data from 288 men from the ULSAM cohort (ULSAM- 88 follow up) when the men were aged 86.7 years (±1). Data were collected from 2008 to 2009. In total, 613 men were invited to the ULSAM-88 follow up, 354 participated and relevant data for Paper IV were available for 288 individuals.
Methods and data collection

Paper I. Physical performance and serum 25(OH)D status in older adults

In this paper, physical function was measured using the Short Physical Performance Battery (SPPB).

**Short Physical Performance Battery**

The SPPB includes measures of lower extremity function and provides a good estimate of the future risk for disability in non-disabled older adults (85, 140). SPPB consists of three subcomponents: chair stand (time to complete five consecutive chair stands- rising from sitting to standing), gait speed (best of two “4 meter walks” at the subject’s usual pace (m/s)) and balance testing (side-by-side and semi- and full-tandem stands for 10 seconds each). Every assessment yields a score between 0-4, with 0 representing inability to do the test and 4 representing the highest level of performance. The maximum total score of the SPPB is 12. The total score can be divided into four categories: 10-12 points representing minimal limitations, 7-9 points mild limitations, 4-6 points moderate limitations and 0-3 severe limitations (85, 141).

At the screening visit for the VIVE2 study, the participants performed the SPPB supervised by trained study staff. Subjects with a SPPB score of ≤9 were invited to continue with the enrollment process and the next step was to give a blood sample.

**Serum 25(OH)D**

In Paper I, eligible participants with an SPPB score of ≤9 and who were interested in continuing with the screening process gave a blood sample so that serum 25(OH)D concentration could be measured. The serum levels of 25(OH)D were determined by using a radioimmunoassay (DiaSorin RIA kit, Diasorin, Stillwater, MA, USA) in the American subjects, and a chemiluminescence method (CLIA, Roche Diagnostics, Basel, Switzerland) in the Swedish subjects.

Anthropometric measurements used in Paper I were collected during the screening visits. Data on intake of vitamin D supplements were self-reported and collected during the telephone screenings before the study started.
Paper II. Effect of exercise and nutritional supplementation on health-related quality of life and mood

Data from the VIVE2 study at baseline- and from the six-month follow-up were used in Paper II.

Medical Outcomes Study 36-Item Short Form Health Survey (SF-36)

To measure health-related quality of life (HRQoL) the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) was used (142). SF-36 consists of 36 items and two summary scores: a Physical Component Summary (PCS) and a Mental Component Summary (MCS). The SF-36 measures HRQoL in eight domains: physical function (PF), role physical (RP), bodily pain (BP), general health perception (GH), vitality (VT), social functioning (SF), role emotional (RE) and mental health (MH). The summary scores ranges from 0-100 and a higher score indicates higher levels of HRQoL (142).

Center for Epidemiologic Studies Depression Scale (CES-D)

In Paper II, the Center for Epidemiologic Studies Depression scale (CES-D) was used to measure symptoms of depression (143). In this short self-reported measure consisting of 20 questions about symptoms that have occurred in the previous week, the response options are scored from 0 to 3 with reference to frequency of the symptoms. The score ranges from 0-60 with higher scores indicating more symptoms (143).

Paper III. Feeling more self-confident, cheerful and safe

Qualitative data were collected through focus groups that were conducted from May to September 2014, 2-4 weeks after the participants had completed the intervention. Focus group interviews collects data through interactions and are suitable option when individuals share a common experience (127). The focus groups were led by a moderator (ÅvB). An observer (MS) was also present taking notes and handling the audio recording devices. The location for the focus groups was the Swedish site where the intervention took place, i.e the Aleris rehab clinic south of Stockholm.

Four focus group interviews were conducted, with each group consisting of 4-8 participants, giving a total of 20 participants. The interviews lasted between 60 and 90 minutes each. A semi-structured interview guide including open ended questions, developed by the researcher and reviewed and revised by the co-authors, was used during the interviews, see Table 1.
Table 1. Primary question guide for the focus group interviews.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short introduction. Information concerning: informed consent, voluntary participation, and recording. Presentation of moderator and observer.</td>
<td></td>
</tr>
<tr>
<td>1. What was your reason for wanting to participate in this intervention?</td>
<td></td>
</tr>
<tr>
<td>2. What has been positive and negative during your participation?</td>
<td></td>
</tr>
<tr>
<td>Potential follow up questions:</td>
<td></td>
</tr>
<tr>
<td>3. Have you made any other changes concerning your lifestyle during this time period?</td>
<td></td>
</tr>
<tr>
<td>4. Now that the intervention is completed, what are your thoughts regarding exercise and lifestyle?</td>
<td></td>
</tr>
<tr>
<td>5. The moderator makes a short summary of the discussion. Did we miss anything? Do you want to add anything?</td>
<td></td>
</tr>
</tbody>
</table>

The participants were encouraged to speak freely about their experiences during the interviews and probes were used to obtain more in-depth information about the participants’ thoughts and feelings. The moderator and the observer agreed after four focus group interviews that no new material was being derived and that the thoughts and opinions of the participants’ experiences therefore had been obtained. The interviews were audio-recorded and transcribed ad verbatim.

Paper IV. Mortality associations for sarcopenic obesity in old age
In this paper anthropometric and body composition measures were used as well as measures of strength and function. Data on mortality were used in the survival analysis.

**Definition of sarcopenia and obesity**
The definitions for sarcopenia and obesity used in this paper are described in Table 2.
Table 2. Definition and cut offs for sarcopenia and obesity

<table>
<thead>
<tr>
<th>Sarcopenia EWGSOP2</th>
<th>Obesity*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H70 men and women</strong></td>
<td></td>
</tr>
<tr>
<td>Grip strength &lt;27 kg (men) &lt;16 kg (women) (12) <strong>or</strong> chair stand &gt;15 sec (12) <strong>and</strong> SMI &lt;8.5 (men)/ &lt;5.75(women) (144)</td>
<td>Body mass index &gt;30 kg/m² (21) <strong>or</strong> body fat mass % ≥30(men) ≥42 (women) (28) <strong>or</strong> waist circumference &gt;102 cm (men)/ &gt;88 cm (women) (25)</td>
</tr>
<tr>
<td><strong>ULSAM</strong></td>
<td></td>
</tr>
<tr>
<td>Grip strength &lt;27 kg (12) <strong>or</strong> chair stand &gt;15 sec (12) <strong>and</strong> ASMI &lt;7 kg/m² (12)</td>
<td>Body mass index &gt;30 kg/m² (21) <strong>or</strong> body fat mass % ≥30 (28) <strong>or</strong> waist circumference &gt;102 cm (25)</td>
</tr>
</tbody>
</table>

*If any one of the obesity criteria was fulfilled the individual was defined as obese. SMI= Skeletal Muscle Index, ASMI= Appendicular Skeletal Muscle Index

*Body Mass index*
A body mass index, BMI, over 30 kg/m² (21) was one of the measures used to define obesity in Paper IV. Weight was measured on a digital medical scale and divided by standing height in meters².

*Waist circumference*
Waist circumferences over 102 cm for men and 88 cm for women (25) was also used to define obesity in Paper IV. The waist circumference was measured (in both H70 and ULSAM) midway between the lowest rib and the iliac crest using a measuring tape.

*Body composition – fat mass and muscle mass*
Body composition data were used to define obesity, a total body fat mass of >30 % for men and >42% for women (28) and also to define low muscle mass using cut-offs for a Skeletal Muscle Index, SMI < 8.5 kg/m² and 5.75 kg/m² for men and women respectively in the H70 (144), and an Appendicular Muscle Mass Index of <7 kg/ m² in ULSAM (12).

To measure body composition in the H70 cohort in Paper IV, Bioimpedans Spectroscopy (BIS) was performed using Xitron Hydra 4200 devices (Xitron technologies, San Diego, USA). BIS measures electrical resistance and fat free mass (FFM) is predicted from information on the distribution of intracellular water and extra cellular water (145). The method is non-invasive and easily performed. To estimate Skeletal muscle mass (SMM) from BIS in Paper IV, the equation (TBSMM_{noBW} = -24.05 + (0.365*height)+(-0.005*Ri)+(-0.012*Re)+(-1.337*gender)(Ri and Re= Intra- and extracellular resistance)) developed and validated by Tengvall et al. was used (146). Skel-
et al muscle index (SMI) was calculated as SMM divided by height in meters².

In the ULSAM cohort Dual–energy X-ray Absorptiometry (DXA), (DPX Prodigy, Lunar corp., Madison, WI, USA) was performed and ASMI was calculated using total muscle mass from arms and legs divided by height in meters². DXA is a measurement most often used in research settings due to its “non-portability”. DXA can determine body composition in terms of fat mass and muscle quantity (total body lean mass).

**Muscle strength and physical performance tests**

*Chair stand test*

In the five repeated chair stand test the individual is asked to rise from a chair five consecutive times without using the handles and the time to perform the rises is measured. This test is one of the subcomponents of the SPPB (85). The chair stand test is also a main component of the EWGSOP2 sarcopenia definition (and used in Paper IV in this thesis), where a time of >15 seconds to perform the test is used as a cut-off to indicate low thigh strength (12).

In the ULSAM cohort, data on time to perform five repeated chair stands were missing for 45 out of the 288 individuals. The reason for this was (except for one individual who did not perform the test due to dizziness) that the participants were not able to complete five stands. These individuals were included in the main analyses as not performing the test under 15 seconds and if they had a low ASMI, they were considered to be sarcopenic and, if they were also obese by any criteria, they were considered to be sarcopenic obese.

*Handgrip strength*

In the sarcopenia definition by EWGSOP2 launched in 2018, handgrip strength is also a vital component in the diagnosis of sarcopenia. Measurement of handgrip strength is performed using a handheld dynamometer. It is an inexpensive and simple measurement and the EWGSOP therefore advise that it is used as a routine measurement in clinical settings for older adults. In Paper IV, hand-grip strength was measured using a Jamar dynamometer in the H70 study and a Baseline hydraulic hand dynamometer in ULSAM.

*Gait speed*

In the EWGSO2 a gait speed below 0.8 m/seconds is considered low and this cut-off indicates that the sarcopenia is severe. In Paper IV, the participants’ mean gait speed is presented in the basic characteristics. In H70, gait speed (meters/seconds) was tested by self-selected walking speed for 20 meters
indoors with a standing start (147). In ULSAM the participants were instructed to walk a 10-meter straight course, where the middle 6 meters were marked and registered. The participants were instructed to walk at their usual comfortable gait speed.

**Mortality data**

Data on all-cause mortality used in Paper IV were obtained from the Swedish Cause of Death registry for all participants for every calendar year.

**Statistics and data analyses**

The statistical analyses performed in Papers I and II were conducted using STATA13 (148), and in Paper IV using STATA15 (149).

**Paper I. Physical performance and serum 25(OH)D status in older adults**

The descriptive analyses in this paper included the t-test for normally distributed data, the Mann-Whitney U-test and the Kruskal-Wallis test for ordinal and non-normally distributed data, respectively, and tests of proportions. In the analyses serum 25(OH)D was treated as a continuous variable, except for the logistic regression models where 25(OH)D was categorized into the three levels suggested in the Endocrine Society Clinical Practice Guidelines (64) or according to the recommendations of the Institute of Medicine (IOM) (65), see table 3.

Table 3. Recommendations from IOM and the Endocrine Society Clinical Practice Guidelines

<table>
<thead>
<tr>
<th>Definitions by IOM</th>
<th>Serum 25(OH)D nmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficient</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Inadequate</td>
<td>30-50</td>
</tr>
<tr>
<td>Sufficient</td>
<td>&gt;50</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Definitions by Endocrine Society Clinical Practice Guidelines</th>
<th>Serum 25(OH)D nmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficient</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Insufficient</td>
<td>50-75</td>
</tr>
<tr>
<td>Sufficient</td>
<td>&gt;75</td>
</tr>
</tbody>
</table>

The SPPB total score was categorized according to the indicated classifications previously described, i.e. 7-9 points mild limitations, 4-6 points moderate limitations, 0-3 points severe limitations and then further transformed into a dichotomous variable, i.e. severe/moderate limitations (score 0-6 points) and mild limitations (score 7-9 points) in the logistic regression model.
When studying the association between the SPPB scores and levels of 25(OH)D, we used logistic regression models with a serum level of <50 nmol/L as a reference. To evaluate the relationship between levels of 25(OH)D and the subcomponents of SPPB, chair stand and gait speed, we used crude and adjusted linear regression models. Owing to an inverted U-shaped relationship, we included a quadratic term for 25(OH)D in the regression model for chair stand and 25(OH)D. By reason of apparent heteroscedasticity, i.e. non-constant variation across the span of 25(OH)D serum concentrations, we used heteroscedasticity-consistent standard errors in the analysis including chair stand. The subcomponent balance was treated as an ordinal variable, and in the analyses of the potential association with 25(OH)D, ordered logistic regression was conducted.

In Paper I the following potential confounders were included in the statistical analysis: age, BMI, country of origin (Sweden or USA), gender and season for the blood samples (dichotomized into winter (November-April) and summer (May-October) (150)). Sensitivity analyses were also conducted where we stratified the analyses by country and by taking a vitamin D supplement or not. All statistical tests were two-sided, and differences at p<0.05 were accepted as significant.

Paper II. Effect of exercise and nutritional supplementation on health-related quality of life and mood

In Paper II, mean and standard deviations or frequencies in percentage were calculated to describe baseline characteristics. Analysis of covariance (ANCOVA) was used to compare the outcomes on the SF-36 and CES-D between the group receiving the nutritional supplement and the placebo. Sensitivity analysis, including Complier Average Causal Effect (CACE estimates), was performed using the ivreg command in STATA (148, 151).

In exploratory analyses using ANCOVA, the potential effects of the intervention were compared between pre-defined subgroups, based on baseline sarcopenia status and BMI. In this paper, sarcopenia status was defined as an ASMI for women <5.5 kg/m² and for men <7.26 kg/m² or low handgrip at <20 kg for women and <30 kg for men (11, 152). The BMI categories were 20-24.9 kg/m², 25-29.9 kg/m² and ≥30 kg/m², respectively.

The models in Paper II were adjusted for baseline values (MCS, PCS and CES-D), sex, age and study site. All statistical tests were two-sided, and differences at p<0.05 were accepted as significant.
Paper III. Feeling more self-confident, cheerful and safe

In Paper III, manifest and latent content analyses were performed (153). The analysis was inductive and based on the methodological approach described by Graneheim and Lundman (154). The analysis was performed stepwise and started with reading through the transcribed material several times. Meaning units were then identified and condensed. The software Opencode was used in this part of the process (155). The meaning units were coded and the codes divided into subcategories; these subcategories were then allocated to categories. Subsequently, the categories were reflected on and discussed. One theme, reflecting the meaning across the categories, was defined. The analysis process involved going back and forth between the steps several times to ensure that the content was appropriately understood.

To support trustworthiness the concepts of credibility, dependability and transferability as described by Graneheim and Lundman were taken into account when conducting the analysis (154). Moreover, quotations were selected to explain the categories presented in the results and help confirm the connection between the results and the data. The analysis was performed in Swedish and the results translated into English.

Paper IV. Mortality associations for sarcopenic obesity in old age

In Paper IV descriptive statistics were presented and survival analysis performed. In the analyses, the cohorts H70 and ULSAM were divided into four groups based on body composition phenotype: sarcopenic obesity, sarcopenia without obesity, obesity without sarcopenia and no sarcopenia or obesity. Sarcopenic obesity was defined as sarcopenia (by EWGSOP2) in combination with any definition for obesity.

The analyses and results for H70 were conducted and presented for men and women separately. In the analysis of the potential association between body composition phenotypes and all-cause mortality, the 10-year survival was examined in H70 (depending on date of examination, maximum years at risk was 9.7) and the 4-year survival in ULSAM (maximum years at risk 4.0). Moreover, the log-rank test, Kaplan–Meier survival curve and the Cox proportional hazard model were used. The Cox regression analyses were presented as hazard ratios with 95% confidence intervals. A p-value <0.05 was considered statistically significant.

In H70, the models were adjusted for the covariates comorbidities and smoking. In ULSAM, the models were adjusted for age, comorbidities, education, exercise, living conditions and smoking. The un-weighted Charlson Comor-
bidity index was used when adjusting for co-morbidities and the index was based on in-patient diagnoses (ICD9-ICD10) in the patient register before the dates of the examinations (156, 157).

In ULSAM, education was defined as years in school divided into categories (7, 8 or 12 years), or college education, or graduate exam. In ULSAM, data concerning regular exercise were available and defined as doing sports/heavy gardening more than three hours per week. In the ULSAM analysis, living condition was defined as living alone or not. In H70, smoking was defined as number of cigarettes per day, and in ULSAM as current smokers or non-smokers. A likelihood ratio test was performed and also a test for proportional hazard assumption including plots of Schoenfeld residuals.

In Paper IV, some sensitivity analyses were performed. Using the H70 data we complemented the primary analyses by performing survival analysis excluding the individuals within the cohort who had passed away within one year after the examination (2005-2006). In addition, we conducted sensitivity analyses where mortality for the women with obesity (only defined as BMI>30 kg/m²) without sarcopenia was compared to the mortality for the group with no sarcopenia or obesity. Since no data on exercise were available for H70 we chose to use the co-variante “spare-time activity during the last year” but this variable was missing for almost half of the H70 sample. We therefore conducted complementary sensitivity analyses on a sub-group using this variable in the models. In the ULSAM cohort, mortality was compared between the men with obesity (without sarcopenia) defined as waist circumference >102 cm and the men with no sarcopenia or obesity. Moreover, we also compared the risk of mortality between the group with obesity by any definition (irrespective of sarcopenia) and the group without obesity (irrespective of sarcopenia).
Ethical considerations

The protocol for the VIVE2 study (Papers I and II) was approved by the Regional Ethical Review Board of Uppsala (# 2012/154) and by the Tufts Health Sciences Campus Institutional Review Board, and was registered at ClinicalTrials.gov (NCT01542892).

Paper III was not included in the first Ethical approval and an addendum was sent to the Regional Ethical Review Board of Uppsala. This addendum was also approved by the Ethics Committee in Uppsala (# 2012/154).

For Paper IV, the H70 study was approved by the Ethics Committee of the University of Gothenburg, Sweden (Dnr S377-99/T45 304) and the UL-SAM- 88 study by the Regional Ethical Committee of Uppsala, Sweden (Dnr 2007/338).

All methods were performed in accordance with relevant guidelines and regulations, e.g. the Helsinki Declaration. Informed consent was obtained from all participants.
Results

Paper I. Physical performance and serum 25(OH)D status in older adults

In this study the results are based on data from 610 participants with a mean age of 77.6 years; 59% were females, 81% American, and the average serum 25(OH)D level for the total sample was 66.3 nmol/L. The American participants had significantly higher levels of 25(OH)D (average 69.9 nmol/L) than the Swedish individuals, but the Americans also used vitamin D supplements (below 10 µg per day) to a higher extent than their Swedish counterparts. Altogether, 29% of the total sample had 25(OH)D levels below 50 nmol/L and 65% below 75 nmol/L.

The main result of this study revealed no clear association between serum 25(OH)D levels and SPPB score and no association between the subcomponents gait speed (Figure 2a) or balance test (Figure 2b) and 25(OH)D level. However, the analyses of the relationship between time to perform five repeated chair stands and 25(OH)D, revealed that higher levels of 25(OH)D (above 74 nmol/L) seemed to decrease the time to perform chair stands, although this association was not apparent at lower 25(OH)D levels (Figure 2c).
Figure 2 a, b and c. The relationships between 25(OH)D and a) gait speed b) balance score and c) seconds to perform five timed chair stand test (crude models)
The sub-analyses in this study showed that the participants with mild limitations (defined as a score on the SPPB of 7-9) had significantly lower levels of 25(OH)D than individuals with moderate to severe limitations (defined as a SPPB score of 0-6).

Paper II. Effect of exercise and nutritional supplementation on health-related quality of life and mood

The 149 participants in this study had a mean age of 77.5 years, 46 % were females and 56% were from the American study site. Mean BMI in the total sample was 28 kg/m^2, ranging from 20-36.6 kg/m^2. The participants had an average 25(OH)D serum concentration of 46.8 nmol/L. A mean score of 13.3 on the Mini Nutritional Assessment SF (0-14) indicated an otherwise good nutritional status.

After the six-month intervention the analyses showed a significant improvement in MCS on the SF36, (Figure 3a), and also a decrease in depressive symptoms measured using the CES-D (Figure 3b). The improvements in MCS were driven by improvements in the domains Role Emotional (RE) and Mental Health (MH). No significant change in PCS score was detected (Figure 3c). Furthermore, there were no differences in effects between the group that received the placebo and the group that received the nutritional supplement. Thus, no additional effect could be attributed to supplementation. In the sensitivity analyses, where the participants’ base-line values of BMI, ASMI, gait speed and grip strength were taken into account, no variations in effect were detected.
Figure 3 a, b and c. Effect of the intervention on health related quality of life (HRQoL) and depressive symptoms. Effect after six months (6M) measured by the SF-36 mental component summary (MCS), the Center for Epidemiologic Studies Depression Scale (CES-D), and the SF-36 physical component summary (PCS) respectively. Presented as the means and 95% confidence intervals (line segments); model estimated mean difference between groups presented in text (complete case analysis, adjusted for baseline values).
Paper III. Feeling more self-confident, cheerful and safe

A total of 20 older individuals who had completed the VIVE2 intervention participated in focus group interviews. The participants had a mean age of 77.5 years, 8 were females, 9 were married and 11 lived alone.

The experiences of the participants were interpreted in one overall theme “Feeling more self-confident, cheerful and safe” that emerged during the analyses. The theme encompasses four categories; psychological effects of participating in the intervention, physical effects of participating in the intervention, the importance of social support and the importance of a tailored set-up. The first two categories describe the effects experienced and the other two describes supporting factors. Each category incorporates 2-4 subcategories, see Table 4.
Table 4. Table of results from the content analysis (Paper III).

<table>
<thead>
<tr>
<th>Theme</th>
<th>Category</th>
<th>Subcategory</th>
<th>Examples of quotations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeling more self-confident, cheerful and safe</td>
<td>Psychological effects of participating in the intervention</td>
<td>Positive effects on frame of mind</td>
<td>“I have become more interested in the outside world…” (Female 86 years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stronger motivation, increased need for physical activity</td>
<td>“Now I think that everything is training and then things are fun” (Female 71 years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Strategies for continued physical activity</td>
<td>“I will do the exercises at the outdoor gym” (Male 85 years)</td>
</tr>
<tr>
<td>Physical effects of participating in the intervention</td>
<td>Positive physical effects</td>
<td></td>
<td>“I usually do not make it in time to the subway if it’s on its way in, but suddenly, I realized ….I walked faster” (Female 78 years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Negative physical effects</td>
<td>“Well, it has been both good and bad for the knees and back…” (Male 76 years)</td>
</tr>
<tr>
<td>The importance of social support</td>
<td>Support as a prerequisite</td>
<td>Support as a prerequisite</td>
<td>“So many people who really did not have the energy to go they just came to meet the group…” (Female 71 years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cheerful atmosphere in the group</td>
<td>“We had great fun in our group, it was very “laughy” and we became close ” (Female 78 years)</td>
</tr>
<tr>
<td>The importance of a tailored set-up</td>
<td>Professional support</td>
<td>Professional support</td>
<td>“….she (the leader) was quite good at seeing if you happened to make mistakes ” (Male 76 years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Schedule</td>
<td>“I think we should have been offered exercise four times a week instead of three…”(Male 85 years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exercises</td>
<td>“Shouldn’t we exercise the upper part of the body as well…”(Female 72 years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Locality</td>
<td>“For me it was very important that the bus to get here stops outside my house…”(Female 71 years)</td>
</tr>
</tbody>
</table>
In the beginning of each interview session, the participants were asked about their motives for participating in the intervention. The answers and discussion concerning this question involved several motives, for example, concerns about the health effects of living a sedentary life, difficulties in starting on their own, wanting to be “monitored”, and several of the participants wanted to become more physically active in order to lose weight.

**Paper IV. Mortality associations for sarcopenic obesity in old age**

In Paper IV data from two different population studies were used. In the H70 cohorts the mean age was 75.6 years for both men and women, whereas the mean age of the men in the ULSAM cohort was 86.6 years.

In the cohort of 75-year-old women (H70), 20% had a BMI above 30 kg/m², 47% a total body fat mass over 42%, and 50% a WC >88cm. Mean grip strength among the women with sarcopenic obesity was 20 kg and among those with no sarcopenia or obesity 24 kg. The mean time to perform five repeated chair stands was 20 seconds in the group with sarcopenic obesity and 11 seconds in the group with no sarcopenia or obesity.

In the cohort of 75-year-old men (H70), 15% of the total sample had a BMI above 30 kg/m², 62% a body fat mass over 30%, and 35% a WC >102 cm. Mean hand grip was 38.5 kg in the total sample of these men and in the group with sarcopenic obesity, the mean hand grip was 33 kg and in the groups with obesity or no sarcopenia or obesity mean hand grip were 39 kg. The mean time to perform five repeated chair stands was 18 seconds in the group with sarcopenic obesity and 11 seconds in the group with no sarcopenia or obesity.

In the ULSAM cohort, where the men were considerably older with a mean age of 86.6 years, 7% had a BMI above 30 kg/m², while 44% had a total body fat mass over 30%, and 37% a WC >102 cm. Mean handgrip strength among those with sarcopenic obesity was 26 kg, compared to 31.5 kg in the group with no sarcopenia or obesity. The mean time to perform five repeated chair stands was 22 seconds in the sarcopenic obese group and 17 seconds in the group with no sarcopenia or obesity.

The main results in this study showed a prevalence of sarcopenic obesity in the H70 cohorts of 4% in the women and 11.5% in men. In ULSAM, the prevalence of sarcopenic obesity was 10%.
In H70, women with sarcopenic obesity had a threefold (HR 3.25(1.2-8.9)) risk of dying within the 10-year follow-up time compared to women with no sarcopenia or obesity (Figure 4a). This association became weaker after adjustments for comorbidities and smoking (HR 2.6 (0.9-7.2)). No statistically significant association with body composition phenotype and mortality was found among the 75-year-old men in H70 (HR 1.5 (0.7-3.5)) (Figure 4b).

In the ULSAM men, obesity without sarcopenia seemed to be associated with better survival 0.6 (0.3-0.9) when compared with no sarcopenia or obesity, after adjustments for comorbidities, education, exercise, living conditions, and smoking (Figure 4c).
Figure 4 a, b and c. Figure a and b show survival rates (unadjusted) in women and men from H70 stratified according to “sarcopenic obesity”, “obesity” (without sarcopenia) and “no sarcopenia or obesity”. Figure c shows corresponding data for ULSAM, with the group with “sarcopenia” (without obesity) included.
Discussion

Vitamin D status and function

As described in the introduction of this thesis, the potential effects of vitamin D on muscle function have received a lot of attention during the past years, however, scientific evidence has been conflicting. When designing the nutritional supplementation used in the VIVE2 study, the hypothesis was that, in accordance with indications from some previous studies, increasing vitamin D levels (and an extra intake of protein) would help to improve physical function and thus provide additional effects to those from the exercise program.

In Paper I, where we examined the potential relationship between vitamin D levels in serum (25(OH)D) and physical function, the results revealed no significant relationship other than an indication that higher levels of vitamin D (above 74 nmol/L) were associated with better results on the chair stand test, levels of 25(OH)D very close to the minimum recommended by the Endocrine Society (64). It should be observed that only subjects with reduced physical function, i.e. SPPB ≤ 9, took part in the study. Quite unexpectedly, the results showed that the individuals with milder limitations had lower levels of 25(OH)D than those with moderate-severe limitations and that for individuals with 25(OH)D levels below 74 nmol/L, an increase in 25(OH)D resulted in an increase in the time taken to perform the chair stand test. In the telephone interviews preceding the SPPB test and blood sampling, 49% of those interviewed stated that they consumed vitamin D supplements, but reported that the vitamin D content was below 10 µg (400IU) per day. We can only speculate as to whether this is a possible source of error. Considering the media coverage over the past years about the potential positive effects of vitamin D supplementation, it is not unlikely that older individuals with reduced physical function would be prescribed vitamin D supplements or would take them on their own initiative.

The result of our study did not show a positive association between 25(OH)D and gait speed, which is in contrast with the results of a recent meta-analysis (158). This meta-analysis was based on data from observational studies. Intervention studies, however, have not shown corresponding improvements in function with vitamin D supplementation (71, 159, 160).
the VIVE2 study, the group receiving the nutritional supplement improved their 25(OH)D by an average of 36% during the intervention, unlike the control-group where 25(OH)D remained largely unchanged. However, both the intervention and control groups improved their gait speed (101).

In our observational study (Paper I) we lacked certain covariates that could have had some impact on the results. For example, amount of time spent outside, which could influence both 25(OH)D levels and function. Altogether, 65% of the participants in Paper I had 25(OH)D levels below 75 nmol/L, i.e. they had deficiency or insufficiency according to the Endocrine Society Clinical Practice Guidelines (64). What might have been of interest when interpreting our results was information about the duration of the participants’ 25(OH)D deficiency, although such information is usually not available.

ICFSR conclude in their guidelines that there is not enough evidence to recommend supplementation of vitamin D with the aim of treating sarcopenia, although in cases of deficiency, or other conditions where this could be of benefit, supplementation may be relevant (100). Moreover, the Institute of Medicine (IOM) and a comprehensive review of meta-analyses and systematic reviews highlights the risks with overtreatment of vitamin D, and that benefits in terms of extra-skeletal effects have not been consistently shown in previous studies (69, 161).

**Effects on wellbeing**

A potential impact of serum level of 25(OH)D was also part of the hypothesis in Paper II where we examined if the nutritional supplement could enhance the effect of the exercise program on health-related quality of life and depressive symptoms. The results in Paper II did not confirm this hypothesis. The results showed that the Mental Component Summary scores (MCS) on the HRQoL form SF-36 became higher and the scores on the CES-D decreased significantly after the exercise intervention irrespective of randomization to the supplementation or the placebo group.

The results in Paper II are in line with several previous studies on the positive effects of participating in exercise interventions (162-164). However, unlike the results from other studies (116, 165), the Physical Component Summary score (PCS) did not increase significantly among the participants completing the VIVE2 intervention. This result was quite unexpected and the reasons behind it can only be speculated upon. One possible reason is the potential response-shift that might have occurred (108, 166). It is not unlikely that the participants’ frames of references and perceptions of health shift-
ed after being part of the intervention for six months and during the process of becoming more active (both physically and socially). The results from Paper III possibly reveal some indications that this was the case. During the interviews, the participants expressed that they experienced stronger motivation and awareness of the need for physical activity. For example, an 86 year old female reported that she had started taking the stairs to her apartment after having used the elevator for 50 years.

The term wellbeing is used in the title of this thesis and there are several specific instruments to measure different approaches of wellbeing, although none is used in the studies in this thesis unless one includes SF-36 (167). Here the term is more generally used as a collective term that includes positive emotions and mood, joy and the aspect of physical wellbeing. Wellbeing is also defined as one dimension of general quality of life as well as the absence of depression (outcomes measured in Paper II) (111).

We used the CES-D questionnaire to measure symptoms of depression and, as also mentioned in Paper II, it is important to keep in mind, that there is a close relationship between the domain mental health in the SF-36 and the CES-D, why the similar/corresponding improvement is not that surprising.

The participants’ positive experiences and feelings of joy described in the qualitative paper (Paper III) also relate to the concept of wellbeing. In the focus group interviews in Paper III, the participants expressed experiencing positive effects on their frame of mind as a result of participating in the intervention; they felt more optimistic and they enjoyed the cheerful atmosphere of the group.

When measuring HRQOL, generic instruments, such as the SF-36, have advantages since they can be used in any population and allow for broad comparisons. However, compared to disease-specific instruments, there is a risk of low responsiveness, i.e. that small changes might not be detected, which could be one explanation for the lack of improvement in PCS in Paper II (107).

Self-reported questionnaires, such as the SF-36 and CES-D used in Paper II, are convenient to use in trials as they require minimal resources, although they entail a risk for missing items. In Paper III data from SF-36 were missing for 21 individuals and data from CES-D for 16 individuals, i.e data were missing for 23 individuals in total. All participants had regular contact with the study staff during the intervention, they received thorough instructions on how to fill out the forms and were encouraged to ask if they had any questions. Despite this, data were still missing for 15 %, numbers that are comparable with the response rate in other studies (168). SF-36 consists of
36 questions on 3 sheets of paper which could be a challenge to fill in, especially for an older individual. Nevertheless, it has been shown to be a good choice of method for home-dwelling older adults (168), but possibly too complex for older adults with disabilities (169).

There has been some critique raised against the concept of health-related quality of life. For example, in the assessment of HRQoL physical symptoms, such as pain or fatigue are combined with emotional states, e.g. happiness. Furthermore, health-related quality of life does not delineate between instrumental values (means to reach good quality of life) and final values (the goals, the aspects of quality of life) (170). Moreover, generic instruments such as the SF-36, are developed based on the assumption that if a person cannot achieve full physical, psychological or social functioning their quality of life is poorer, an assumption that might not always be adequate. A person might experience a low quality of life because of pain or fatigue irrespective of their functional status. Reactions to health impairments could most likely vary between individuals and mobility impairment might therefore not automatically imply a low quality of life.

Since VIVE2 was designed, the instrument Sarcopenia and Quality Of Life, (SARQoL) has been developed to specifically evaluate HRQoL in individuals with sarcopenia (87, 171). If it had been available in both English and Swedish, it could have been a suitable instrument to use in the VIVE2 study. However, the participants did not have sarcopenia, but were at risk of developing it. SARQoL consists of 22 questions, i.e. fewer than SF-36, and since SARQoL is a disease-specific instrument, the questions concern aspects related to muscle weakness and impact on daily life. Nevertheless, in Paper II, the main focus of interest was the difference between the groups after the intervention and the potential effect of the nutritional supplement and although SF-36 has some limitations, we considered it an appropriate instrument to test the hypotheses of Paper II.

The qualitative approach

Inductive content analysis was conducted when analyzing the data from the focus group interviews in Paper III. Content analysis focuses on differences and similarities within the data and can be applicable at various depths (153). We chose to perform both manifest and latent content analysis; the manifest is very close to the text and describes “what the text says” and the latent involves a deeper interpretation and is an analysis of “what the text talks about” (154).

The results from Paper III were interpreted in one overall theme “Feeling self-confident, cheerful and safe”, which is a formulation of the thread of the
underlying meaning across the categories. These categories included both experienced effects, for example psychological and physical effects, and supporting factors, such as the importance of social support. The social support was described as a prerequisite for success, but also as a bonus, something they had not counted on, and the cheerful atmosphere they experienced was described as being great fun. It was quite interesting that when asked about motives for wanting to participate in the intervention, no one mentioned seeking social support as a reason. However, the importance of fun and enjoyment, and also the social support in interventions for older adults, has been emphasized in other studies as being a main motivator for engaging in and maintaining physical activity in old age (133, 172).

The results from Paper III did not only relate to increased well-being as discussed earlier, but the participants also expressed and emphasized the importance of a tailored set-up. This category comprised the subcategories: professional support, schedule, exercises and locality, factors that have also been described earlier in the literature as important facilitators for older adults engaging in physical activity interventions (133, 172, 173). Furthermore, the results from Paper III revealed that being taken care of by healthcare professionals contributed to the participants feeling of safety and they valued the professional support. These results are also in line with previous research in the field, indicating that there is an additional value of interventions being associated with “trusted organizations” and that interaction with healthcare professionals enhances the perceived safety of the intervention (133).

During the focus groups interviews the participants were asked about how they experienced the intervention. Very few of the participants chose to talk about the nutritional supplementation, i.e. the drink they consumed every day for six months. There were only a few incidental comments about the distribution of the drinks. We can only speculate about the reasons for this, but it could be that it was a double-blind trial and the participants were asked not to discuss the taste or other features of the drink with each other during the intervention. When the focus group interviews were held, the participants had not been informed whether they had consumed the supplement or the placebo. Another reason could be that the participants associated their experiences so strongly with the exercise and the social interaction in the groups, which the result implies, and therefore did not pay much attention to the drink.

Trustworthiness
Trustworthiness is important in qualitative inquiries in order to support the argument that the results are “worth paying attention to” as stated by Lincoln & Guba, in 1985 (174). In Paper III the concepts of credibility, dependability
and transferability were taken into account throughout the planning-, analysis- and reporting phases in order to support trustworthiness (154, 175). The sampling strategy and methods for data collection and analyses were considered appropriate to answer the research question after thoroughly discussing these considerations in the author group. The choice of method was primarily based on the aim of the study, which was to explore the experiences of the participants, and was judged to be appropriate when other factors were also considered, for example the experience of the authors and the resources within the project.

Furthermore, the analysis in Paper III involved going back and forth between the different steps, and the first and last authors had continuous discussions during the process of dividing into meaning units, coding, sorting into subcategories, categories and finally defining the theme. Descriptions of the context, the participants and the analysis process were also included to strengthen trustworthiness.

Self-efficacy
The concept of self-efficacy was helpful in understanding and discussing the results from the qualitative study (Paper III) in this thesis. Although there are instruments to measure level of self-efficacy, this was not measured in the VIVE2 intervention. The relationship between self-efficacy and physical activity has been described as complex, and self-efficacy has been considered to be both a consequence of and a determinant for physical activity (176). It could be interpreted from the results from Paper III that the level of self-efficacy was enhanced, i.e. that the intervention increased the participants’ outcome expectations, which might facilitate physical activity participation in the future. The participants expressed strategies for how they would continue to be physically active and that it had exerted a ripple effect on their daily lives, which could be interpreted as the intervention having an effect “way beyond” the time frame of this intervention.

However, not all participants described distinct strategies for continuing to be physically active, others focused on barriers and expressed concerns about being able to continue on their own. It is possible that their self-efficacy, the increased belief in their ability to perform physical activity, could for some, be restricted to this context. It has also been shown that although physical exercise might increase self-efficacy in older adults, this increase is most apparent at the beginning of the intervention, and while the effect could decrease when the organized intervention is terminated (177).
Sarcopenia

During the writing of this thesis and completion of Paper IV, the European Working Group on Sarcopenia in Older People (EWGSOP) launched an updated consensus on the definition of sarcopenia, EWGSOP2 (12). This new definition emphasizes that sarcopenia is a muscle disease and included new recommendations concerning physical performance measures and cut-offs. In the cohort of 75-year-olds (in Paper IV), the prevalence of sarcopenia was low at 0.5-1%. Thus, these individuals were excluded from further analyses. In ULSAM the prevalence of sarcopenia was higher, i.e. 10%.

Measures of sarcopenia

In Paper IV the individuals were considered to have sarcopenia if their results from the chair stand test were 15 seconds or longer, or the hand-grip strength was reduced, in combination with reduced muscle mass.

It is worth noticing that among the 88-year-old men in ULSAM, 45 individuals were not able to complete the five repeated chair stands test. In Paper I, the participants were on average 10 years younger than the ULSAM men, and when the individuals performed the SPPB, 103 individuals (of a total of 610) were not able to perform the chair stand test. This test has been shown to identify participants at high risk of functional limitations and it is therefore part of the definition of sarcopenia according to EWGSOP2 (178). In Paper IV, those not being able to complete the test were included in the main analyses and defined as having sarcopenia if muscle mass was also low, and as having sarcopenic obesity in the case of concurrent obesity. From ULSAM, no further information was available on the explicit reasons hindering the individuals from performing the test (except for one individual who declined because of dizziness). Such data was also lacking for the individuals in Paper I.

The other option proposed in EWGSOP2 for determining low skeletal muscle strength is hand-grip strength. This measure is easy and inexpensive, and a predictor of longer hospital stays, increased functional limitations and mortality (12, 179). However, using different methods to measure hand-grip strength could complicate comparisons between studies as emphasized both in EWGSOP2 and earlier by Roberts et al. (12, 180). In Paper IV hand-grip was measured with different hydraulic instruments, Jamar and Baseline in H70 and ULSAM respectively, but studies have shown that these methods can be used interchangeably (181).

The prevalence figures presented in Paper IV are, however, difficult to compare between the included cohorts due to the age difference and because
different body composition assessment methods were used. Although BIS has been validated against DXA (146), different cut-offs were used as SMI was applied for the participants of the H70 Study and ASMI for the ULSAM Study. The prevalence figures could also be difficult to compare to figures from studies in other populations because the publication of the EWGSOP2 consensus was so recent. Research in this area, also using the updated consensus, will most certainly be published soon.

Obesity and sarcopenic obesity in older adults

An interesting finding in the qualitative evaluation of the VIVE2 (Paper III) was that participants expressed a desire to lose weight, which was quite different from the aim defined by the research team when designing the intervention. Slenderness is, in our society, often associated with health and social acceptability and, of course, there is the possibility that the desire expressed was an after-construction influenced by social desirability. Nevertheless, this was an interesting result. It is a fact that a growing section of the population reaching older age is either overweight or obese, and research on the effects of obesity in older ages has attracted increasing attention. There is an ongoing debate in the scientific and clinical community as to whether the obesity paradox (related to ageing) actually exists. In Paper IV, it seemed that the consequences related to sarcopenic obesity and obesity (without sarcopenia) differed between the 75-year-olds and the 88-year-olds and also between women and men. In the oldest men, obesity (without sarcopenia) was associated with lower mortality when compared to those not having obesity. A corresponding result could not be shown for the 75-year-old men. This could indicate that obesity at such an advanced age as 88 years is an indication of health, and that the men who survive until 88 years, despite obesity, display a less metabolically active obesity compared to those who have already passed away. Several observational and intervention studies have shown that the quantity and quality of food intake affects the risk of developing cardiovascular diseases and risk of all-cause mortality (182-184). Dietary intake was not adjusted for in the analysis in Paper IV, which is important to take into consideration when interpreting the results. It is not unlikely that food intake could have been an important factor potentially affecting the association of interest in our studies.

In the 75-year-old women, sarcopenic obesity seemed to be associated with an increased risk of mortality, a result not statistically significant among the group of 75-year-old men. This result was opposite to that of a meta-analysis from 2016, which showed an increased risk of mortality in men with sarcopenic obesity (185). Inconsistent findings in this young field of research
could easily be related to the extensive heterogeneities in the definitions of obesity and sarcopenic obesity in older adults and the measuring techniques.

**Measures of obesity**

In Paper IV, we decided to define sarcopenic obesity by combining the definition for sarcopenia from EWGSOP2 with three different measures of obesity: BMI, waist circumference or high fat mass.

To calculate Body Mass Index, total body weight (kg) is divided by height in meters\(^2\). This is an inexpensive method for determining for example, obesity, although there are some pitfalls when using BMI, especially in older adults. BMI does not reflect body composition, and ageing is associated with changes in body composition, e.g. loss of muscle mass, an increase in fat mass and changes in body fat distribution. Also, as age increases, height decreases, which in turn affects BMI (34). Although, most collective evidence shows that BMI cut-offs should be higher for older adults, and also for older-older adults, there is no consensus concerning the specific cut-off values.

Body composition measurements were made using BIS in the H70 cohorts and DXA in the ULSAM Study. Although BIS has some advantages in that it is easier to use and to implement in clinical settings, DXA is the gold standard method. Tengvall et al. showed in the validation of their equation for estimating SMM that BIS results are comparable to DXA and only small systematic biases were reported (146).

Another way of defining obesity, in particular central obesity, is to measure waist-circumference. This is a measurement that is easy to perform in everyday practice and higher values are positively associated with increased mortality (186). For older adults, the recommended cut-offs for waist-circumference differs between studies and settings (187). The WHO report (2000) concluded that risks associated with particular waist-circumferences differ between populations (21). The cut-offs used in Paper IV, \(>102\) cm for men and \(>88\) cm for women, are examples of cut-offs that are associated with obesity and negative outcomes in Caucasians (21, 25).

**Strengths and limitations**

Among the major strengths of this thesis are that the VIVE2 study was multicenter randomized and double-blinded, i.e. all study personnel remained blinded throughout the intervention. Another strength is that the exercise- and nutrition intervention was evaluated by both quantitative and qualitative
techniques. Furthermore, the sample in Paper I was relatively large, with a high proportion of individuals with vitamin D deficiency. In Paper II, strengths also include the use of SF-36 as it enables broad comparisons with other similar trials. Strengths in Paper III include the choice of method, i.e. focus group interviews, which is preferable when aiming to obtain data with a broad perspective, and the transparent analysis process. In Paper IV, the major strength was the choice of cohorts, which included both women and men, and also men at different ages, i.e. 75 and 88 years. The study was also based on the most recent consensus sarcopenia definition in combination with three different measures of obesity.

There are also limitations that need to be acknowledged. A limitation in the VIVE2 study was the lack of data on the participants’ food intake, and especially their habitual protein intake during the intervention. This limitation affects the interpretation of the primary outcome results from the VIVE2 study, but also potentially the interpretation of the results from Paper II in this thesis. Paper IV also lacked data on dietary habits and as discussed above, this could be a factor affecting the associations of interest for our study.

Furthermore, when interpreting the results from Paper I, it is important to take into consideration the cross-sectional design which limits conclusions about causality. In addition, different methods were used to analyze 25(OH)D at the American and Swedish sites. In Paper II, limitations included the missing data, of which a relatively higher percentage (74%) were from the Swedish study site and perhaps, although also a strength, the choice of a generic instrument, since generic instruments could have lower responsiveness than disease-specific instruments. A limitation in the qualitative study, Paper III, was that the study was only conducted at the Swedish study site. It is most likely that if focus group interviews had also been conducted at the American site, the results would have provided more insights and perspectives of value for future trials, and for implementing similar interventions for older adults. In Paper IV, limitations included the relatively small sample size and few events. Moreover, the groups compared in Paper IV were based on baseline measures of anthropometry, body composition, strength and function. These variables could, and probably did, change over time, and an individual with obesity at baseline could potentially have sarcopenia after a couple of years, which is important to take into consideration when interpreting the results.
Clinical implications and future perspectives

The positive effects of the exercise intervention on mental health and potentially also on self-efficacy imply that interventions in this domain could be very beneficial for older adults. This claim is further supported if the improvements in physical performance are also taken into account.

The participants’ expressions about feeling safe during the intervention, the importance of professional support and a tailored set-up further indicates that these kinds of health-promoting interventions might be best supervised by physiotherapists, maybe in a team with dietitians, and they could be implemented in primary health-care or elderly care settings. The fact that the nutritional supplementation did not have any extra effect in the VIVE2 study should be interpreted in light of the fairly good nutritional status of the participants. Several lines of research show that an adequate nutritional status is important for older adults. Dietitians have the competence to determine the need for, and also individualize, nutritional advice and support.

Moreover, the results from the fourth study in this thesis showed that there might be a difference in how body composition phenotypes are related to survival, depending on both gender and age. Sarcopenic obesity and obesity seemed to be associated with a higher mortality in the 75-year-old women, however in the oldest men, obesity seemed to be protective. This area of research is emerging, and more studies are needed to fully understand the health consequences of sarcopenic obesity and obesity. Special efforts are needed to understand whether the consequences differ depending on age and gender. To further improve our knowledge in this field, a consensus concerning the definition for sarcopenic obesity is warranted (40). Also, from a clinical perspective, there is not only a need for consensus concerning definition but also for simple tools to identify sarcopenic obesity as well as for guidelines concerning optimal weight management for older adults.
The overall conclusion of this thesis is that the exercise intervention improved the mental status of the participants, which was apparent both in the quantitative and qualitative evaluations. However, no effect could be attributed to the protein-rich nutritional supplementation, a finding that needs to be evaluated in light of the good nutritional status among the participants. In a sample of older community-dwelling adults with some limitations in their mobility, no clear association was revealed between physical function and serum 25(OH)D other than an implication that higher levels of 25(OH)D were associated with better result on the chair stand test.

Body composition phenotypes, including sarcopenic obesity, seemed to be associated with a risk of mortality, associations probably dependent on both age and gender.

The specific conclusions for Papers I-IV are:

I. There was no clear association between serum 25(OH)D levels and physical performance in the sample of mobility-limited older adults. However, a potentially interesting observation was that higher serum levels of 25(OH)D indicated a better performance on the chair stand test.

II. The VIVE2 intervention exercise program had positive effects on mental status, but no additional effects from the nutritional supplementation were detected.

III. The central understanding of the VIVE2 participants’ experiences was that the intervention affected them in several ways, both psychologically and physically, and that the social support became a prerequisite for success. A noticeable finding was the discrepancy between the participants’ main reason for taking part, to lose weight, and the aim of the study, to improve muscle function.

I. Sarcopenic obesity was observed in 4-15% of community-dwelling Swedish older adults. In contrast to older men, the 75-year-old women with sarcopenic obesity appeared to have an increased risk of dying within 10 years compared to women with no sarcopenia or obesity. In 88-year-old men, the results indicat-
ed that obesity was associated with a lower risk of dying within four years.
Svensk sammanfattning


Sarkopeni, ett begrepp som är i fokus i denna avhandling, är ett geriatriskt tillstånd som definieras som ålders-, sjukdoms-, och nutritions-relaterad förlust av muskelfunktion och muskel massa. Studier har visat en association mellan sarkopeni och flera negativa utfall som ökad risk för fall och fracture, oförmåga till att klara sig självständigt, låg livskvalitet och ökad dödlighet. Sarkopeni orsakas och förvärras av otillräcklig fysisk aktivitet samt lågt intag av protein. Forskningen visar att fysisk aktivitet kan vara effektivt både för att förebygga och behandla sarkopeni, medan det behövs mer forskning kring värdet av att kombinera träning med proteintrika kosttillägg.

Prevelens av fetma ökar i världen och antal vuxna med fetma har tredubblats mellan 1975-2016. Studier har visat att både sarkopeni och fetma kan påverka den fysiska funktionen negativt, liksom sjuklighet och dödlighet också påverkas särskilt hos äldre individer. Det behövs fler studier på förekomst av det som kallas sarkopen obesitas, dvs. kombinationen av sarkopeni och fetma, och kring eventuella negativa hälsoeffekter av detta tillstånd.

Det övergripande syftet med denna avhandling var att undersöka betydelsen av nutrition, träning och kroppssammansättning för funktion, välmående och mortalitet hos äldre hemmaboende individer. Avhandlingen syftar dessutom till att undersöka; en eventuell association mellan vitamin D status i serum (mått som serum 25(OH)D) och fysisk funktion; att utvärdera effekterna på hälsorelaterad livskvalitet och depression av en intervention (The Vitality, Independence and Vigor in the Elderly 2 Study (VIVE 2)) som kombinerade ett proteinrikt kosttillägg med fysisk träning för äldre hemmaboende individer; att utforska deltagarnas erfarenheter av sin medverkan i VIVE2 studien. Slutligen avsågs att undersöka prevalens av sarkopen obesitas och studera huruvida olika kroppssammansättningsfenotyper är kopplade till ökade risk för dödlighet hos äldre svenskar.
Avhandlingen består av totalt fyra studier, varav tre baseras på data från VIVE2-studien och en fjärde studie som baseras på data från tre svenska kohorter på äldre individer; 1) 75 åringar från the Gothenburg H70 Birth Cohort Studies och 2) the Prospective Population Study of Women in Gothenburg (PPSW), samt 3) och från Uppsala Longitudinal Study of Adult Men (ULSAM).


Resultaten från studierna i denna avhandling, dvs. effekterna av träning i kombination med kosttillägget, deltagarnas upplevelser och betydelsen av olika kroppssammansättningsfenotyper för överlevnad vid hög ålder, kan vara av nytta för hälso- och sjukvården i mötet med äldre patienter och vid utformning av program för prevention eller behandling av t.ex. sarkopeni.
Acknowledgements

During the years as a PhD student several people have given me support and I am more than grateful. You all made this journey possible.

First of all, I want to acknowledge my team of supervisors. I feel really privileged to have had the opportunity to work with you.

Tommy Cederholm, thank you for believing in me and for supporting me. Thanks for sharing your impressive knowledge, your networks and your kindness with me along the way.
Afsaneh Koochek, thank you for talking me into this, for your friendship, your knowledge and support and for always believing in me.
Margaretha Nydahl, thanks for your support, for your knowledge and for reminding me frequently about the “dietitian aspects” of this work.

I also want to acknowledge:
Elisabet Rothenberg, thanks for your invaluable support and kindness.
Marita Friberg, thanks for your work and engagement with the third paper; it was a real pleasure working with you.
Jenny McGreevy, thanks for the admirably careful proofreading.
All my colleagues at CNM/Geriatrics and APC. Thanks for your support, interesting discussions and fun talks.
Lena Törnkvist, my boss at APC, who suggested that I become a PhD student before the thought had even hit me. Thanks for all your support.
My colleagues at Aleris rehab for encouraging me along the way.

My most beloved ones, Johan, Erik and Hedvig (and Chanti 🌷). Thanks for always standing by me. I love you more than words can express.
My fantastic parents. Thanks for believing in me, always supporting me and for being there for me, Johan, Erik and Hedvig. I love you dearly.
To my siblings, my relatives and to all my dear friends, none mentioned none forgotten. I feel blessed for having every one of you in my life.
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Appendix I
Inclusion/exclusion criteria VIVE2

Inclusion criteria
Males and females age ≥70 years
Community dwelling
Short Physical Performance Battery ≤9
Willing to be randomized and make visits to the laboratory during 6-month period
Body mass index ≤35
Mini Mental State Examination ≥24
Serum 25(OH) D 22.5–60 nmol/L
Informed consent obtained
Able to complete 400-meter walk within 15 min

Exclusion criteria
Current health status
Acute or terminal illness
Myocardial infarction during previous 6 months, symptomatic coronary artery disease, or congestive heart failure
Upper or lower extremity fracture during previous 6 months
Uncontrolled hypertension (≥150/90 mm Hg)
Hemoglobin b10 g/dl
Estimated GFR b30 ml/min/1.73 m2
Major surgery in the past 6 months (requiring general anesthesia)
Other significant co-morbid disease that would impair ability to participate in an exercise-based intervention, e.g. renal failure and on hemodialysis, severe psychiatric disorder (e.g. bipolar, schizophrenia)
Wheelchair bound
Inability to communicate due to severe, uncorrectable hearing loss or speech disorder
Severe visual impairment (if this precludes completion of assessments and/or intervention)
Severe progressive, degenerative neurologic disease
Severe rheumatologic or orthopedic diseases, e.g., awaiting joint replacement, active inflammatory disease
Terminal illness with life expectancy less than 12 months, as determined by a physician
Cancer requiring treatment in the past 3 years, except for non-melanoma skin cancers or cancers that have clearly been cured or, in the opinion of the investigator, carry an excellent prognosis (e.g., stage 1 cervical cancer)
Severe pulmonary disease, requiring either steroid pills or injections or the use of supplemental oxygen
Severe cardiac disease, clinically significant aortic stenosis, history of cardiac arrest, use of a cardiac defibrillator, or uncontrolled angina
Current regular use of high protein oral supplements
Vitamin D supplements ≥400 IU/day
Milk protein allergy
Excessive alcohol use
Appendix II
## Composition of nutritional supplement

<table>
<thead>
<tr>
<th>Nutrients</th>
<th>Amount per serving (119 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy (kcal)</td>
<td>151.6</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>20</td>
</tr>
<tr>
<td>Carbohydrate (g)</td>
<td>7.2</td>
</tr>
<tr>
<td>Fat (g)</td>
<td>4.7</td>
</tr>
<tr>
<td>Sodium (mg)</td>
<td>102</td>
</tr>
<tr>
<td>Chloride (mg)</td>
<td>89</td>
</tr>
<tr>
<td>Potassium (mg)</td>
<td>267</td>
</tr>
<tr>
<td>Calcium (mg)</td>
<td>350</td>
</tr>
<tr>
<td>Phosphorus (mg)</td>
<td>52</td>
</tr>
<tr>
<td>Magnesium (mg)</td>
<td>60</td>
</tr>
<tr>
<td>Vit A (IU RE)</td>
<td>833</td>
</tr>
<tr>
<td>Vit D3 (IU)</td>
<td>800</td>
</tr>
<tr>
<td>Vit E (IU)</td>
<td>7.5</td>
</tr>
<tr>
<td>Vit K (μg)</td>
<td>16</td>
</tr>
<tr>
<td>Vit C (mg)</td>
<td>30</td>
</tr>
<tr>
<td>Vit B1 (mg)</td>
<td>0.38</td>
</tr>
<tr>
<td>Vit B2 (mg)</td>
<td>0.43</td>
</tr>
<tr>
<td>Vit B6 (mg)</td>
<td>0.50</td>
</tr>
<tr>
<td>Niacin (mg NE)</td>
<td>4</td>
</tr>
<tr>
<td>Folic acid (μg)</td>
<td>64.4</td>
</tr>
<tr>
<td>Vit B12 (μg)</td>
<td>0.91</td>
</tr>
<tr>
<td>Panthotenic acid (mg)</td>
<td>1</td>
</tr>
<tr>
<td>Biotin (μg)</td>
<td>9.7</td>
</tr>
<tr>
<td>Nutrient</td>
<td>Amount (mg/μg)</td>
</tr>
<tr>
<td>-------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Iron (mg)</td>
<td>1.8</td>
</tr>
<tr>
<td>Zinc (mg)</td>
<td>4.6</td>
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<tr>
<td>Copper (μg)</td>
<td>200</td>
</tr>
<tr>
<td>Iodine (μg)</td>
<td>30</td>
</tr>
<tr>
<td>Selenium (μg)</td>
<td>20</td>
</tr>
<tr>
<td>Manganese (mg)</td>
<td>0.3</td>
</tr>
<tr>
<td>Chromium (μg)</td>
<td>12</td>
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<tr>
<td>Molybdenum (μg)</td>
<td>14.9</td>
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<tr>
<td>L-Carnitine (mg)</td>
<td>18.2</td>
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<td>Taurine (mg)</td>
<td>14.1</td>
</tr>
<tr>
<td>Choline (mg)</td>
<td>109.2</td>
</tr>
</tbody>
</table>
A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine”.)