Physical exercise for older people
– focusing on people living in residential care facilities
and people with dementia

Håkan Littbrand
To my wonderful family, Ann Helen, Rebecka, Pauline, and Tomas
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ABSTRACT

The main purposes of this thesis were to evaluate a high-intensity functional weight-bearing exercise programme, regarding its applicability (attendance, achieved intensity, adverse events) as well as its effect on physical functions and activities of daily living (ADL) among older people living in residential care facilities, with a special focus on people with dementia. Furthermore, a main purpose was to systematically review the applicability and effects of physical exercise on physical functions, cognitive functions, and ADL among people with dementia.

A high-intensity functional weight-bearing exercise programme that includes lower-limb strength and balance exercises in standing and walking, was evaluated in a randomised controlled trial among 191 older people, dependent in ADL, living in residential care facilities, and with a Mini-Mental State Examination (MMSE) score of ten or more. One hundred (52.4%) of the participants had dementia. Participants were randomised to an exercise programme or a control activity, consisting of 29 supervised sessions over 3 months, as well as to an intake of a protein-enriched energy supplement or a placebo drink immediately after each session. The effect on physical functions was evaluated using the Berg Balance Scale, usual and maximum gait speed, and one-repetition maximum in a leg press machine measuring lower-limb strength. The effect on ADL was evaluated using the Barthel Index. These outcome measures were followed up at 3 and 6 months by blinded assessors and analysed using the intention-to-treat principle.

The evaluation of the applicability of the high-intensity functional weight-bearing exercise programme showed that there was a high rate of attendance, a relatively high achieved intensity in the exercises, and all except two adverse events were assessed as minor or temporary and none led to manifest injury or disease. No statistically significant differences were observed in applicability when comparing participants with dementia and participants without dementia. In addition, the applicability of the programme was not associated with the participants’ cognitive function. Significant long-term effects of the exercise programme were seen regarding functional balance, gait ability and lower-limb strength in comparison with the control activity. The intake of the protein-enriched energy supplement did not increase the effect of the training. Age, sex, depression, dementia disorder, nutritional status, and level of functional balance capacity did not influence the effect on functional balance of the high-intensity functional weight-bearing exercise programme. There were no significant differences between the groups regarding overall ADL performance. Analyses for each item revealed that a significantly smaller proportion of participants in the exercise group had deteriorated regarding indoor mobility at 3 and 6 months. For people with dementia, there was a significant difference in overall
ADL performance in favour of the exercise group at 3 months, but not at 6 months.

In a systematic review, randomised controlled trials, evaluating the effects of physical exercise among people with dementia, were identified according to pre-defined inclusion criteria. Two reviewers independently extracted predetermined data and assessed methodological quality. Ten studies were included in the review and the majority of the participants were older people with Alzheimer’s disease living in residential care facilities. Four studies reached “moderate” methodological quality and six “low”. The results showed that among older people with Alzheimer’s disease in residential care facilities, combined functional weight-bearing exercise over 12 months at an intended moderate intensity seems applicable for use regarding attendance and adverse events and there is some evidence that the exercise improves walking performance and reduces ADL decline. Furthermore, there is some evidence that walking exercise over 16 weeks performed individually, where the participant walks as far as possible during the session, reduces decline in walking performance, but adverse events need to be evaluated.

In conclusion, among older people who are dependent in ADL, living in residential care facilities, and have an MMSE score of 10 or more, a high-intensity functional weight-bearing exercise programme is applicable for use and has positive long-term effects on functional balance, gait ability, and lower-limb strength and seems to reduce ADL decline related to indoor mobility. An intake of a protein-enriched energy supplement immediately after the exercise does not appear to increase the effect of the training. In people with dementia, the exercise programme may prevent decline in overall ADL performance, but continuous training may be needed to maintain that effect. The positive results regarding applicability and effects of combined functional weight-bearing exercise among people with dementia is confirmed when the scientific literature is systematically reviewed. It seems to be important that exercise interventions among people with dementia last for at least a few months and that the exercises are task-specific and intended to challenge the individual’s physical capacity. Whether physical exercise can improve cognitive functions among people with dementia remains unclear. There is a need for more exercise studies of high methodological quality among people with dementia disorders.

Keywords: aged, dementia, exercise, frail elderly, nutrition, randomized controlled trial, residential facilities
SVENSK SAMMANFATTNING
(SUMMARY IN SWEDISH)

Nedsatt fysisk och kognitiv funktion är vanligt bland äldre personer som bor på särskilt boende och bidrar till beroende av hjälp i aktiverter i det dagliga livet (ADL) t.ex. personlig vård och förflyttning inomhus. Fysisk träning skulle, genom en positiv påverkan på fysisk och kognitiv funktion, kunna vara en viktig metod för att förebygga eller minska hjälpberoendet i ADL. Det övergripande syftet med avhandlingen var att utvärdera genomförbarheten och effekten på fysisk funktion och ADL av högintensiv funktionell viktbärande träning (d.v.s. vardagliga rörelser utförda i stående position) bland äldre personer som är beroende av hjälp i ADL och bor på särskilt boende, med speciellt fokus på personer med demenssjukdom, samt att genom en systematisk litteraturgenomgång undersöka genomförbarheten och effekten av fysisk träning på fysisk och kognitiv funktion samt ADL bland personer med demenssjukdom.

Ett högintensivt funktionell viktbärande träningssprogram (the HIFE Program) som innehåller benstyrke- och balansövningar i stående och gående utvärderades i en randomiserad kontrollerad studie på nio särskilda boendena. 191 personer ingick i studien och cirka hälften hade lätt till mättligt svår demenssjukdom. Deltagarna lottades till att delta i det högintensiva träningssprogrammet eller i en kontrollaktivitet. Båda aktiviteterna inkluderade 29 tillfällen under 3 månader och de leddes av sjukgymnast respektive arbetsterapeut. Deltagarna lottades även till att få ett mjölkbaserat proteinrikt näringsstillskott eller placebodryck som intogs omedelbart efter varje träningsspecifik aktivitetstillfälle. Deltagarna följdes upp direkt efter och 3 månader efter interventionen med Bergs balansskala, 2,4 meters gångtest, test av maximal benstyrka i en benpress och Barthel ADI Index. Personerna som utförde mätningarna kände inte till deltagarens grupptillhörighet. Alla analyser utfördes enligt "intention-to treat" principen vilket innebär att alla deltagare ingick i analyserna enligt den grupp de lottats till oavsett hur mycket de hade deltagit i interventionen.

Utvärderingen av genomförbarheten av träningssprogrammet visade att det var en hög närvaro, en relativt hög uppnådd träningssinliggjort och att träningen inte ledde till någon bestående skada eller sjukdom. Det var ingen skillnad i genomförbarheten av träningssprogrammet mellan deltagarna med demenssjukdom och de utan demenssjukdom. Analyserna av effekten av det högintensiva funktionella viktbärande träningssprogrammet visade på långtidseffekter på benstyrka, funktionell balansförmåga och gångförmåga jämfört med kontrollaktiviteten. Intaget av det proteinrika näringsstillskottet ökade inte effekten av träningen. Ålder, kön, depression, demenssjukdom, näringsstatus och fysisk funktionsförmåga påverkade inte effekten på
**ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ADL</td>
<td>Activities of daily living</td>
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<tr>
<td>ANCOVA</td>
<td>Analysis of covariance</td>
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<td>BBS</td>
<td>Berg Balance Scale</td>
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<tr>
<td>BPSD</td>
<td>Behavioural and Psychological Symptoms of Dementia</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, fourth edition</td>
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<td>ES</td>
<td>Effect size</td>
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<td>FAC</td>
<td>Functional Ambulation Categories</td>
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<td>FOPANU Study</td>
<td>Frail Older People–Activity and Nutrition Study in Umeå</td>
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<tr>
<td>GDS</td>
<td>Geriatric Depression Scale</td>
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<td>HIFE Program</td>
<td>High-Intensity Functional Exercise Program</td>
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<td>MMSE</td>
<td>Mini-Mental State Examination</td>
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<tr>
<td>MNA</td>
<td>Mini Nutritional Assessment</td>
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<td>PEDro scale</td>
<td>Physiotherapy Evidence Database scale</td>
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<tr>
<td>PRISMA</td>
<td>Preferred Reporting Items for Systematic Reviews and Meta-Analyses</td>
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<td>RM</td>
<td>Repetition maximum</td>
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<td>SD</td>
<td>Standard deviation</td>
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<td>SE</td>
<td>Standard error</td>
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ORIGINAL PAPERS

The thesis is based on the following papers, which will be referred in the text to by their Roman numerals:


V. Littbrand H, Stenvall M, Rosendahl E. Applicability and effects of physical exercise on physical and cognitive functions and ADL among people with dementia: a systematic review. Submitted.

The original articles are reprinted in this thesis with the kind permission of the respective publishers.
INTRODUCTION

Physical exercise could, through positively influencing physical and cognitive functions, be one important method of preventing or reducing dependency in activities of daily living (ADL), which in turn might increase life satisfaction and reduce societal costs. In this thesis the applicability and effects of physical exercise are investigated, focusing on older people (i.e. ≥ 65 years) living in residential care facilities and people with dementia disorders.

DEMOGRAPHICS

As a result of the transition from high to low fertility and the continuous decline in adult mortality, the population of most countries of the world is ageing. Globally, the population aged 60 years or over is growing at a rate of 2.6% per year. This is considerably faster than the global population as whole, which is increasing at 1.2% annually. The older global population is expected to continue growing more rapidly until at least 2050 and the fastest growing population is that of people aged 80 years or over. In Sweden in 2009, 18% of the population was aged 65 years or over and 5%, i.e. almost half a million, was aged 80 years or over. By 2060, it is estimated that the proportion of the Swedish population aged 65 years or over will have increased to 25% and those aged 80 years or over will have increased to almost 1 million, approximately 9% of the total population.

After the age of 80 it becomes increasingly common for people to need support in performing ADL. In a population-based study in northern Sweden half of the population aged 85 years or older were dependent in ADL and the prevalence of dependence was even higher in the older age-groups. Cognitive and physical impairments are two important factors that are associated with ADL dependence. In the future in Sweden, the number of people with cognitive impairments will probably increase as the prevalence of dementia increases with advanced age, and the age-specific prevalence of dementia seems to be stable over time, or even increases. Regarding the prevalence of physical impairments, two population-based studies have investigated whether it has changed over time among older people in Sweden. One study, the Swedish Panel Study of the Living Conditions of the Oldest Old (SWEOLD), showed some increases in the prevalence of self-reported mobility limitations from 1992 to 2002 among people aged 77 years and older. However, the other study, the Statistics Sweden Surveys of Living Conditions (ULF), showed no significant change in self-reported mobility limitations among people aged 65 to 84 years over the time period 1996–2005. On the basis of these two studies it is difficult to predict the development of the prevalence of physical
impairments among older people in Sweden, since their results differ. However, since the older population is growing fast and there is no visible trend for showing a decline in age-specific prevalence of physical impairments, it is likely that the number of people aged 80 years or over with physical impairments in Sweden will increase in the near future. In addition, based on the trends apparent in the number of older people with cognitive and physical impairments, there is a strong possibility that the number of older people dependent in ADL will also increase.

RESIDENTIAL CARE FACILITIES

In Sweden the municipalities are responsible for care of the elderly. The municipalities can offer older people to live in residential care facilities when they need extensive care. In Sweden in 2008, almost 100,000 people were living in residential care facilities e.g. nursing homes or group dwellings for people with dementia. As a consequence of an ageing-in-place policy, the number of beds in residential care facilities decreased by approximately 18,000 between 2000 and 2005. Older people moving to residential care facilities today are therefore more dependent in ADL and cognitively impaired.

In residential care facilities there are a large proportion of people with high age and the majority of the residents are women. Furthermore, conditions such as depression, dementia disorders, and malnutrition are common and most of the residents have moderate or severe physical impairments. Consequently, the residents need supervision, functional support or nursing care. Over time it is common for residents to increase their dependency in ADL. One study reported that over a period of 12 months approximately one third of the residents had deteriorated regarding ADL. Another study of residential care facilities, which included only people with moderate to severe dementia, reported that more than half of the residents deteriorated regarding ADL over a period of six months.

DEMENTIA DISORDERS

Prevalence, diagnostic criteria and costs

The incidence of dementia increases with age and is a common diagnosis among people aged 80 years or over. The prevalence is approximately 13% at ages 80–84, 24% at 85–89, 34% at 90–94 and 45% at 95 and over. The prevalence seems to be higher among women than men, particular in the older age groups. The most common types of dementia are Alzheimer’s disease and vascular dementia, or a combination of both. Of the total prevalence for dementia in Europe, North America and Africa, 60–70% seems to be attributable to Alzheimer’s disease and 10–20% to vascular dementia.
prevalence of other types of dementia e.g. dementia of Lewy bodies and frontotemporal dementia has been less investigated, but has been said to account for approximately 10%.22

According to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, (DSM-IV),23 symptoms that are essential for a diagnosis of dementia disorder is the development of cognitive deficits where memory impairment (impaired ability to learn new information or to recall previously learned information) is required and at least one of the following cognitive disturbances: aphasia (language disturbance), apraxia (impaired ability to carry out motor activities despite intact motor function), agnosia (failure to recognize or identify objects despite intact sensory function) or disturbance in executing functioning (i.e. planning, organization, sequencing, abstracting). The cognitive disturbance must be sufficiently severe to cause impairment in occupational or social functioning and must represent a decline from a previously higher level of functioning.23 In addition, the diagnosis of specific dementia subtypes requires that certain other criteria, specific for that particular subtype, are met.

As the world population ages, it is estimated that there will be a fourfold increase in the number of people with dementia from the beginning of the century to the year 2040.24 Thus, the costs for society associated with the care and treatment of people with dementia will increase dramatically. In Sweden, in 2009, approximately 150 000 people suffered from dementia and around 45% of those were living in residential care facilities.25 In 2050, the number of people with dementia will increase to approximately 250 000.26 The cost for society related to dementia disorders was estimated at 35-38 billion Swedish crowns in 2005, which implies that dementia disorders are one of the most costly diseases. The municipalities fund 85% of the costs through care and treatment in residential care facilities and in independent housing.26

**Physical impairments**

Investigation into the prevalence of physical impairments among people with dementia disorders has intensified over the last two decades. Studies have shown that gait and balance disorders, when compared to non-dementia controls, are frequent among people with Alzheimer’s disease, vascular dementia, Parkinson’s disease with dementia, and dementia with Lewy bodies,27-35 and are more pronounced in the later stages.27,30,34,36 The prevalence of gait disorders seems to be higher in cases of vascular dementia, Parkinson’s disease with dementia, and dementia with Lewy bodies compared to Alzheimer’s disease.27,34 The types of gait and balance disorders that have been reported are, for example, lower gait velocity,29,31,35 shortened step length,34,35 and poorer performance in static (i.e. the base of support is fixed) and dynamic (i.e. the base of support is changing) balance when standing and balance when
walking. In addition, the gait velocity declines more, compared to non-dementia controls, when people with Alzheimer’s disease perform another activity simultaneously e.g. carrying a glass of water or performing a cognitive task.

Gait and balance disorders have been reported in cases of mild non-Alzheimer’s dementia, but there seem to be conflicting results concerning whether they are also evident among people with mild Alzheimer’s disease. One study, published in 1995, reviewed the medical records to determine whether any gait disturbance among people with Alzheimer’s disease was reported and found that none of the patients with mild Alzheimer’s disease had reported gait abnormalities. However, during the last decades there are five studies to my knowledge that have investigated the prevalence of gait and balance disorders among people with mild Alzheimer’s disease using a standardized gait and balance assessment and comparing the results to those from cognitive intact controls. Of those five studies, four studies reported impaired gait and balance and one study reported no impairments. The conflicting results may arise from the use of different diagnostic criteria or different measurements.

**Physical inactivity and lack of social interaction**

Apart from the neurodegenerative process, limited daily physical activity (i.e. bodily movement produced by contraction of skeletal muscle that substantially increases energy expenditure) among people with dementia might explain some part of the reduced gait and balance ability. Studies that have observed people with dementia in residential care facilities have reported that physical activity and social interaction are rare. One explanation for this could be the lack of initiative and interest, which are common symptoms among people with dementia. Another reason for the reduced level of physical activity could be that the environment in residential care facilities does not promote activity. One study reported that for more than one-third of the residents, physical activity decreased after the move into residential care facilities.

**Rehabilitation**

The impairments in balance and gait ability in people with dementia, together with cognitive decline, contribute to an increased dependence in ADL as well as an increased fall risk. The fall risk is approximately at least twice that of people without cognitive impairments and the risk for fracture is also substantially higher. Altogether, this implies that people with dementia have a great need for rehabilitation, i.e. efforts that help people with acquired physical impairments, based on their needs and preconditions, to restore or maintain an optimal level of function. Physical exercise could be one important aspect in rehabilitation. When offering rehabilitation to people with dementia there are
many symptoms connected with the disease that must be taken into consideration e.g. impaired memory, aphasia, and the Behavioural and Psychological Symptoms of Dementia (BPSD). In addition, the symptoms vary among people with dementia. This implies, that in order to be successful, rehabilitation has to be individualized.

Studies have reported that older people with dementia can benefit from rehabilitation after acute illness when it is offered. Older people with dementia or with impaired cognitive functions derive comparable to, or possibly even greater than, those experienced by cognitively intact subjects from comprehensive rehabilitation after hip fracture. Furthermore, discharge to a rehabilitation unit has been reported to be associated with preserved walking ability and ADL in cognitively impaired subjects with hip fracture. However, despite these facts, it has been reported that people with cognitive impairments are offered less physiotherapist-led exercise during the rehabilitation in clinics than people without cognitive impairments.

**CONSEQUENCES OF PHYSICAL IMPAIRMENTS**

Impaired physical functions, including walking, balance, and lower-limb strength, are associated with risk of falls, hospitalization, nursing home admission, and mortality. Furthermore, an association between a decline in physical function and disability (experienced difficulty doing activities in any domain of life, e.g. ADL or hobbies, due to a health or physical problem) has been reported in longitudinal cohort studies. In an extensive systematic review among older people living in the community, impairments in lower extremity function e.g. difficulties in standing up and sitting down, walking or balance when standing, were reported to be one of the risk factors that provided the highest strength of evidence for ADL decline and increased difficulties in performing physical activities independently, such as climbing stairs. The other reported risk factors were cognitive impairment, depression, comorbidity, increased or decreased body mass index, low frequency of social contacts, low level of physical activity, no alcohol use compared to moderate use, poor self-perceived health, smoking, and vision impairment. Longitudinal studies published since this review confirm that measures of lower-extremity function are predictive of subsequent disability among community-living older people, and it has been proposed that physical performance tests could be used in the health care system to recognize people at risk of future disability. Among people living in residential care facilities, including both people with and without dementia, change over 12 months in balance ability while standing has been reported to be associated with change in dependence in ADL.
Thus, impaired physical function seems to be one factor that contributes to dependency in ADL, which often deteriorates over time in residential care facilities. This implies that physical exercise (i.e. planned, structured, and repetitive bodily movements to improve or maintain physical fitness)\(^40\) by improving physical function may be one important method of positively influencing ADL dependency, which in turn could have an impact on life satisfaction\(^48\) and reduce societal costs.

**CONSEQUENCES OF PHYSICAL INACTIVITY**

Physical inactivity can have serious consequences. Low level of physical activity have shown to increase the risk of developing a number of chronic diseases such as cardiovascular disease, hypertension, osteoporosis, and type 2 diabetes.\(^69\)\(^71\) In Sweden, it is recommended that all individuals perform a physical activity with moderate intensity e.g. brisk walking at least 30 minutes every day.\(^70\) Low level of physical activity is also related to the development of disability in older adults.\(^8\)\(^69\) Physical inactivity results in loss of muscle strength (i.e. ability to exert maximal muscular force), muscle power (i.e. product of force and velocity of movement), muscle mass, and aerobic capacity.\(^72\)\(^76\) Lower-limb muscle strength\(^77\)\(^79\) and muscle power,\(^80\)\(^83\) which are closely related aspects of muscle function,\(^90\) are important factors when performing daily physical activities such as standing up from a sitting position or walking. However, the relationship between muscle strength or muscle power and the performance of daily physical activities is not linear.\(^77\)\(^81\) The association is stronger among weaker subjects than stronger and, moreover, there seem to be threshold values where a further small decline in muscle function can result in the inability to perform an activity independently.\(^83\)\(^84\) This implies that weaker subjects are more vulnerable to the consequences of physical inactivity, but also that they could benefit more from strength exercise. Furthermore, older women have been shown to have less muscle strength and muscle power than men in analyses adjusted for weight.\(^79\)\(^82\)\(^85\) Consequently, it is especially important for women to avoid physical inactivity because they are closer to the threshold values for losing their independence in ADL.\(^83\) Older women report higher rates for problems with daily activities that require muscle strength such as house cleaning and shopping compared to older men.\(^3\)

Inactivity-loss of muscle mass predominantly affects the lower-limb muscles and is more rapid during the initial days/weeks of inactivity.\(^72\) The loss of muscle mass affects the muscle strength and muscle power.\(^86\) After a period of muscle disuse, younger people seem to have a relative greater magnitude of muscle atrophy compared to older people, but older people seem to have a diminished capacity to regain muscle size during subsequent exercise.\(^75\) In addition, older people seem to have a larger decrease in rapid force capacity,
which may also be more difficult to recover.\textsuperscript{76} Consequently, older people seem to require a longer exercise period to recover after a period of muscle disuse.\textsuperscript{76} It is also notable that reduced physical function during acute illness e.g. pneumonia or heart failure, improves at a much slower rate than recovery from the acute illness itself among older people, and an exercise period might be necessary if permanent functional decline is to be avoided.\textsuperscript{87}

**EXERCISE TO IMPROVE PHYSICAL FUNCTIONS AND ADL**

**Effects among older people who are healthy and those with moderate impairments**

Physical exercise programmes have shown positive effects on physical functions among older people who are healthy and among those with moderate cognitive and physical impairments.\textsuperscript{71,78,88,89} In a recent systematic review by Howe et al., different types of exercise interventions e.g. programmes involving gait, balance, co-ordination, and functional exercises or strength exercises showed beneficial effects on balance ability.\textsuperscript{89} However, long-term follow-ups were lacking and a majority of the studies included had methodological weaknesses. Strength exercise performed progressively (i.e. the load is adjusted gradually according to the strength development of the individual) has been shown to be effective in substantially increasing muscle power and muscle strength.\textsuperscript{71,78} In a recently published systematic review by Liu and Latham it was also shown that progressive strength exercise improved the capacity to perform daily physical activities such as getting out of a chair, climbing stairs, and walk.\textsuperscript{78} Earlier, there has been a lack of evidence to support the view that physical exercise programmes are an effective method of reducing disability e.g. reducing dependency in personal care and mobility.\textsuperscript{69,90} However, in the systematic review by Liu and Latham there was a small but significant effect on disability when the studies that measured this domain were pooled.\textsuperscript{78} Measures used to evaluate disability were, for example, the Barthel ADL Index and the physical function domain of Short-Form-36 (SF-36). As in the systematic review by Howe et al.,\textsuperscript{89} this review showed there was insufficient evidence to comment on the long-term effects and, furthermore, poor methodological quality was common in the included studies.\textsuperscript{78}

**Neural adaptation and muscle hypertrophy**

Both neural adaptation and skeletal muscle hypertrophy contribute to the increase in muscular strength after a period of strength exercise among older people.\textsuperscript{91,92} It has been shown that, among older people, strength exercise 2-3 times per week over nine weeks or more has resulted in muscle hypertrophy.\textsuperscript{93} Until recently, the prevailing opinion has been that the role of the neural factors was particularly strong during the first 6-7 weeks of strength exercise, since it was believed that skeletal muscle hypertrophy required 6-7 weeks to occur.\textsuperscript{94}
However, it appears that this can happen earlier, at least in younger people. Studies have reported skeletal muscle hypertrophy as early as after 3-5 weeks of strength exercise among younger people.⁹⁴

The influence of age on muscle hypertrophy response and the capacity to increase muscle strength is complex. Several studies have demonstrated similar relative strength gains after strength exercise when comparing younger and older people, but some have reported a smaller effect for older people.⁷¹ The results also conflict as to whether the hypertrophic skeletal muscle responses are different between younger and older people. Some studies have shown similar relative increases,⁹⁵-⁹⁷ whereas others have presented less of an effect among older people.⁹⁸-¹⁰¹ Furthermore, regarding the influence of sex on the relative effect on muscle strength, there are insufficient data available to draw conclusions,⁷⁸ but skeletal muscle hypertrophy in response to strength exercise tends to be smaller in older women than in older men.⁹³

**Impact of protein supplementation**

Muscle hypertrophy can only occur following strength exercises when muscle protein synthesis rates exceed muscle protein breakdown rates for a prolonged period of time.¹⁰² The protein synthesis is stimulated following strength exercise, but so is the protein breakdown. In the absence of protein intake after exercise net muscle protein balance will be negative. Therefore, both strength exercise and protein are required to allow muscle to hypertrophy.¹⁰²-¹⁰⁴ Accelerated protein synthesis rates have been reported to persist for up to 48 hours after strength exercise, but are reduced over time.¹⁰⁵ Among younger adults it was reported that the protein synthesis was more enhanced when a protein-enriched energy supplement was given immediately compared to three hours after exercise.¹⁰⁶ Therefore, an early intake of protein could be of benefit in achieving optimal effects on muscle hypertrophy and muscle strength.¹⁰⁶ To my knowledge there are only two studies which have evaluated the effects of an immediate intake of protein after strength exercise among older people and their results are conflicting. A study by Esmarck et al., reported that an immediate intake of a protein-enriched energy supplement (10 g of protein) after strength exercise increased muscle strength and muscle hypertrophy after a 12-week exercise period compared with a later intake of protein (two hours) among healthy older men.¹⁰⁷ However, a study by Candow et al. reported that a protein-enriched energy supplement (0.3 g protein/kg) either before or immediately after training did not increase the exercise effects on muscle strength and muscle mass compared to a placebo after a 12-week exercise period among healthy older men.¹⁰⁸ The conflicting results indicate that more studies are needed in this area.
**Impact of duration, frequency, and sets**

In the systematic review by Howe et al., which showed positive effects of physical exercise on balance ability, the most frequent duration in the included studies was three months and the frequency was typically three times a week. Regarding progressive strength exercise, the frequency has been 2-3 times a week and the duration of the intervention 8-12 weeks in most of the studies in the systematic review by Liu and Latham. The effect on strength outcome appears to be similar between trials where the duration was greater than twelve weeks compared to less than twelve weeks. However, the frequency might influence the effects. A meta-analysis on studies of various age-groups, including older people, concluded that progressive strength exercise three times a week produced maximal gains among untrained individuals. Strength exercise once a week seems sufficient to maintain the muscle strength after an exercise period among older people. Regarding the optimal number of sets for each exercise, it seems that multiple sets are better than one set for developing muscle strength. However, a single set also has positive effects and it is recommended that novice individuals should initially perform one to three sets per exercise.

**Impact of exercise intensity**

Intensity is a concept that is described in various ways in the exercise literature. In this thesis, the intensity of the exercise is related to the individual’s capacity, and the overall definition of high-intensity exercise is that the training is performed near an individual’s maximum capacity. This means that the intensity of e.g. strength exercise can be defined as high regardless of whether or not the particular weights used are heavy, or whether weights are used at all. The intensity of the strength exercises could have a major impact on the results. A greater effect on muscle strength has been reported after strength exercise with high intensity compared to exercise with low to moderate intensity among older people.

The intensity of strength exercise can be described either as the absolute maximum number of weight lifts, or as the percentage of the maximum load. The term RM (repetition maximum) is used in the literature to describe absolute maximum number of weight lifts. The term was presented by DeLorme in 1945 and he defined 1 RM as the maximum weight that could be lifted one time. Thus, 10 RM is the weight that can be lifted ten times but not more. The recommended intensity among older people when performing strength exercise is to use loads of 60-80% of 1 RM, which is assumed to correspond to 8-12 RM. For novice individuals, it is suggested that moderate loading (50-60% of 1 RM or less) is used initially as it is important to learn proper technique.
The assumption that 60-80% of 1 RM corresponds to 8-12 RM is widespread in the literature, but with no references to validation studies.\textsuperscript{88,92,109,112} However, the average number of repetitions that could be performed at 40, 60, and 80% of 1 RM were investigated among healthy younger people in a study by Hoeger et al. published in 1990.\textsuperscript{113} The study showed that the number of repetitions that could be performed at a selected percent of 1 RM varied widely among the participants and among different types of lifts.\textsuperscript{113} Thus, the assumption in the literature that 60-80% of 1 RM corresponds to 8-12 RM was not confirmed. For example, among young trained women, 60% of 1 RM in a leg press corresponded on average to 57 repetitions and 80% of 1 RM corresponded to 22 repetitions. The corresponding figures for leg curl was 12 and 5 repetitions respectively. Consequently, describing the absolute maximum number of weight lifts seems to be a more valid way of describing the intensity compared to using a percentage of 1 RM among younger people. It seems possible to generalize the interpretation to older people since there is nothing to indicate that there would be less variation in repetitions at a selected percent of 1 RM in this group.

To achieve optimal effects on balance ability and prevention of falls from balance exercises, it is recommended that postural stability be challenged and the difficulty progressively increased, as the participant improves their capacity.\textsuperscript{71,88,114,115} A systematic review reported that a greater relative effect were seen on fall prevention in programmes that included exercises that challenged postural stability.\textsuperscript{115} The American College of Sports Medicine (ACSM) recommends that when performing balance exercise, the activities should include the following: (1) progressively difficult postures that gradually reduce the base of support; (2) dynamic movements that perturb the centre of gravity; (3) stressing postural muscle groups; and (4) reducing sensory input.\textsuperscript{71} To ensure that the balance programme remains challenging it needs to be progressed. It is also essential that the balance exercises can be performed safely. Thus, balance exercise might be less effective where close supervision is not possible e.g. at home or in a group setting. In the literature there is no consensus concerning a model for differing intensity levels in balance exercises. In this thesis, training performed near an individual’s maximum capacity is the overall definition of high-intensity exercise. Accordingly, the specific definition for balance exercise with high intensity is that postural stability is fully challenged, i.e. the balance exercise is performed near the limits of maintaining postural stability.
Impact of exercise specificity
In addition to the intensity, the type of exercise could also have a major impact on the effects of performing daily activities. Studies that have compared the effects of different types of training regimes have indicated the importance of the exercises being task-specific, including both posture and movement pattern, if functional ability is to be optimally improved in the short and long term.¹²³ In strength-training programmes, individual muscles are often exercised in isolation without reference to the context in which that muscle is required to function. However, as early as 1957, Rasch et al. showed that it is important to select exercises in which the posture is similar to that of the movements they are attempting to facilitate.¹²⁴ In that study they showed that the increases in elbow flexor strength after a period of strength exercise were considerably larger when the subjects were tested in the position in which they had practised (standing) than when the elbow flexor muscles were tested with the body in another position (supine). Consequently, strength training for isolated muscle groups in a position that is not similar to the position at which the improvement is aimed seems not to be the most effective way of increasing the performance of a specific task or an activity. It would appear better to incorporate the strength exercises into those tasks which it is the aim to improve, where the subject learns optimally how to coordinate the various muscle groups involved in the movements.

Effects among older people living in residential care facilities
There are fewer studies that have evaluated the effects of physical exercise on physical functions and ADL among people with multiple diagnoses living in residential care facilities than among healthier people living in the community. One systematic review by Rydwik et al. published in 2004 evaluated the effect of physical exercise among institutionalised older people.¹²⁵ The review reported that there was strong evidence that physical exercise had beneficial effects on muscle strength and mobility, but contradictory evidence regarding effects on balance, gait, and ADL. No conclusion was drawn in the review concerning the specific type of physical exercise that was beneficial or the optimal exercise intensity, duration, frequency, or number of sets. Another systematic review by Forster et al. published in 2009 evaluated the effects of physical rehabilitation in long-term care.¹²⁶ The authors concluded that physical rehabilitation has positive effects on physical functions, but since they also included multi-factorial interventions in the review the effect of physical exercise alone could not be identified. Thus, despite these positive findings regarding physical exercise, there is no consensus concerning the optimal type of physical exercise to offer older people living in residential care facilities.
Applicability and effects of high-intensity exercise
To achieve optimal effects from physical exercise on physical functions it seems important to perform the exercises at a high intensity.\textsuperscript{78,98,92} To my knowledge there is only one randomised controlled trial that has evaluated the effects of a high-intensity exercise programme in residential care facilities, including mainly residents with severe cognitive and physical impairments.\textsuperscript{20} The intervention included strength and endurance (walking) exercise and the study reported positive effects on ADL and endurance but no effects on balance and muscle power. However, as the study design did not include any activities for the control group, the amount of attention given to the individuals was not equally distributed between the groups. It is, therefore, difficult to draw any conclusions about the effects of the physical exercise per se,\textsuperscript{127} since the increased amount of attention given to the intervention group may have had a significant impact for this group of older people as they generally have few social contacts.\textsuperscript{42,43,128}

People living in residential care facilities form a heterogeneous group. Conditions such as fluctuating health status, depression, dementia disorders, and severe physical impairments may negatively affect the possibility of participating in and perform physical exercise with high intensity, and, consequently, may reduce the effects of physical exercise. To achieve high intensity in the exercises it is necessary for participants to be motivated and able to perform the exercises near the limit of their maximum capacity. A recent systematic review showed that progressive strength training was less effective among older people with physical impairments compared to older people who had no physical impairments.\textsuperscript{78} The lower intensity of the exercises in the studies including older people with physical impairments\textsuperscript{78} indicates that they may have difficulties performing exercises near the limit of their maximum capacity. Among older people with depression, symptoms such as fatigue, reduced ability to concentrate or interest in participating in activities\textsuperscript{21} may result in low attendance and difficulties achieving high-intensity when performing the exercises. A high drop-out rate has been reported in exercise studies that included people with depression.\textsuperscript{125} Furthermore, older people with dementia may also have difficulties participating in and performing physical exercise programmes because of the symptoms of the disease e.g. memory impairment, apraxia, aphasia,\textsuperscript{23} or BPSD.\textsuperscript{52,53} Apart from difficulties in participating in and performing high-intensity exercise, physiological factors can also influence the effects of exercise on physical functions. High age, female sex and malnutrition are common in residential care facilities and might limit the hypertrophic muscle responses.\textsuperscript{95,98,102}
The high prevalence of diseases such as coronary heart disease, osteoporosis, and dementia may lead to a high risk of adverse events when performing high-intensity exercise. It therefore seems vital that trained, experienced supervisors are involved in the planning and performance of the exercise programme. No serious adverse events in high-intensity exercise programmes among older people who are healthy and those with moderate impairments have been reported in the literature. However, systematic and accurate registration of adverse events is often lacking in the studies.

**Functional weight-bearing exercise**

Functional weight-bearing exercise seems to be suitable for people living in residential care facilities, including those with severe cognitive impairments, because the exercises are easy to follow and there is no need for specific exercise facilities. The exercises, such as rising from a chair or climbing stairs, are performed in weight-bearing positions i.e. the exercises are performed in a standing position. This type of exercise follows the principle of exercise specificity, since it mimics movements used in everyday tasks and, thus, represents a promising method for reducing dependency in ADL. Mobility problems e.g. difficulties in getting out of a chair, walking or climbing stairs, which are common among people living residential care facilities, are often related to a combination of impairments in balance in standing and walking, and lower-limb strength. It is, therefore, important to design an exercise programme aimed at improving all these three functions. Functional weight-bearing exercise programmes have been shown to have wide-ranging effects on physical functions e.g. lower-limb strength, balance, and gait ability among older people who are healthy and those with moderate impairments. In this type of exercise it is possible to achieve high intensity in the exercise by exercising with high loads on the lower-limb muscle groups and near the limit of postural stability. The load can be increased by adjusting the performance of the exercises (e.g. by doing deeper squats) or by using weights e.g. a weighted belt worn around the waist. A pilot study was performed in 1999 at the Geriatric Centre, Umeå University Hospital, to investigate the effects and the subjects’ experience of weighted belt exercise among older women with residual mobility problems following hip fracture. The subjects improved their lower-limb muscle strength, balance, and gait ability after a 10-week period of exercise and they reported no discomfort.

**Effects among people with dementia disorders**

People with dementia might derive great benefits from physical exercise, as impaired physical functions are common and studies have shown that people with dementia, even those with severe dementia, have the capacity to improve their motor skills. However, difficulties in participating and performing physical exercise as well as the neurodegenerative process may have a negative
impact on the effects. In recent years, four systematic reviews have investigated the effects of physical exercise among people with cognitive impairment.\textsuperscript{135-138} These reviews do not answer the question about the effects physical exercise as a single intervention among people with dementia may have, because multi-factorial interventions were included in the analyses and the target group was people with cognitive impairment, irrespective of aetiology. However, a systematic review by Forbes et al., published in 2008, was intended to investigate the effects of physical activity programmes as a single intervention on ADL, cognition, behaviour, depression and mortality among people with dementia.\textsuperscript{139} Unfortunately, no evaluation was made of the effects on physical functions. In order to understand the pathways by which physical exercise could affect ADL among people with dementia, it is essential to know how various physical exercise programmes affect both physical and cognitive functions. Only four studies were included in the review.\textsuperscript{139} The inclusion of two of these studies is, however, questionable. In one study, it seems that not all participants had a diagnosis of dementia\textsuperscript{140} and in the other study evaluation of the effects of physical exercise as a single intervention seems not possible as the intervention was multi-factorial.\textsuperscript{141} The authors concluded that there was insufficient evidence to say whether or not physical exercise programmes are beneficial for people with dementia.\textsuperscript{139} However, since the literature search in this review performed in September 2007, several randomised controlled trials examining the effects of physical exercise among people with dementia disorders have been published. Thus, it is important to conduct a new systematic review.

**Exercise to improve cognitive functions**

**Effects among older people who are healthy and those with mild cognitive impairments**

Apart from the reported positive effects on physical functions, physical exercise also seems to have beneficial effects on cognitive functions.\textsuperscript{142,143} A systematic review by Angevaren et al. investigated whether aerobic exercise was beneficial for cognitive functions, since increased aerobic fitness is found to increase cerebral blood flow, oxygen extraction and glucose utilisation as well as an activation of growth factors which mediate structural changes such as capillary density.\textsuperscript{142} The systematic review, which included cognitively intact people, aged over 55 years, reported positive effects of aerobic exercise on some cognitive functions (cognitive speed, motor function, auditory and visual attention), where most of the studies were 8-16 weeks long.\textsuperscript{142} In addition, aerobic exercise three times a week over six months has been reported to increase brain volume among older healthy people.\textsuperscript{144} Another recently published systematic review by Smith et al., which had 18 years as a lower age limit for inclusion, confirmed that aerobic exercise has positive effects on cognitive functions.\textsuperscript{143} The majority
of the studies were 8-16 weeks long and the review reported positive effects on attention and processing speed, executive function, and declarative memory. It was also reported that the effects among people with mild cognitive impairments (MCI) were similar to those for people without cognitive impairments. Furthermore, combined aerobic exercise and strength exercise improved some of the cognitive functions (attention and processing speed, and working memory) to a greater extent than aerobic exercise alone.143 The positive effects of strength exercise have been confirmed in two randomised controlled trials, which reported cognitive benefits from moderate- and high-intensity strength exercise alone among healthy older people.145,146

**Effects among people with dementia disorders**

Despite the development of cognitive impairments in people with dementia disorders and the positive findings concerning cognitive functions among more healthy people, the effects on cognitive functions have been poorly evaluated in randomised controlled trials in people with dementia. In the systematic review by Forbes et al (2008),139 no conclusion could be made as to whether physical exercise is beneficial for cognitive functioning due to limited data.

**EVALUATION OF METHODOLOGICAL QUALITY IN CLINICAL TRIALS**

The degree of accuracy of the conclusions about the effects of an intervention depends on the internal validity of the study.147-149 Internal validity is the extent to which the results are correct for the subjects under investigation i.e. the extent to which systematic error (bias) is minimised in a clinical trial.147,148 Thus, it is essential to measure methodological quality items related to the internal validity in a study because variations in the quality of trials can affect conclusion about the existing evidence. However, it is impossible to know exactly to what extent biases have influenced the results in a study. Therefore, it is recommended that the risk of bias be considered when assessing the methodological quality in a study.149 In a systematic review, that evaluated the effect of progressive strength exercise among older people, the effect sizes were lower in high quality trials (i.e. low risk of bias) compared to lower quality trials.78 These results indicate that there is a risk that low quality studies will overestimate the effect.

There are many aspects of methodological quality to consider when assessing randomised controlled trials.150 No scale completely covers every aspect and no golden standard exists.149-151 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement recommends considering, for example, the following common markers of internal validity for randomised controlled trials: appropriate generation of random allocation sequence;
concealment of the allocation sequence; blinding participants, health care providers, and data collectors; proportion of patients lost to follow-up; and whether the analysis followed the intention-to-treat principle. The PRISMA statement also recommends considering other aspects of study quality specific to the topic of the review. In physiotherapist area the Physiotherapy Evidence Database scale (the PEDro scale) is a commonly used, valid and reliable measure of the methodological quality of clinical trials. The scale consists of eleven items, ten (items 2-11) related to the internal validity or the interpretability of the trial. However, the items in the PEDro scale seem to need to be complemented with some other methodological quality items related to internal validity when comprehensively assessing the methodological quality of clinical trials among older people with severe physical or cognitive impairments. For example, it seems that there is a risk of bias if there is an unequal distribution of attention in the groups since people with physical or cognitive impairments generally have few social contacts and studies that have evaluated the effects of cognitive functions and ADL have shown that an unequal distribution of attention in groups could have an impact on the results among people with dementia. Furthermore, in people without dementia it has been shown that studies which have attention control groups in their study design have lower levels of effects than studies that have not included this design feature.
RATIONALE FOR THE THESIS

Impairments in physical and cognitive functions are common among people living in residential care facilities and contribute to dependence in ADL. Among older people who are healthy and those with moderate cognitive and physical impairments, physical exercise programmes have been shown to have positive effects on physical and cognitive functions, and ADL. Furthermore, performing the exercises with high intensity seems important in achieving optimal effects and an immediate intake of protein supplementation might increase the exercise effects. Despite these positive findings there are relatively few studies that have evaluated the effects of physical exercise among people with multiple diagnoses living in residential care facilities. Physical exercise could be one important method for preventing or reducing the dependency in ADL among people living in residential care facilities, which in turn might increase life satisfaction and reduce societal costs.

There are some positive findings regarding physical exercise among people living in residential care facilities but there is no consensus concerning the optimal type of physical exercise and no study has investigated the effects of an immediate intake of protein supplementation in this population. Knowledge is very limited concerning the applicability and effects of high-intensity exercise programmes among people living in residential care facilities, including also people with severe cognitive or physical impairments. People living in residential care facilities form a heterogeneous group. Conditions such as fluctuating health status, depression, dementia disorders, and severe physical or cognitive impairments may negatively affect the possibility of participating in and performing physical exercise with high intensity, and, consequently, reduce the effects. Furthermore, people with increasing age and people suffering from malnutrition might have limited effect of strength exercise, which might also be smaller among older women than among older men. The high prevalence of diseases such as coronary heart disease, osteoporosis, and dementia may lead to a high risk of adverse events when performing high-intensity exercise. No serious adverse events in high-intensity exercise programmes among older people who are healthy and those with moderate impairments have been reported in the literature. However, systematic and accurate registration of adverse events is often lacking in the studies. Thus, it is important to evaluate applicability with regard to attendance, achieved intensity, and adverse events and the effects of high-intensity exercise among people living in residential care facilities, including those with severe cognitive or physical impairments, and to evaluate whether certain subgroups in residential care facilities benefit less or more from high-intensity exercise programmes.
Functional weight-bearing exercise programmes have been shown to have wide-ranging effects on physical functions among older people who are healthy and those with moderate impairments. This type of exercise seems suitable for people living in residential care facilities, including those with severe cognitive impairments, because the exercises are easy to follow and there is no need for specific exercise facilities. Furthermore, it is possible to achieve high intensity in the training, and as the exercises mimic movements used in everyday tasks, functional weight-bearing exercise programmes represent a promising method for reducing dependency in ADL.

Despite the development of physical and cognitive impairments in people with dementia, the effect of physical exercise on physical impairments, cognitive functions, and ADL have been poorly evaluated in randomised controlled trials. A systematic review, published in 2008, concluded that there was insufficient evidence to say whether or not physical exercise programmes are beneficial for people with dementia. However, since the literature search performed in this review, several randomised controlled trials examining the effects of physical exercise among people with dementia disorders have been published. Thus, it is important to conduct a new systematic review.
AIMS OF THE THESIS

The overall aim of this thesis was to evaluate the applicability and effects on physical functions and ADL of a high-intensity functional weight-bearing exercise programme carried out among older people living in residential care facilities, with a special focus on people with dementia, and to systematically review the scientific literature regarding the applicability and effects of physical exercise on physical functions, cognitive functions, and ADL among people with dementia disorders.

Specific aims

Paper I - To evaluate the applicability of a high-intensity functional weight-bearing exercise programme with regard to attendance, achieved intensity and adverse events among older people dependent in ADL and living in residential care facilities and, further, to analyse whether cognitive function was associated with the applicability of the programme.

Paper II - To evaluate whether a high-intensity functional exercise programme improves functional balance, gait ability, and lower-limb strength among older people dependent in ADL and living in residential care facilities, and whether an intake of protein-enriched energy supplement immediately after the exercises increases the effects of the training.

Paper III - To evaluate whether a high-intensity functional weight-bearing exercise programme reduces dependency in ADL among older people dependent in ADL and living in residential care facilities, focusing on people with dementia.

Paper IV - To evaluate whether age, sex, depression, dementia disorder, nutritional status, or level of functional balance capacity influence the effect of a high-intensity functional weight-bearing exercise programme on functional balance among older people dependent in ADL and living in residential care facilities.

Paper V - To systematically review the scientific literature regarding the applicability (attendance, achieved intensity, and adverse events) and effects of physical exercise on physical functions, cognitive functions, and ADL among people with dementia.
METHODS

This thesis is based on two studies; one randomised controlled trial and one systematic review. The randomised controlled trial was carried out 2002 in Umeå, Sweden, among people living in residential care facilities. The study, entitled The Frail Older People–Activity and Nutrition Study in Umeå (the FOPANU Study), evaluated the applicability and effects of a high-intensity functional weight-bearing exercise programme. The systematic review evaluated the applicability and effects of physical exercise among people with dementia disorders and the electronic searches were carried out in 2010.

THE FOPANU STUDY (Papers I-IV)

Settings and participants
The participants in the FOPANU Study (logo shown below) lived in nine residential care facilities in Umeå; all with private apartments with access to dining facilities, alarms and on-site nursing and care. Four facilities had specialised units, with private rooms and staff on hand, for persons with dementia. To be eligible for inclusion in the study residents had to be aged 65 years or over, dependent on assistance from a person in one or more personal ADL according to the Katz Index, able to stand up from a chair with armrests with help from no more than one person, have a Mini-Mental State Examination (MMSE) score of ten or more, and have the approval of their physician. Before inclusion, all residents (n = 487) were screened by physiotherapists and 191, aged 65–100 years, were included in the study. There were no differences regarding age, sex, and Katz ADL Index score between the residents who were included in the study and those who declined the offer to participate (n = 71). A flowchart of the inclusion process is presented in Figure 1.
Figure 1. Flow of the participants through the FOPANU Study (Papers I-IV).
Ethical approval
The FOPANU Study was approved by the Ethics Committee of the Medical Faculty of Umeå University (391/01). The residents who met the inclusion criteria were given written and oral information about the study regarding e.g. the assessments and interventions, and told that participation was voluntary and could be discontinued at any time without any given reason. The residents or their relatives, when appropriate due to cognitive impairment, gave their informed oral consent to participating in the FOPANU Study.

Study design
The FOPANU Study is a stratified cluster-randomised controlled trial comprising both an exercise intervention compared with a control activity and a nutrition intervention compared with a placebo, in a 2 x 2 factorial model. The exercise intervention and control activity were presented to participants and staff at the facilities with no indication of the study hypotheses. The assessors were blinded to group allocations and previous test results for all outcome measures in Papers II-IV. Regarding the assessment of ADL in Paper III, the interviewed licensed practical nurses or nurses’ aide were blinded to the study hypotheses, but not to group allocations. Concerning the nutrition intervention, participants as well as therapists, who administered the nutrition intervention and supervised the exercise and control activities, were blinded.

Randomisation
To reduce contamination by the exercise intervention, 34 clusters, comprising three to nine participants living on the same floor, in the same wing or unit, were randomly assigned to the exercise or the control activity. The randomisation was stratified by facility in order to have both groups distributed as equally as possible in each facility, to minimise the risk of impact by factors associated with the facility itself. Within each cluster the nutrition intervention was randomised individually. To exclude the possibility of selection bias, randomisation was performed after inclusion of the participants and baseline assessments. Researchers not involved in the study performed the randomisation using lots in sealed non-transparent envelopes.

Intervention procedure
The intervention was performed in groups of three to nine participants supervised by two physiotherapists (exercise) or one occupational therapist (control) throughout the session. The sessions were approximately 45 minutes long and were held five times during each period of two weeks over 3 months (13 weeks), a total of 29 occasions. A schedule for all sessions was given to the participants as well as to the staff at the facility. When needed, a verbal reminder or help with transfer to the group session was provided by the staff or the supervisors. Both the exercise and the control activity were performed
within the facility at a similar distance from the participants’ apartments or rooms. When a participant did not attend the group session, individual activity was offered if possible. There were no restrictions regarding other activities during the study. The nutrition drinks were offered within five minutes after each session and were collected and weighed after 15 minutes to assess the amount that had been consumed. If the participant did not attend the activity, the drink was offered when possible.

**Exercise intervention**
The exercise intervention was based on the High-Intensity Functional Exercise Program (the HIFE Program), which was developed for this study. The objective of the intervention was to improve the participants’ lower-limb strength, balance, and gait ability. The HIFE Program was distributed in written form (booklet with drawings and instructions) to the physiotherapists, and a meeting was held before the start of the intervention in order to learn the programme.

The HIFE Program was based on exercising in functional weight-bearing positions and included lower-limb strength and balance exercises in standing and walking. The exercises mimicked movements used in everyday tasks, for example, standing-up from a sitting position, step-up, squats, turning trunk and head while standing, and walking over obstacles. The collection of exercises was developed according to three criteria: (1) applicable without access to special exercise facilities, (2) adaptable for older people with different functional levels, including independent walkers and those needing help with all mobility, and (3) possibility for progression of the exercises in two ways; either to increase the difficulty in a specific exercise or to change to another, more challenging, exercise. In all, 41 exercises, distributed over five categories, were included in the collection of exercises (Table 1).
**Table 1.** Collection of exercises in the High-Intensity Functional Exercise Program (the HIFE Program): categories and examples

<table>
<thead>
<tr>
<th>Category</th>
<th>Name</th>
<th>Examples of exercises</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Static* and dynamic† balance exercises in combination with lower-limb strength exercises</td>
<td>Squat in a parallel or walking stance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Step-up on to boxes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Forward or side lunge</td>
</tr>
<tr>
<td>B</td>
<td>Dynamic balance exercises in walking</td>
<td>Walking over obstacles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Walking on a soft surface</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Walking with numerous turns</td>
</tr>
<tr>
<td>C</td>
<td>Static and dynamic balance exercises in standing</td>
<td>Trunk rotation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Body weight transfer in a parallel or walking stance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Side step and return</td>
</tr>
<tr>
<td>D</td>
<td>Lower-limb strength exercises with continuous balance support</td>
<td>Squat in a parallel or walking stance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Standing-up from sitting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heel-raise</td>
</tr>
<tr>
<td>E</td>
<td>Walking with continuous balance support</td>
<td>Walking in various directions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Walking with numerous turns</td>
</tr>
</tbody>
</table>

* Static balance exercises: fixed base of support.
† Dynamic balance exercises: changing base of support.

For the selection of exercise categories, a hierarchical model in the HIFE Program, based on the participant’s walking ability without walking aid, was used as a guideline (Table 2). Within each category, the physiotherapist selected exercises for each participant according to their functional deficits to obtain an individually tailored programme. They encouraged the participants to exercise with a high intensity and to progressively increase the load in the lower-limb strength exercises and the difficulty in the balance exercises. The exercises were adjusted to meet changes in health and functional status for each session. It was recommended that the participants perform at least two lower-limb strength exercises and two balance exercises in two sets at each session and that the exercises be preceded by a warm-up for five minutes while sitting. Strength exercises were intended to be performed at 8–12 RM, thus increasing the load.
as soon as the participant performed more than 12 repetitions. For the first two weeks, 13–15 RM was recommended as a build-up period. The load of the leg extensor muscle groups was determined, for each strength exercise separately, during each session according to the participant’s performance. The load was increased by adjusting the performance of the exercise (e.g. by doing deeper squats or doing step-ups on to a higher box) or by using a weighted belt worn around the waist, loaded with a maximum weight of 12 kg. The balance exercises were intended to fully challenge the participant’s postural stability (i.e. to be performed near the limits of maintaining postural stability). The difficulty of each balance exercise was increased, for example, by standing or walking with a narrower base of support or on a more challenging surface. All exercise equipment was portable.

**Table 2.** Model in the High-Intensity Functional Exercise Program (the HIFE Program) for selection of exercise categories

<table>
<thead>
<tr>
<th>Physical function group*</th>
<th>Recommended categories in the collection of exercises</th>
</tr>
</thead>
</table>
| Walking without any physical support or supervision (n = 27) | A. Static and dynamic balance exercises in combination with lower-limb strength exercises  
B. Dynamic balance exercises in walking |
| Walking with supervision or minor physical support from one person (n = 35) | A. Static and dynamic balance exercises in combination with lower-limb strength exercises  
B. Dynamic balance exercises in walking  
C. Static and dynamic balance exercises in standing |
| Walking with major physical support or not able to walk (n = 29) | C. Static and dynamic balance exercises in standing  
D. Lower-limb strength exercises with continuous balance support  
E. Walking with continuous balance support |

* Number of participants categorized to the physical function group shown in parentheses.  
* The participant’s need for personal support when walking a short distance (5–10 m) without a walking aid.
At the end of the 3-month exercise period, the physiotherapists introduced physical tasks for the participants, in cooperation with a staff member at the facility, for the purpose of maintaining physical function. The tasks, performed with or without staff supervision, were integrated into daily life activities. They were individually recommended according to the participants’ functional deficits and motivation regarding type (e.g. walking, squats, and standing without balance support), number (one to four) and frequency (weekly up to daily). The tasks were followed-up after three months (at the 6-month follow-up), by interviewing staff about compliance during the preceding two weeks.

At the end of the 3-month exercise period, 81 (93%) of the remaining 87 participants in the exercise group were given 2.0 ± 0.8 (mean ± SD) physical tasks. Also in the subgroup of people with dementia, 2.0 ± 0.8 (mean ± SD) physical tasks were given. At the 6-month follow-up, 29 (39%) of the remaining 74 participants had performed one task or more as frequently as recommended, and 29 (39%) had not done any. Corresponding figures for people with dementia were 14 (36%) and 18 (46%), respectively.

**Control activity**

The control activity consisted of a programme developed specifically for this study by occupational therapists, which included activities while sitting, e.g. watching films, reading, singing, and conversation. The programme was based on themes, e.g. the old country shop, famous people, and games from the past and was expected to be interesting and stimulating for older persons, including those with severe cognitive impairment.

**Nutrition intervention and placebo**

The nutrition intervention consisted of a protein-enriched energy supplement. The supplement was a milk-based 200 ml drink that contained 7.4 g protein, 15.7 g carbohydrate, corresponding to 408 kJ per 100 g. The placebo drink (200 ml) contained 0.2 g protein, 10.8 g carbohydrate, corresponding to 191 kJ per 100 g. Both drinks were served in the same type of non-transparent package (identical design) and had similar flavours.

**Outcomes**

Data regarding the outcome variables in Paper I were registered after each exercise session. The outcome measures in Papers II-IV were assessed at baseline and at the 3- and 6-month follow-ups.
Applicability of the exercise programme

The outcome in Paper I was applicability of the exercise programme. In evaluating the applicability, the outcome variables were attendance, intensity of lower-limb strength and balance exercises, and occurrence and seriousness of adverse events. After each exercise session, the physiotherapists completed a structured report for each participant, including exercises performed, reason for not attending the exercise session, estimated intensity of the lower-limb strength and balance exercises (Table 3), reason for not achieving high intensity, and occurrence of adverse events. Adverse events during the exercise session were defined as discomfort that manifested itself or became worse because of the exercises. The adverse events were either expressed spontaneously by the participant or observed by the physiotherapist. In addition, the physiotherapist asked participants during the exercise session whether they were experiencing any discomfort.

The seriousness of the adverse events was assessed by 3 people (2 specialists in geriatric medicine and 1 physiotherapist) independently according to 4 different categories: (1) minor and temporary, (2) serious symptoms (potential risk of severe injury or life-threatening), (3) manifest injury or disease, and (4) death. In cases of disagreement between assessors, a consensus was reached after a discussion.

**Table 3. Intensity scales of the lower-limb strength and balance exercises**

<table>
<thead>
<tr>
<th></th>
<th>High intensity</th>
<th>Medium intensity</th>
<th>Low intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower-limb strength exercises</td>
<td>Sets of 8–12 repetition maximum</td>
<td>Sets of 13–15 repetition maximum</td>
<td>Sets of &gt;15 repetition maximum</td>
</tr>
<tr>
<td>Balance exercises</td>
<td>Postural stability fully challenged*</td>
<td>Postural stability not fully challenged or fully challenged in only a minority of the exercises</td>
<td>Postural stability in no way challenged</td>
</tr>
</tbody>
</table>

* The intensity scales were developed for this study. Intensity for each participant was estimated by the physiotherapist for lower-limb strength and balance exercises separately, as an average for each exercise session.

* Postural stability fully challenged = balance exercises performed near the limits of maintaining postural stability.
Functional balance, gait ability and lower-limb strength

The outcomes in Paper II were functional balance, gait ability and lower-limb strength and, in Paper IV, functional balance. These three outcomes were the primary outcomes in the POPANU Study. Functional balance capacity was assessed using the Berg Balance Scale (BBS). The BBS is a valid and reliable instrument for evaluating the effectiveness of interventions in research. It consists of 14 tasks with varied difficulty of balance that are common in everyday life, for example, standing up from sitting, transferring from one chair to another, and, while standing, reaching forward, turning 360 degrees, or placing alternate feet onto a step. Thus, BBS also reflects other aspects of physical function than balance, such as lower-limb strength and gait. Each item in the BBS is graded 0-4 with a maximum score of 56. Lower points are given for people in need of supervision, physical or verbal guidance, or if given time limits are exceeded.

Gait ability was measured by a 2.4 metre timed test, starting from a standing position, first twice at a self-paced gait speed and then twice at maximum speed. The participants used their ordinary walking aid and walked to a visible goal approximately three meters away. The timing, with a digital stopwatch, was stopped when the participant’s chest crossed the finish line marked on the wall. The assessor walked alongside the participant if necessary for safety reasons, but no physical contact was allowed.

Lower-limb strength was measured by establishing 1 RM in a leg press machine (Steens Industrier AS, Norway). The test was performed, normally bilaterally, from a 90 degree knee angle to the participant’s complete knee extension. A unilateral 1 RM was established if the participant, e.g. due to paresis, was unable to use both legs. The load was increased by 10 kg per attempt with 45 s rest between. When the participant did not succeed in an attempt, the load was increased by 2 kg from the last successful attempt until 1 RM was obtained. For safety reasons, participants who had sustained a hip fracture within the past 6 months or a who had hip prosthesis were not assessed.

The participant’s use of a walking aid and position in the leg press machine were used equally on the test occasions. Interrater reliability for BBS and 2.4-meter gait speed, calculated by Intra Class Correlation (ICC 3.1), ranged from 0.99 to 1.00.

ADL

The outcome in Paper III was ADL, assessed using the Barthel ADL Index (the ten-item version). The Barthel ADL Index is a well-established and valid measure of functional independence in personal care and mobility.
Interrater reliability has also been evaluated for the individual item scores and reported to be fair to very good (kappa values from 0.41 to 0.85) among older people with impaired physical and cognitive functions. The Barthel ADL Index measures what a person actually does rather than what they could do in daily life and has a total score of 0-20, with a higher score indicating greater independence. A weighting system of the scoring for the items reflects their relative importance in terms of the level of social acceptability and the nursing care required. The scale is appropriate for evaluating a clinically meaningful effect of the intervention since each point in each item is clearly separated in terms of dependence in ADL. A licensed practical nurse or a nurse’s aide, who knew the participant well, was questioned with reference to the items about performance in ADL.

**Baseline descriptive assessments**

The resident’s registered nurse recorded diagnoses, clinical characteristics, and prescribed drugs from the medical records and from all other available documentation at the residential care facility. All baseline assessments, except for the Mini Nutritional Assessment (MNA), were performed by trained physiotherapists. The Functional Ambulation Categories (FAC) was used to measure walking ability in 6 levels (0–5). This categorization does not take account of any walking aid used. A score of 3 (verbal supervision or standby help from one person without physical contact) or less was chosen to indicate severe physical impairment. Cognitive function was assessed using the MMSE (0-30) where a score of 17 or less indicates severe cognitive impairment. Depressive symptoms were screened using the Geriatric Depression Scale (GDS-15). Vision impairment was noted if the participant, with or without glasses, was unable to read a word written in 5-mm capital letters at reading distance. Hearing impairment was noted if the participant was unable to hear a conversation at normal voice level at a distance of 1 meter or used a hearing aid. A dietician assessed nutritional status by using the MNA (0-30), including Body Mass Index (BMI) (kg/m²). MNA scores below 24 indicate risk of malnutrition and below 17 indicate the presence of malnutrition. Self-perceived health was assessed using one item in the MNA. A specialist in geriatric medicine evaluated the documentation of diagnoses, drug treatments, assessments, and measurements for completion of the final diagnoses. Dementia and depression were diagnosed using the DSM-IV criteria. Consequently, in the few cases when the participant had a low score on the MMSE but did not have a dementia diagnosis or had a high score on the GDS but did not have a depression diagnosis, the specialist in geriatric medicine decided whether or not the participant met the DSM-IV criteria based on all available information, including assessments and information from medical records.
Data analyses
All analyses in the FOPANU Study (Papers I–IV) were based on the intention-to-treat principle using all available data on each participant according to their original group assignment, regardless of level of attendance in the intervention. All statistical tests were 2-tailed; \( p < 0.05 \) was considered to indicate statistical significance.

The results of the outcome analyses in Papers II–IV are presented without adjustments for the randomization in clusters. The rationale for this is that the randomisation was stratified in order to have both groups distributed as equally as possible in each facility and, further, that there were few participants per cluster (at the 3- and 6-month follow-ups mean 5.3 ± 1.6, 5.0 ± 1.6, respectively) and that the intervention was directed to the individuals instead of to the clusters.\(^{171} \) Nevertheless, the cluster effect was examined in additional analyses by adjusting the outcome regression analyses for clustering.\(^{172} \) These analyses produced essentially the same results as the unadjusted analyses (data not shown). Analyses for the cluster adjustments were performed using Stata software version 9.1 (StataCorp, College Station, Texas).

Effect sizes for outcome measures in Papers II and III were calculated as the difference between the exercise and the control group in the estimated marginal means divided by the pooled standard deviations of the difference between post- and pre-intervention values (square root of the mean square error).\(^{173} \)

Paper I
An attendance rate was calculated for each participant as the number of attended sessions divided by total sessions (\( n = 29 \)). An intensity rate was calculated for each participant as the number of sessions of the specific intensity divided by total attended sessions. Likewise, an adverse event rate was calculated for each participant as the number of sessions with an adverse event divided by total attended sessions.

Dementia diagnosis and MMSE score were the variables used to evaluate whether cognitive function was associated with the applicability of the programme. Rates for attendance, intensity (of high-intensity lower-limb strength and balance exercises), and adverse events were compared between participants with and without dementia using the Mann-Whitney \( U \) test (due to skewed distribution). The correlations between these rates and the MMSE score were analysed using the Spearman rank correlation. Analyses were performed using the SPSS software, version 10.0 (SPSS Inc., Chicago, IL).
**Paper II**

The study was designed to have 80% power to detect a significant difference ($p$ value of $< 0.05$, two-sided) between the exercise and control groups of $\geq 3$ points in BBS, considering an estimated dropout rate of 20%.

The mean of the two attempts for self-paced gait speed and the best time measured for maximum speed, were chosen. If there was only one time measured, this was used. Imputations with 0.01 m/s were made in cases where the participant was unable to perform the test because of impaired physical function. No imputations were made for the other variables.

Baseline characteristics were compared between allocation to activity (exercise/control) and nutrition (protein/placebo) group by one-way analysis of variance (ANOVA) or the chi-square test. Within-group effects were analysed by paired sample $t$-tests, comparing outcome measures at baseline (pre-intervention) with 3- and 6-month follow-ups (post-intervention), respectively.

Outcome measures (the BBS, gait speed, 1 RM in lower-limb strength) were evaluated, at 3- and 6-month follow-ups, in between-group analyses by 2 x 2 factorial analysis of covariance (ANCOVA), in which the post-intervention value was the dependent variable. Fixed factors were allocation to activity and nutrition groups. The other independent variables were the pre-intervention value, age, sex, and covariates adjusting for differences ($p \leq 0.15$) between the groups at baseline (angina pectoris, proton pump inhibitors, Barthel ADL Index, and self-perceived health). The analyses were tested for interactions between allocation to activity and nutrition groups. Analyses were performed using the SPSS software, version 10.0 (SPSS Inc., Chicago, IL).

**Paper III**

Baseline characteristics and baseline values of the Barthel ADL Index (total score and for each item) were compared between the two groups (exercise/control) using Student’s $t$-test or the chi-square test. To describe change over time in total score of the Barthel ADL Index, within-group effects were analysed in each group (exercise/control) using paired sample $t$-tests, comparing the total score at baseline (pre-intervention) with the total score at the 3- and 6-month follow-ups (post-intervention), respectively. Comparisons of baseline characteristics and total score of the Barthel ADL Index at baseline as well as analyses of within-group effects were also made (in the exercise and control groups respectively) with the participants divided into groups with and without dementia.
Between-group differences in the total score of the Barthel ADL Index were analysed using ANCOVA, at the 3- and 6-month follow-ups (post-intervention) respectively, in which the post-intervention total score was the dependent variable. Fixed factor was allocation to group (exercise/control). The other independent variables were the pre-intervention total score for the Barthel ADL Index, age, sex, and covariates adjusting for differences \((p \leq 0.15)\) between the groups in baseline characteristics (vision impairment and self-perceived health).

The effect on the total score for the Barthel ADL Index was also compared between people with and without dementia, respectively. For this purpose a variable of four categories was formed in the ANCOVA: `control-dementia`, `exercise-dementia`, `control-no dementia` and `exercise-no dementia`. The independent variables were the same as in the between-group analyses above, since no other baseline characteristics differed between the subgroups (`control-dementia` versus `exercise-dementia` and `control-no dementia` versus `exercise-no dementia`, respectively). The analyses were tested for interactions between allocation to activity group and presence of dementia.

As a complementary analysis of the whole sample and people with dementia, the effect on each item of the Barthel ADL Index was evaluated using logistic regression (improvement or unchanged score versus deterioration) with the same independent variables as in the ANCOVA analysing between-group differences in the total score. The rationale for including unchanged and improvement in score in the same category was that even an unchanged score in an item could be considered a positive result because of the high risk of deterioration in ADL over time in this group of older people. Analyses were performed using the SPSS software, version 11.0 (SPSS Inc., Chicago, IL).

**Paper IV**

The independent variables for the preplanned subgroup analyses were age, sex, depression, dementia disorder, nutritional status (MNA score), and level of functional balance capacity (BBS score) at baseline. Age and BBS score were dichotomised on the median value. MNA score was dichotomised on 17, since a score below 17 indicates the presence of malnutrition. In addition, age, BBS and MNA scores at baseline were evaluated as continuous variables. To complement the subgroup analyses of depression and dementia disorder, GDS and MMSE scores at baseline were analysed as continuous variables to evaluate whether the amount of depressive symptoms and cognitive level, respectively, influenced the effects.
Baseline characteristics were compared between exercise and control groups using Student’s t-test or the chi-square test. To describe change over time in total score for the BBS, within-group effects were analysed in both exercise and control groups using paired sample t-test, comparing the total score at baseline (preintervention) with the total score at the 3- and 6-month follow-ups (postintervention). Comparison of baseline characteristics and analyses of within-group effects (in the exercise and control groups, respectively) were also made with the participants divided into the predefined subgroups.

Interactions between allocation to activity group and each subgroup were evaluated using ANCOVA. Between-group differences were analysed at the 3- and 6-month follow-ups (postintervention), respectively, in which the postintervention total BBS score was the dependent variable. Independent variables were allocation to activity (exercise or control) and one of the subgroups in each analysis. The analyses were adjusted for preintervention total score for the BBS, age (not in the analyses when dichotomised age was the independent variable), sex, and differences ($p \leq 0.15$) between the groups (exercise and control) at baseline (vision impairment and self-perceived health). For the subgroup analysis regarding level of functional balance capacity (dichotomised BBS score), the difference between post- and preintervention values of the total score for the BBS was the dependent variable with no adjustments for the preintervention total score for the BBS. All the analyses were tested for interactions between allocation to activity group and each subgroup. In addition, all the analyses using ANCOVA were also performed with adjustments for the differences ($p \leq 0.15$) between the exercise and control groups with the participants divided into the subgroups. These analyses produced essentially the same results as the analyses adjusted for the differences between the exercise and control groups (data not shown).

Interactions between allocation to activity group and age, BBS, MNA, MMSE, and GDS scores at baseline, respectively, were evaluated using multiple linear regression analysis. The dependent variable was the total score for the BBS at the 3- and 6-month follow-ups (postintervention). For testing interaction effects, a variable of the product of activity group and each of the variables was added. The multiple linear regression analyses were adjusted for the same variables as in the ANCOVA. Analyses were performed using PASW Statistics 17.0 (SPSS Inc., Chicago, IL).
THE SYSTEMATIC REVIEW (Paper V)

Literature search and study selection
A librarian carried out extensive electronic searches on 30 August and 1 September 2010 using search terms related to dementia, physical exercise, and randomised controlled trials in the following databases: PubMed, CINAHL, AMED, and the Cochrane Library. The authors of the paper supplemented the electronic searches by checking reference lists in the relevant papers found in the electronic searches. In addition, papers related to the topic that were known by the authors at that time, but were not found in the searches, were also reviewed for inclusion. The predetermined inclusion criteria were: (1) paper published in English or in a Scandinavian language; (2) randomised controlled trial that included only people with a diagnosed dementia disorder; (3) effect of physical exercise as a single intervention was evaluated and was compared to usual care or a control activity; (4) effect on physical functions (e.g. balance, mobility, or muscle strength), cognitive functions, or ADL was evaluated; and (5) result of between-group analysis was reported. Two reviewers independently screened the titles and abstracts of the papers that were identified in the electronic searches and studies that obviously did not meet the inclusion criteria were discarded. Full paper copies were obtained of the remaining papers and those found by the authors. These papers were independently reviewed by the two reviewers, followed by a consensus meeting. If there were disagreements or doubts about how to interpret the reported data, a third reviewer was consulted and a consensual decision was reached about whether or not the study met the inclusion criteria. A flowchart of the inclusion process is presented in Figure 2.
Figure 2. Flow of studies through the review (Paper V).
RCT = randomised controlled trial
* Studies that obviously did not meet the inclusion criteria were discarded.
† Papers were excluded from the review when one of the inclusion criteria (a to e) was not met.
‡ Nine of the included papers were identified in the electronic literature searches and one paper was identified in reference lists.
Procedure of data extraction and methodological quality rating
Based on data reported in the papers, methodological quality was rated and data regarding participants, intervention, and outcome measures were extracted. A standardised data collection form was used by two reviewers (various combinations of the three authors of the paper) independently of each other, followed by the same consensus procedure as when selecting studies. In a few cases, when there was doubt among reviewers about how the analyses were performed, a statistician was consulted.

Quality assessment
To assess the risk of bias regarding the effect of the exercise intervention,149 the methodological quality of the included studies was described by extracting the scores from the PEDro scale as reported in the Physiotherapy Evidence Database (http://www.pedro.org.au). At the Physiotherapy Evidence Database, two raters independently rate each trial and, if necessary, a third rater resolves disagreements. Of the eleven items, ten (items 2-11), related to the internal validity or the interpretability of the trial, were used in this systematic review. These items are: 2) subjects were randomly allocated to groups; 3) allocation was concealed; 4) the groups were similar at baseline regarding the most important prognostic indicators; 5) there was blinding of all subjects; 6) there was blinding of all therapists who administered the therapy; 7) there was blinding of all assessors who measured at least one key outcome; 8) measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups; 9) all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome were analysed by “intention to treat”; 10) the results of between-group statistical comparisons are reported for at least one key outcome; and 11) the study provides both point measures and measures of variability for at least one key outcome. Operational definitions of each item are given in the Physiotherapy Evidence Database (http://www.pedro.org.au).

As recommended in the PRISMA statement,149 aspects of study quality specific to the topic of the review were also considered. To complement the assessment by the PEDro scale, before the review the authors developed five items with operational definitions reflecting aspects of methodological quality related to internal validity, where some of the aspects seem of particular importance when assessing studies evaluating the effects of physical exercise among older people with severe physical or cognitive impairments. It seems that there is risk of bias if the criterion for each item is not met. These five additional items are described in Table 4. The items were rated in all included studies and each item received, as in the PEDro scale, either a “no” or a “yes”. In addition, outcome measures that met the criterion were specified by the reviewers, at each follow-
up, in those cases where an item was rated “yes” (in the PEDro scale or for one of the five additional items).

**Table 4.** Additional items for assessing the methodological quality

A) The control group has received similar attention as the intervention group.

*Rationale:* An unequal distribution of attention in the groups could have an important impact on the results, especially among people with physical or cognitive impairments since they generally have few social contacts.

B) The number of participants is sufficient for at least one of the outcome analyses.

*Rationale:* It is important that the study is designed to be large enough to have a high probability of detecting a statistically significant difference of a given size if such a difference exists.

C) The baseline values of the outcome measure are accounted for in at least one of the outcome analyses.

*Rationale:* It is essential to consider differences in baseline values between groups when analyzing (preferably by using the baseline value as independent variable). Among older people with physical and cognitive impairments, the differences in baseline values are likely to be seen in intervention studies, despite them being randomised, since the studies are often relatively small and the people included are heterogeneous regarding physical and cognitive functions, and diseases.

D) The drop-out rates in the intervention and control groups are similar for at least one outcome measure.

*Rationale:* A higher drop-out rate in one of the compared groups could bias the results of the study. In older people, higher drop-out rates have been reported in exercise groups when performing progressive resistance training than in control groups. The people who drop out might have more co-morbidity and impairments than those who complete the trial.

E) A use of randomisation in clusters was adjusted for, when appropriate, in at least one of the outcome analyses.

*Rationale:* Failing to adjust for clustering when appropriate in the analysis will result in confidence intervals that are falsely narrowed and p-values that are falsely low.
To summarize the risk of bias for each outcome measure in each study, as recommended in the PRISMA statement, the overall methodological quality was rated by two reviewers independently, followed by a consensus procedure, using a three-point rating scale developed by the authors before the review (Table 5). For studies with more than one follow-up, the rating was conducted at each follow-up. The rating of the overall methodological quality score (low, moderate, and high) was based on the results of the ten items of the PEDro scale and the five additional items, with no defined cut-off values between scores. The rationale for not having cut-off values is that each item might have a different impact on the internal validity.

Table 5. Rating scale for overall methodological quality in an RCT

<table>
<thead>
<tr>
<th>High quality</th>
<th>Appropriate design, well performed, and well analysed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate quality</td>
<td>Criteria for high quality are partly but not fully met</td>
</tr>
<tr>
<td>Low quality</td>
<td>Criteria for high quality are not at all or only slightly met</td>
</tr>
</tbody>
</table>

RCT = randomised controlled trial

Data extraction

Participants and intervention
Data on setting, type of dementia disorder, number of participants, proportion of females, mean age, and level of cognitive and physical functions were identified. If baseline characteristics were not reported for all participants in the study, data for the exercise group were used in the text of the result section for the description of the participants.

The type of physical exercise, frequency, duration of session, time period, the intention of intensity level, use of progression in the physical exercise, and use of individual adjustments of the intervention were identified. For the comparison group, data were identified regarding type of activity, frequency, duration of session, time period, and use of individual adjustments. In studies involving more than two groups, the authors selected the two groups that fitted the inclusion criterion to evaluate physical exercise as a single intervention compared to usual care or a control activity.

Outcome Measures
Data were identified concerning the applicability (attendance, achieved intensity, and adverse events) of the exercise, as well as results from between-group analyses on outcome measures that could be related to physical functions, cognitive functions, or ADL.
Data analyses
Statistical pooling (quantitative analysis) was not performed since the exercise interventions in the included trials were not sufficiently similar to combine results. The level of evidence regarding the effect of a treatment was summarized by means of qualitative analysis. Qualitative analysis consists of using various levels of evidence regarding the effectiveness of a treatment. A system described by van Tulder et al.\textsuperscript{17} was used to estimate levels of evidence. This system considers number of studies, methodological quality of the studies, and consistency of results. The system was modified by the authors (Table 6) to fit the inclusion of RCTs only and the three-point rating scale of the overall methodological quality. Regarding the evaluation of the applicability of the exercise, the evidence system was not used.

Table 6. Levels of evidence from RCTs

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>Consistent findings* among multiple high quality RCTs</td>
</tr>
<tr>
<td>Moderate</td>
<td>Consistent findings among multiple moderate quality RCTs and/or one high quality RCT</td>
</tr>
<tr>
<td>Limited</td>
<td>Consistent findings among multiple low quality RCTs and/or one moderate quality RCT</td>
</tr>
<tr>
<td>Conflicting</td>
<td>Conflicting findings among multiple RCTs</td>
</tr>
<tr>
<td>No evidence</td>
<td>No RCTs or one low quality RCT</td>
</tr>
</tbody>
</table>

* For criteria for high, moderate, and low quality, see Table 5.

RCT = randomised controlled trial

* Consistent findings: similar effects in an outcome between the studies evaluating a specific intervention, i.e. that not both positive and negative effects are reported.
RESULTS

THE FOPANU STUDY

Table 7. Baseline characteristics of the participants in FOPANU study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total n = 191</th>
<th>Exercise n = 91</th>
<th>Control n = 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD</td>
<td>84.7 ± 6.5</td>
<td>85.3 ± 6.1</td>
<td>84.2 ± 6.8</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>139 (73)</td>
<td>67 (74)</td>
<td>72 (72)</td>
</tr>
<tr>
<td>Diagnoses and medical conditions, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td>100 (52)</td>
<td>47 (52)</td>
<td>53 (53)</td>
</tr>
<tr>
<td>Depression</td>
<td>116 (61)</td>
<td>55 (60)</td>
<td>61 (61)</td>
</tr>
<tr>
<td>Delirium episodes, in the last month</td>
<td>50 (26)</td>
<td>21 (23)</td>
<td>29 (29)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>54 (28)</td>
<td>26 (29)</td>
<td>28 (28)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>37 (19)</td>
<td>14 (15)</td>
<td>23 (23)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>52 (27)</td>
<td>25 (28)</td>
<td>27 (27)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>53 (28)</td>
<td>27 (30)</td>
<td>26 (26)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>50 (26)</td>
<td>23 (25)</td>
<td>27 (27)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>46 (24)</td>
<td>17 (19)</td>
<td>29 (29)</td>
</tr>
<tr>
<td>Routine prescription medications, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>94 (49)</td>
<td>45 (50)</td>
<td>49 (49)</td>
</tr>
<tr>
<td>Analgesics</td>
<td>111 (58)</td>
<td>56 (62)</td>
<td>55 (55)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>76 (40)</td>
<td>35 (39)</td>
<td>41 (41)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>94 (49)</td>
<td>46 (51)</td>
<td>48 (48)</td>
</tr>
<tr>
<td>Neuroleptics</td>
<td>42 (22)</td>
<td>17 (19)</td>
<td>25 (25)</td>
</tr>
<tr>
<td>Oestrogens</td>
<td>51 (27)</td>
<td>20 (22)</td>
<td>31 (31)</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>40 (21)</td>
<td>17 (19)</td>
<td>23 (23)</td>
</tr>
<tr>
<td>Number of drugs, mean ± SD (range)</td>
<td>9.1 ± 4.4</td>
<td>9.2 ± 5.0</td>
<td>9.0 ± 3.9</td>
</tr>
<tr>
<td>Assessments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional Ambulation Categories (0-5) ≤ 3*, n (%)</td>
<td>81 (42)</td>
<td>40 (44)</td>
<td>41 (41)</td>
</tr>
<tr>
<td>Mini Mental State Examination (0-30), mean ± SD</td>
<td>17.8 ± 5.1</td>
<td>17.5 ± 5.0</td>
<td>18.0 ± 5.3</td>
</tr>
<tr>
<td>Mini Mental State Examination (0-30) ≤ 17†, n (%)</td>
<td>92 (48)</td>
<td>47 (52)</td>
<td>45 (45)</td>
</tr>
<tr>
<td>Geriatric Depression Scale (0-15), mean ± SD</td>
<td>4.4 ± 3.2</td>
<td>4.6 ± 3.4</td>
<td>4.2 ± 2.9</td>
</tr>
<tr>
<td>(n = 180)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vision impairment, n (%)</td>
<td>56 (29)</td>
<td>32 (35)</td>
<td>24 (24)</td>
</tr>
<tr>
<td>Hearing impairment, n (%)</td>
<td>46 (24)</td>
<td>24 (26)</td>
<td>22 (22)</td>
</tr>
<tr>
<td>Body Mass Index, mean ± SD (n = 189)</td>
<td>24.8 ± 4.5</td>
<td>24.9 ± 4.4</td>
<td>24.7 ± 4.6</td>
</tr>
<tr>
<td>Mini Nutritional Assessment (0-30), mean ± SD</td>
<td>20.5 ± 3.7</td>
<td>20.4 ± 3.9</td>
<td>20.6 ± 3.6</td>
</tr>
<tr>
<td>(n = 188)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health, self-perceived as better than age peers‡, n (%)</td>
<td>77 (41)</td>
<td>30 (33)</td>
<td>47 (48)</td>
</tr>
<tr>
<td>(n = 189)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berg Balance Scale (0-56), mean ± SD (n = 190)</td>
<td>26.6 ± 14.8</td>
<td>26.6 ± 15.3</td>
<td>26.6 ± 14.4</td>
</tr>
<tr>
<td>Gait speed, self-paced, m/s, mean ± SD (n = 188)</td>
<td>0.36 ± 0.20</td>
<td>0.35 ± 0.20</td>
<td>0.37 ± 0.20</td>
</tr>
<tr>
<td>Gait speed, maximum, m/s, mean ± SD (n = 187)</td>
<td>0.55 ± 0.31</td>
<td>0.54 ± 0.32</td>
<td>0.55 ± 0.31</td>
</tr>
<tr>
<td>1 RM in lower-limb strength, kg, mean ± SD (n = 128)</td>
<td>89.5 ± 38.7</td>
<td>88.0 ± 38.6</td>
<td>91.8 ± 39.0</td>
</tr>
<tr>
<td>Barthel ADL Index (0-20), mean ± SD</td>
<td>13.1 ± 4.2</td>
<td>12.8 ± 4.5</td>
<td>13.4 ± 3.8</td>
</tr>
</tbody>
</table>

Note: The range of each assessment is indicated in parentheses. For all assessments, except the Geriatric Depression Scale, higher scores indicate better status. Numbers after a characteristic indicate that there are missing assessments. SD = Standard deviation.

* A score of ≤ 3 indicates severe physical impairment, † A score of ≤ 17 indicates severe cognitive impairment, ‡ Assessed using the Mini Nutritional Assessment item P (no = 0–1, yes = 2)
Baseline characteristics of the 191 participants are presented in Table 7. For the total sample, the mean age was 84.7 years, 73% were women, 52% had a dementia disorder, and 61% had a diagnosis of depression. The mean scores for MNA and BBS were 20.5 and 26.6, respectively. Ninety-two participants (48%) had severe cognitive impairment (MMSE ≤ 17) and 81 (42%) severe physical impairment (FAC ≤ 3). One hundred and thirty participants (68%) had either severe cognitive or physical impairment.

**Paper I: The applicability of a high-intensity functional exercise programme**

*Attendance*

The attendance rate was in median (interquartile range) 76% (62–93%). Six percent of the sessions were performed individually. The participants performed 5.1 ± 1.4 (mean ± SD) different exercises per attended session. The most common reasons for not participating in an exercise session were the participant’s lack of motivation (7% of the total sessions for all participants), acute disease (7%), hospital treatment or visit to the primary health care centre (3%), and pain (3%).

*Intensity of the exercise*

Lower-limb strength exercises of high intensity were performed in a median (interquartile range) of 53% (17%–72%) of the attended exercise sessions, and lower-limb strength exercises of medium or high intensity were performed in a median of 92% (85–100%) of the attended exercise sessions. Corresponding figures for balance were 73% (40%–89%) for high intensity and 96% (89%–100%) for medium or high intensity. In 42% (14%–68%) of the attended sessions, both high-intensity lower-limb strength and balance exercises were performed. The most common reasons for not achieving high intensity for lower-limb strength and balance exercises were pain (11% and 4% of the attended sessions, respectively), lack of motivation (9% and 8%, respectively), build-up period at the start of the intervention period or after a disease or injury (8% and 5%, respectively), and fatigue (4% and 4%, respectively).

*Adverse events*

In all, 179 adverse events occurred in 166 (9%) of the 1906 attended exercise sessions among 57 participants (63%). For all participants, the median (interquartile range) rate of sessions with adverse event per attended session was 5% (0%–14%). All except 2 adverse events were assessed as “minor and temporary”, and none led to manifest injury or disease. Two adverse events were assessed as “serious symptoms”: one participant stopped training during an exercise session because of pain in the chest, and in one case the physiotherapists prevented a fall by gently helping a participant down to the
floor when balance was lost. The adverse events were “musculoskeletal” (e.g. pain or soreness) (53%), “dizziness” (22%), “respiration/circulation” (e.g. breathlessness or discomfort from the chest) (18%), “general/unspecifed” (e.g. stomach pain) (4%), “psychological” (e.g. fear of falling) (3%), and “near fall accident” (described above) (1%).

**Association between applicability and cognitive function**

Regarding attendance, intensity, and adverse events, no significant differences were observed when comparing participants with dementia \((n = 47)\) with participants without dementia \((n = 44)\), nor was there any significant correlation to the MMSE score (Table 8).

**Table 8.** Applicability of the exercise programme related to dementia and cognitive function

<table>
<thead>
<tr>
<th>Variable</th>
<th>Participants with dementia ((n = 47))</th>
<th>Participants without dementia ((n = 44))</th>
<th>Correlation with the MMSE score, (r)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attendance rate,(*%)</td>
<td>76 (59–93)</td>
<td>76 (63–93)</td>
<td>0.62</td>
<td>0.022</td>
</tr>
<tr>
<td>High-intensity rate in strength and balance exercises,(†%)</td>
<td>29 (12–64)</td>
<td>50 (16–70)</td>
<td>0.51</td>
<td>0.115</td>
</tr>
<tr>
<td>Adverse event rate,(‡%)</td>
<td>7 (0–19)</td>
<td>4 (0–8)</td>
<td>0.09</td>
<td>0.073</td>
</tr>
</tbody>
</table>

\* MMSE = Mini-Mental State Examination; \(r\) = correlation coefficient.

\† Median (interquartile range): number of attended sessions divided by total sessions \((n=29)\) for each participant.

\‡ Median (interquartile range): number of sessions of high-intensity strength and balance exercises divided by total attended sessions for each participant.
Paper II: The effect on physical functions of a high-intensity functional exercise programme and protein-enriched energy supplementation

Compliance
The attendance was 72% for the exercise group and 70% for the control group. The protein-enriched energy supplement was taken on 82% of the occasions and the placebo drink on 78%. The package was completely emptied in 80% of these occasions.

Between-group differences and interaction effects
At 3-month follow-up, the exercise group had improved significantly in self-paced gait speed compared with the control group (Table 9). At 6-month follow-up, significant improvements in favour of the exercise group were obtained in BBS, self-paced gait speed, and 1 RM in lower-limb strength. No interaction effects were seen between the exercise and nutrition interventions for any of the outcome measures at any of the follow-ups (data not shown).

Within-group differences
All groups showed within-group improvements in BBS and in 1 RM in lower-limb strength at both follow-ups (Table 10). In most cases these improvements were statistically significant for the exercise groups, but not for the control groups.

Drop-outs
The relations between cause of death and the interventions and test procedures were evaluated by a specialist in geriatric medicine. In one case, an association with the study could not be definitely excluded. This participant died suddenly of an acute ruptured aortic-abdominal aneurysm one week after the 3-month follow-up tests were performed.
Table 9. Between-group differences at 3- and 6-month follow-ups, outcome analyses of functional balance, gait and lower-limb strength

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Follow-up</th>
<th>n</th>
<th>Exercise mean±SE</th>
<th>Control mean±SE</th>
<th>Difference Mean (95% CI)</th>
<th>p</th>
<th>ES</th>
<th>Protein mean±SE</th>
<th>Placebo mean±SE</th>
<th>Difference Mean (95% CI)</th>
<th>p</th>
<th>ES</th>
</tr>
</thead>
<tbody>
<tr>
<td>BBS, points</td>
<td>3 mo</td>
<td>172</td>
<td>29.5±0.7</td>
<td>28.0±0.7</td>
<td>1.5 (-0.4 to 3.4)</td>
<td>0.13</td>
<td>0.24</td>
<td>28.2±0.7</td>
<td>29.3±0.7</td>
<td>-1.1 (-3.1 to 0.8)</td>
<td>0.26</td>
<td>-0.18</td>
</tr>
<tr>
<td></td>
<td>6 mo</td>
<td>161</td>
<td>31.0±0.7</td>
<td>29.1±0.6</td>
<td>1.9 (0.004 to 3.8)</td>
<td><strong>0.046</strong></td>
<td>0.33</td>
<td>29.8±0.7</td>
<td>30.3±0.7</td>
<td>-0.6 (-2.5 to 1.4)</td>
<td>0.56</td>
<td>-0.10</td>
</tr>
<tr>
<td>Gait speed, self-paced, m/s</td>
<td>3 mo</td>
<td>166</td>
<td>0.40±0.01</td>
<td>0.36±0.01</td>
<td>0.04 (0.01 to 0.08)</td>
<td><strong>0.02</strong></td>
<td>0.36</td>
<td>0.38±0.01</td>
<td>0.38±0.01</td>
<td>0.00 (-0.04 to 0.04)</td>
<td>0.96</td>
<td>-0.01</td>
</tr>
<tr>
<td></td>
<td>6 mo</td>
<td>156</td>
<td>0.41±0.01</td>
<td>0.37±0.01</td>
<td>0.05 (0.01 to 0.08)</td>
<td><strong>0.009</strong></td>
<td>0.44</td>
<td>0.37±0.01</td>
<td>0.41±0.01</td>
<td>-0.04 (-0.07 to -0.03)</td>
<td><strong>0.03</strong></td>
<td>-0.37</td>
</tr>
<tr>
<td>Gait speed, maximum, m/s</td>
<td>3 mo</td>
<td>165</td>
<td>0.57±0.02</td>
<td>0.54±0.02</td>
<td>0.03 (-0.02 to 0.08)</td>
<td>0.30</td>
<td>0.17</td>
<td>0.54±0.02</td>
<td>0.57±0.02</td>
<td>-0.04 (-0.09 to 0.01)</td>
<td>0.16</td>
<td>-0.23</td>
</tr>
<tr>
<td></td>
<td>6 mo</td>
<td>154</td>
<td>0.62±0.02</td>
<td>0.59±0.02</td>
<td>0.03 (-0.03 to 0.09)</td>
<td>0.30</td>
<td>0.17</td>
<td>0.58±0.02</td>
<td>0.62±0.02</td>
<td>-0.04 (-0.10 to 0.02)</td>
<td>0.16</td>
<td>-0.24</td>
</tr>
<tr>
<td>1 RM in lower-limb strength, kg</td>
<td>3 mo</td>
<td>103</td>
<td>102.9±3.0</td>
<td>97.9±3.2</td>
<td>5.1 (-3.9 to 14.0)</td>
<td>0.26</td>
<td>0.23</td>
<td>99.7±3.0</td>
<td>101.1±3.2</td>
<td>-1.4 (-10.3 to 7.5)</td>
<td>0.76</td>
<td>-0.06</td>
</tr>
<tr>
<td></td>
<td>6 mo</td>
<td>97</td>
<td>105.4±3.3</td>
<td>94.5±3.3</td>
<td>10.8 (1.3 to 20.4)</td>
<td><strong>0.03</strong></td>
<td>0.49</td>
<td>100.0±3.2</td>
<td>99.9±3.4</td>
<td>0.2 (-9.4 to 9.7)</td>
<td>0.97</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Between-group effects analysed by 2 x 2 factorial ANCOVA in which the post-intervention value was the dependent variable. Independent variables were the allocation to activity (exercise/control) and nutrition (protein/placebo) groups, pre-intervention value, age, sex and covariates adjusting for differences (p ≤ 0.15) between the groups at baseline (angina pectoris, proton pump inhibitors, Barthel ADL Index and self-perceived health). Effect sizes were calculated as the difference between the marginal means divided by the pooled standard deviations of the difference between post- and pre-intervention values (square root of the mean square error).

SE = standard error; CI = confidence interval; ES = effect size; BBS = the Berg Balance Scale; RM = repetition maximum.
Table 10. Within-group differences between post- and pre-intervention values, outcome analyses of functional balance, gait and lower-limb strength

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Follow-up</th>
<th>Exercise &amp; Protein</th>
<th>Exercise &amp; Placebo</th>
<th>Control &amp; Protein</th>
<th>Control &amp; Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>mean±SD</td>
<td>p</td>
<td>n</td>
<td>mean±SD</td>
</tr>
<tr>
<td>BBS, points</td>
<td>3 mo</td>
<td>44 1.3±7.5 0.26</td>
<td>0.001</td>
<td>38 3.3±6.0</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>6 mo</td>
<td>41 2.4±6.2 0.02</td>
<td>36 3.5±5.7</td>
<td>0.001</td>
<td>40 0.8±5.8</td>
</tr>
<tr>
<td>Gait speed, self-paced, m/s</td>
<td>3 mo</td>
<td>42 0.02±0.12 0.36</td>
<td>36 0.02±0.13 0.32</td>
<td>44 0.00±0.12 0.91</td>
<td>45 -0.02±0.12 0.18</td>
</tr>
<tr>
<td></td>
<td>6 mo</td>
<td>39 0.00±0.11 0.80</td>
<td>36 0.05±0.12 0.02</td>
<td>44 0.00±0.11 0.81</td>
<td>42 -0.01±0.11 0.47</td>
</tr>
<tr>
<td>Gait speed, maximum, m/s</td>
<td>3 mo</td>
<td>42 -0.03±0.15 0.18</td>
<td>36 0.03±0.17 0.33</td>
<td>44 -0.03±0.19 0.26</td>
<td>44 -0.01±0.14 0.69</td>
</tr>
<tr>
<td></td>
<td>6 mo</td>
<td>39 -0.02±0.22 0.63</td>
<td>36 0.07±0.20 0.03</td>
<td>44 0.01±0.17 0.68</td>
<td>40 0.00±0.13 0.87</td>
</tr>
<tr>
<td>1 RM in lower-limb strength, kg</td>
<td>3 mo</td>
<td>31 11.3±21.2 0.006</td>
<td>24 10.9±18.0 0.007</td>
<td>25 7.1±22.9 0.13</td>
<td>23 8.2±24.7 0.13</td>
</tr>
<tr>
<td></td>
<td>6 mo</td>
<td>28 11.6±28.8 0.04</td>
<td>22 10.1±20.6 0.03</td>
<td>23 1.5±20.9 0.74</td>
<td>24 2.8±17.4 0.43</td>
</tr>
</tbody>
</table>

Within-group effects were analysed using paired sample t-tests.
SD = standard deviation; BBS = the Berg Balance Scale; RM = repetition maximum.
Paper III: The effect on ADL of a high-intensity functional exercise programme

Between- and within-group differences in the total sample

When all participants were analysed, there were no statistically significant differences in the total Barthel ADL Index score between the groups at the 3- and 6-month follow-ups (Table 11). The analyses for each item of the Barthel ADL Index showed a significant between-group difference for item 7, which measures the participants’ indoor mobility in daily life. A significantly lower proportion of the participants in the exercise group had deteriorated compared to the control group at the 3-month follow-up (exercise group 4% versus control group 16%, \( p = 0.01 \)) and at the 6-month follow-up (exercise 8% versus control 20%, \( p = 0.03 \)). This corresponds to a six-fold and a three-fold increased risk at the 3- and 6-month follow-ups, respectively, of having deteriorated in indoor mobility in the control group compared to the exercise group (Odds ratio [95% confidence interval] 6.03 [1.54 – 23.67] and 3.10 [1.12 – 8.58], respectively). There were no significant differences for the other items (data not shown). The within-group analyses showed a significant decline in the total Barthel ADL Index score for the control group, but not for the exercise group, at both the 3- and 6-month follow-ups (Table 12).

Between- and within-group differences among people with dementia

The between-group analyses of people with dementia showed a significant difference in the total Barthel ADL Index score (mean difference 1.1, \( p = 0.03 \)), in favour of the exercise group, at the 3-month follow-up, but the difference was not significant at the 6-month follow-up (Table 11). No significant interaction effects were seen between the exercise intervention and dementia for the total score at the 3-month follow-up (\( p = 0.11 \)) and 6-month follow-up (\( p = 0.85 \)). The analyses for each item of the Barthel ADL Index showed no significant between-group differences (data not shown). The within-group analyses among people with dementia showed a significant decline in the total Barthel ADL Index score for the control group at both the 3- and 6-month follow-ups and for the exercise group at the 6-month follow-up (Table 12).
Table 11. Between-group differences of the Barthel ADL Index at 3- and 6-month follow-ups

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Exercise mean±SE</th>
<th>Control mean±SE</th>
<th>Difference mean (95% CI)</th>
<th>p</th>
<th>ES</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mo</td>
<td>179</td>
<td>12.95±0.27</td>
<td>12.39±0.26</td>
<td>0.56 (-0.18 to 1.29)</td>
<td>0.14</td>
</tr>
<tr>
<td>6 mo</td>
<td>168</td>
<td>12.80±0.32</td>
<td>12.10±0.30</td>
<td>0.70 (-0.17 to 1.57)</td>
<td>0.11</td>
</tr>
<tr>
<td>Participants with dementia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mo</td>
<td>95</td>
<td>13.07±0.37</td>
<td>11.94±0.35</td>
<td>1.13 (0.12 to 2.13)</td>
<td>0.03</td>
</tr>
<tr>
<td>6 mo</td>
<td>91</td>
<td>12.40±0.43</td>
<td>11.60±0.41</td>
<td>0.80 (-0.38 to 1.98)</td>
<td>0.18</td>
</tr>
<tr>
<td>Participants without dementia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mo</td>
<td>84</td>
<td>12.84±0.38</td>
<td>12.89±0.37</td>
<td>-0.05 (-1.10 to 1.00)</td>
<td>0.93</td>
</tr>
<tr>
<td>6 mo</td>
<td>77</td>
<td>13.30±0.47</td>
<td>12.66±0.43</td>
<td>0.64 (-0.63 to 1.91)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Between-group effects analysed using ANCOVA in which the post-intervention value was the dependent variable. Independent variables were the allocation to activity (exercise/control), pre-intervention value of the Barthel ADL Index, age, sex and covariates adjusting for differences (p ≤ 0.15) between the groups at baseline (vision impairment and self-perceived health). Effect sizes were calculated as the difference between the exercise and the control group in the estimated marginal means divided by the pooled standard deviations of the difference between post- and pre-intervention values (square root of the mean square error).

SE = standard error; CI = confidence interval; ES = effect size

Table 12. Within-group differences of the Barthel ADL Index between post- and pre-intervention values 3- and 6-month follow-ups

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Exercise</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>mean±SD</td>
</tr>
<tr>
<td>All</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mo</td>
<td>86</td>
<td>-0.22±2.36</td>
</tr>
<tr>
<td>6 mo</td>
<td>78</td>
<td>-0.55±2.46</td>
</tr>
<tr>
<td>Participants with dementia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mo</td>
<td>45</td>
<td>-0.13±2.11</td>
</tr>
<tr>
<td>6 mo</td>
<td>43</td>
<td>-1.00±2.72</td>
</tr>
<tr>
<td>Participants without dementia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mo</td>
<td>41</td>
<td>-0.32±2.64</td>
</tr>
<tr>
<td>6 mo</td>
<td>35</td>
<td>0.00±2.00</td>
</tr>
</tbody>
</table>

Within-group effects were analysed using paired sample t-tests. A negative difference of the Barthel ADL Index indicates increased dependency in ADL.
Paper IV: The effect on functional balance in subgroups of a high-intensity functional exercise programme

Compliance in the subgroups
In the exercise group, the attendance was 62.3% for participants with malnutrition and 81.0% for men. The attendance in the remaining subgroups ranged from 67.2 to 78.4%. Proportions of attended sessions with high-intensity strength exercises were 68.4% for men and ranged from 50.0% to 58.6% in the remaining subgroups. The proportions of attended sessions with high-intensity balance exercises were 60.0% for people with malnutrition and ranged from 71.4 to 77.2% for the remaining subgroups.

Between-group differences and interaction effects, stratified according to the subgroups
Mean differences for the BBS at the 3- and 6-month follow-ups between the exercise and control groups, stratified according to the preplanned subgroups, are presented in Table 13. The subgroup analyses revealed no statistically significant interaction for age, sex, depression, dementia disorder, nutritional status, or level of functional balance capacity at the 3- and 6-month follow-ups (Table 13). In addition, when the variables age, BBS, and MNA scores at baseline were respectively evaluated as continuous variable there was no significant interaction at the 3- (p = 0.32, 0.57, 0.07, respectively) or 6-month follow-ups (p = 0.75, 0.70, 0.22, respectively). Moreover, at 3- and 6-month follow-ups there was no significant interaction for cognitive level (MMSE score) (p = 0.28, 0.47, respectively) or amount of depressive symptoms (GDS score) (p = 0.85, 0.49, respectively).

Within-group differences in the total sample and in the subgroups
Overall, the within-group analyses in the exercise group revealed significant improvements in the BBS at the 3-month follow-up (mean difference 2.23, 95% CI = 0.73–3.74) and the 6-month follow-up (mean difference 2.92, 95% CI = 1.57–4.27). For the control group there was a significant mean difference at the 6-month follow-up (mean difference 1.32, 95% CI = 0.04–2.60) but not at the 3-month follow-up (mean difference 1.19, 95% CI = -0.04–2.41). The within-group analyses for all the subgroups revealed a trend for all mean differences in the exercise group to be positive and to be higher compared to the subgroups in the control group at the 3- and 6-month follow-ups (Table 14).
Table 13. Between-group differences of the Berg Balance Scale and interactions effects at 3- and 6-month follow-ups, stratified according to participant characteristics

<table>
<thead>
<tr>
<th>Participants</th>
<th>Difference between Exercise – Control</th>
<th>p-value for interaction</th>
<th>Difference between Exercise – Control</th>
<th>p-value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 months</td>
<td></td>
<td>6 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>mean (95% CI)</td>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 85</td>
<td>90</td>
<td>0.92 (-1.74 – 3.58)</td>
<td>0.65</td>
<td>82</td>
</tr>
<tr>
<td>&lt; 85</td>
<td>82</td>
<td>1.79 (-0.98 – 4.56)</td>
<td></td>
<td>79</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>124</td>
<td>1.62 (-0.69 – 3.93)</td>
<td>0.65</td>
<td>116</td>
</tr>
<tr>
<td>Male</td>
<td>48</td>
<td>0.65 (-2.93 – 4.21)</td>
<td></td>
<td>45</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>100</td>
<td>0.76 (-1.84 – 3.37)</td>
<td>0.51</td>
<td>95</td>
</tr>
<tr>
<td>No</td>
<td>72</td>
<td>2.08 (-0.86 – 5.03)</td>
<td></td>
<td>66</td>
</tr>
<tr>
<td>Dementia disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>90</td>
<td>1.59 (-1.08 – 4.26)</td>
<td>0.78</td>
<td>87</td>
</tr>
<tr>
<td>No</td>
<td>82</td>
<td>1.04 (-1.72 – 3.80)</td>
<td></td>
<td>74</td>
</tr>
<tr>
<td>Nutritional status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MNA score &lt; 17</td>
<td>25</td>
<td>5.42 (0.38 – 10.46)</td>
<td>0.09</td>
<td>24</td>
</tr>
<tr>
<td>MNA score ≥ 17</td>
<td>146</td>
<td>0.70 (-1.38 – 2.77)</td>
<td></td>
<td>137</td>
</tr>
<tr>
<td>Functional balance capacity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BBS score &lt; 29</td>
<td>84</td>
<td>1.12 (-1.62 – 3.85)</td>
<td>0.67</td>
<td>73</td>
</tr>
<tr>
<td>BBS score ≥ 29</td>
<td>88</td>
<td>1.93 (-0.76 – 4.61)</td>
<td></td>
<td>88</td>
</tr>
</tbody>
</table>

For subgroup analyses, all variables were dichotomised. Between-group differences in the total score for the BBS were analysed using ANCOVA at the 3- and 6-month follow-ups (postintervention). All the analyses were tested for interactions between allocation to activity group and each subgroup. CI = confidence interval; MNA = the Mini Nutritional Assessment; BBS = the Berg Balance Scale.
Table 14. Within-group differences of the Berg Balance Scale between post- and preintervention values at 3- and 6-month follow-ups, stratified according to participant characteristics

<table>
<thead>
<tr>
<th>Participants</th>
<th>3 months mean (95% CI)</th>
<th>6 months mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exercise n = 47</td>
<td>Control n = 44</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 85</td>
<td>2.36 (0.34 – 4.38)</td>
<td>1.84 (-0.01 – 3.70)</td>
</tr>
<tr>
<td>&lt; 85</td>
<td>2.06 (-0.32 – 4.43)</td>
<td>0.57 (-1.08 – 2.23)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2.00 (0.19 – 3.81)</td>
<td>0.92 (-0.41 – 2.25)</td>
</tr>
<tr>
<td>Male</td>
<td>2.83 (-0.06 – 5.72)</td>
<td>1.88 (-1.01 – 4.77)</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.13 (0.17 – 4.08)</td>
<td>1.78 (0.41 – 3.14)</td>
</tr>
<tr>
<td>No</td>
<td>2.37 (-0.10 – 4.85)</td>
<td>0.32 (-1.98 – 2.63)</td>
</tr>
<tr>
<td>Dementia disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.86 (-0.42 – 4.13)</td>
<td>0.92 (-0.69 – 2.52)</td>
</tr>
<tr>
<td>No</td>
<td>2.63 (0.57 – 4.68)</td>
<td>1.49 (-0.45 – 3.42)</td>
</tr>
<tr>
<td>Nutritional status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MNA &lt; 17</td>
<td>1.47 (-2.99 – 5.93)</td>
<td>-4.00 (-9.26 – 1.26)</td>
</tr>
<tr>
<td>MNA ≥ 17</td>
<td>2.40 (0.79 – 4.02)</td>
<td>1.90 (0.68 – 3.11)</td>
</tr>
<tr>
<td>Functional balance capacity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BBS &lt; 29</td>
<td>2.94 (0.26 – 5.63)</td>
<td>2.04 (0.29 – 3.79)</td>
</tr>
<tr>
<td>BBS ≥ 29</td>
<td>1.67 (-0.08 – 3.43)</td>
<td>0.19 (-1.52 – 1.90)</td>
</tr>
</tbody>
</table>

Within-group effects in all subgroups were analysed using paired sample t-test. CI = confidence interval; MNA = the Mini Nutritional Assessment; BBS = the Berg Balance Scale.
THE SYSTEMATIC REVIEW

Paper V: The applicability and effects of physical exercise on physical and cognitive functions and ADL among people with dementia

Participants
Ten studies were included in the systematic review (Table 15). Eight studies were performed in residential care facilities,\(^{178,185}\) one in independent housing,\(^{186}\) and one in hospital.\(^{187}\) The majority of studies included people with Alzheimer’s disease;\(^{179,181,186}\) One study also included participants with other types of dementia\(^{187}\) and in two studies the type of dementia was not reported.\(^{178,180}\) The mean age ranged from 74 to 87 years and the proportion of women ranged from 53 to 84%. One study did not report the participants’ sex or age.\(^{181}\) The level of cognitive function among the participants, assessed by the MMSE (score 0-30), ranged from a mean score of 6 to 13 in five of the studies\(^{178,179,182,183,185}\) and from a mean score of 18 to 20 in three studies.\(^{180,184,186}\) One study reported a mean score of 2 for the Clifton Assessment Procedure for the Elderly Information/Orientation (score 0-12)\(^{187}\) and one study did not report the level of cognitive function.\(^{181}\)

Overall methodological quality
The rating of overall methodological quality in each study did not differ for outcome measures and follow-ups. The overall methodological quality was rated as “Low” in six studies\(^{178,179,181,182,184,186}\) and as “Moderate” in four studies.\(^{180,183,185,187}\)

Intervention
Four studies evaluated combined exercise (i.e. more than one exercise type is used) performed individually,\(^{178,182,186,187}\) of which one evaluated functional and non-functional exercises including balance, walking, joint mobility, bed mobility, and lower-limb strength exercises.\(^{187}\) Combined exercise performed in groups was evaluated in three studies,\(^{181,183,184}\) of which one focused on functional weight-bearing exercises including aerobic (walking), balance, lower-limb strength and flexibility exercises.\(^{183}\) Three studies evaluated walking exercise, one performed in pairs\(^{179}\) and two performed individually.\(^{180,185}\)
Table 15. Participants, exercise interventions, outcomes and overall methodological quality in the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Exercise intervention</th>
<th>Outcome</th>
<th>Overall quality</th>
</tr>
</thead>
</table>
| Christofoliti et al, 2008<sup>74</sup> | Setting: Long-term psychiatric institution  
Type of dementia disorder: -  
Number: 54  
Female sex, %: 69  
Age, mean: 74 | Individual physical exercise, concentrated on specific kinesitherapeutic exercises that stimulated strength, balance and cognition.  
Frequency: 3 times per week  
Duration: 60 minutes  
Time period: 6 months  
Intensity level (intention): - | Balance  
Mobility  
Cognitive functions | Low |
| Cott et al, 2002<sup>79</sup> | Setting: Long-term care facilities  
Type of dementia disorder: Alzheimer's disease  
Number: 86  
Female sex, %: 53  
Age, mean: 82 | Walking exercise in pairs and conversation simultaneously.  
Frequency: 5 times per week  
Duration: 30 minutes  
Time period: 16 weeks  
Intensity level (intention): Not explicitly reported but the participants were encouraged to walk as much of the session as possible. | Mobility  
ADL | Low |
| Eggemont et al, 2009<sup>80</sup> | Setting: Nursing homes  
Type of dementia disorder: -  
Number: 103  
Female sex, %: 81  
Age, mean: 85 | Individual walking exercise.  
Frequency: 5 times per week  
Duration: 30 minutes  
Time period: 6 weeks  
Intensity level (intention): - | Cognitive functions | Moderate |
| Francese et al, 1997<sup>81</sup> | Setting: Medicaid nursing facility  
Type of dementia disorder: Alzheimer's disease  
Number: 12  
Female sex: -  
Age: - | Group exercise including catching, throwing, and kicking balls and lower-limb strength exercises, and parachute reaches.<sup>188</sup>  
Frequency: 3 times per week  
Duration: 20 minutes  
Time period: 7 weeks  
Intensity level (intention): - | Balance  
Muscle strength  
Cognitive functions and ADL | Low |
<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Type of dementia disorder: Alzheimer's disease</th>
<th>Number: 38</th>
<th>Female sex, %: 74</th>
<th>Age, mean: 82</th>
<th>Exercise including walking, balance, and aerobic exercises. Each week, in one session, walking exercises were performed e.g. walking by striding over boards or going up a step, in the second session aerobic exercise with ergocycle with the arms and legs was performed, and in the third session activities that combined walking, balance, and aerobic exercises were performed e.g. dance and stepping. Frequency: 3 times per week</th>
<th>Duration: 60 minutes</th>
<th>Time period: 15 weeks</th>
<th>Intensity level (intention):</th>
<th>Mobility</th>
<th>Cognitive functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kemoun et al., 2010[^2]</td>
<td>Nursing home</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Pomeroy et al., 1999[^8]</td>
<td>Hospital respite admission</td>
<td>56%, undifferentiated dementia 32%, multi-infarct dementia 10%, mixed dementia 2%</td>
<td>81</td>
<td>74</td>
<td>82</td>
<td>Individual exercise including functional weight-bearing exercise including balance, walking, and lower-limb strength exercises; balance exercises while sitting; joint mobility and strength exercises in isolated movements; and bed mobility training. Frequency: 5 times per week</td>
<td>Duration: 30 minutes</td>
<td>Time period: 2 weeks</td>
<td>Intensity level (intention): -</td>
<td>Mobility</td>
<td>Moderate</td>
</tr>
<tr>
<td>Rolland et al., 2007[^8]</td>
<td>Nursing homes</td>
<td>Alzheimer's disease</td>
<td>134</td>
<td>75</td>
<td>83</td>
<td>Functional weight-bearing exercise in groups including aerobic (walking for at least half of the session), balance, lower-limb strength, and flexibility exercises. Frequency: 2 times per week</td>
<td>Duration: 60 minutes</td>
<td>Time period: 12 months</td>
<td>Intensity level (intention): Moderate</td>
<td>Balance</td>
<td>Mobility ADL</td>
</tr>
<tr>
<td>Study</td>
<td>Setting</td>
<td>Type of dementia disorder: Alzheimer's disease</td>
<td>Intervention</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Santana-Sosa et al., 2008184</td>
<td>Nursing home</td>
<td>- Group exercise including balance/coordination exercises; joint mobility, flexibility, and strength exercises with elastic resistance bands for upper and lower extremity. Frequency: 3 times per week Duration: 75 minutes Time period: 12 weeks Intensity level (intention): Exercises began at individualized very light intensities.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steinberg et al., 2009186</td>
<td>Independent housing</td>
<td>- Individual home-based exercise programme consisting of three components: 1) Aerobic fitness: brisk walking. 2) Strength training targeting major muscle groups and utilizing resistive bands and ankle weights. 3) Balance and flexibility training: exercises incorporating shifting center of gravity, chair sit to stand, forward, backward, and tandem walks. Frequency: 7 times per week Duration: - Time period: 12 weeks Intensity level (intention): Aerobic exercise; moderate intensity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tappen et al., 200055</td>
<td>Long-term care facilities</td>
<td>- Individual walking exercise and conversation treatment simultaneously. Frequency: 3 times per week Duration: 30 minutes Time period: 16 weeks Intensity level (intention): Not explicitly reported but the participants were encouraged to walk as far as possible during the session.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

- = data not reported
Outcome Measures
All studies, except one, evaluated the effect on any kind of physical function, using a variety of outcomes and outcome measures. Four studies evaluated cognitive functions. Three studies evaluated the effect on ADL. One study used an outcome measure that evaluated both cognitive functions and ADL.

Applicability of the exercise interventions
Five studies reported attendance which ranged from 33 to 99%. Rolland et al. reported that the mean number of hospitalizations per patient was significantly higher in the exercise programme group but there were no significant differences between the intervention and control groups regarding number of falls, fractures or deaths. Santana-Sosa et al. reported that no major adverse effect or health problem was noted during the intervention period. Steinberg et al. reported that no serious adverse events were related to the exercise intervention.

Effect of the exercise interventions
Of the four studies of moderate overall methodological quality, three studies evaluated the effect on physical functions, one on cognitive functions, and one on ADL. Two studies reported positive effects and two no effects. Rolland et al. reported that the combined functional weight-bearing exercise over a period of 12 months reduced ADL decline, but had no effect on balance when compared to routine medical care. Regarding mobility, the programme improved walking performance after 6 and 12 months of exercising but had no effect on get-up-and-go performance. Tappen et al. reported that the walking exercise in combination with conversation treatment over 16 weeks prevented decline in mobility regarding walking performance compared to conversation treatment only. Pomeroy et al. reported no effect on mobility after the combined functional and non-functional exercise over 2 weeks compared to non-physical activity. Eggermont et al. reported no effect on cognitive functions after walking exercise at a self-selected speed over 6 weeks compared to social visits.

Of the six studies of low methodological quality, three evaluated the effect on cognitive functions. All three studies evaluated combined exercise. Only one from a total of four studies evaluating cognitive functions (one of moderate and three of low overall methodological quality) reported a positive effect. In that study by Kemoun et al., rated as having low overall methodological quality, an exercise
intervention including walking, balance and aerobic exercises over 15 weeks was compared to routine medical care.

**Synthesis of results**

**Combined Exercise**
Combined exercise performed individually in hospital or in groups in residential care facilities seems applicable regarding attendance among older people with Alzheimer's disease, but the attendance seems to be lower when the exercise period is longer. Furthermore, combined exercise at an intended moderate intensity or lower performed in groups in residential care facilities or performed individually in independent housing seems applicable, with regard to adverse events among older people with Alzheimer's disease.

Individually adjusted functional weight-bearing exercise including aerobic (walking), balance, lower-limb strength and flexibility exercises performed in groups at an intended moderate intensity over 12 months among older people with Alzheimer's disease living in residential care facilities has an effect on ADL and walking performance, but not on balance and get-up-and-go performance (Limited evidence).

Individually adjusted and performed combined exercise, functional and non-functional, including balance, walking, joint mobility, bed mobility, and strength exercises, with non-specified intensity over two weeks among older people with various types of dementia disorders in hospital has no effect on mobility (Limited evidence).

**Walking Exercise**
Walking exercise performed individually, where the participant walks as far as possible during the session, among older people with Alzheimer's disease in residential care facilities seems applicable regarding attendance but adverse events need to be evaluated. This walking exercise over 16 weeks has an effect on walking performance among older people with Alzheimer's disease in residential care facilities (Limited evidence).

Walking exercise performed individually at a self-selected speed over 6 weeks has no effect on cognitive functions among older people with unspecified dementia disorders in residential care facilities (Limited evidence).
DISCUSSION

The HIFE Program evaluated in the FOPANU Study was applicable for use with regard to attendance, achieved intensity and adverse events among older people who are dependent in ADL, living in residential care facilities, and have an MMSE score of ten or more. Although most of the participants had severe cognitive or physical impairments, there was a high rate of attendance, a relatively high achieved intensity in the exercises, and all except two adverse events were assessed as minor or temporary and none led to manifest injury or disease. There were no significant differences regarding the applicability of the programme between people with dementia and those without dementia and, furthermore, the applicability was not associated with cognitive function. The exercise programme resulted in positive long-term effects on physical functions i.e. functional balance, gait ability and lower-limb strength. An intake of a protein-enriched energy supplement immediately after the exercises did not increase the effect of the training. High age, female sex, a diagnosis of depression or dementia disorder, malnutrition, or severe physical impairment, all common characteristics of people living in residential care facilities, did not influence the effect on functional balance. This indicates that residents with these characteristics benefit similarly to the opposing subgroup from a high-intensity functional weight-bearing exercise programme. In addition, level of cognitive impairment or amount of depressive symptoms had no significant impact on the effects. Furthermore, the exercise programme had a positive effect on indoor mobility and, among people with dementia, a positive short-term effect on overall ADL performance.

The systematic review included ten studies that evaluated the effect of physical exercise as a single intervention among people with dementia disorders. The majority of the participants were older people with Alzheimer’s disease living in residential care facilities. The results showed that walking and combined exercise seem to be applicable regarding attendance among people with Alzheimer’s disease. Adverse events were poorly reported in most of the studies, but combined exercise with an intended moderate intensity or lower among people with Alzheimer’s disease in residential care facilities and independent housing seems to be applicable regarding adverse events, since no serious complications occurred. The higher number of hospitalizations in the combined exercise group compared to the control group in the study by Rolland et al.\textsuperscript{183} may be explained by the higher proportion of participants in the exercise group with comorbidities at baseline. The results from the studies of moderate quality show that there is some evidence that walking exercise performed individually, where the participants walk as far as possible during the sessions over a period of 16 weeks, prevents decline in walking performance
and that combined functional weight-bearing exercise over 12 months reduces ADL decline and improves walking performance among people with Alzheimer’s disease in residential care facilities, but has no effect on balance or get-up-and-go performance. The FOPANU Study was not included in the systematic review since it did not exclusively include people with dementia. However, the results from the FOPANU Study strengthen the results of the systematic review since the participants with dementia derived benefit of a combined functional weight-bearing exercise programme.

**High Intensity Functional Exercise Programme in Residential Care Facilities**

**Applicability**

Important factors for the relatively high attendance in the exercise intervention in the FOPANU Study, especially for the participants with severe cognitive or physical impairment, were probably that a schedule for all sessions was provided to the participants as well as to the staff at the facility and, when needed, a verbal reminder or help with transfer to the exercise session was given by the staff or the physiotherapist. The low rate of adverse events and the positive effects of the exercise were other additional factors that probably had a positive influence on the attendance rate.

The rates for achieved high intensity were high for balance exercises but moderate for strength exercises. The most common reason for not achieving high intensity in lower-limb strength exercises was pain, which was given nearly three times more frequently as a reason than for balance exercises. The high prevalence of pain conditions (indicated by common regular use of analgesics), osteoarthritis, and osteoporosis might indicate difficulties in exercising with higher loads.

The rate of adverse events, including only two serious symptoms which did not lead to manifest injury or disease, may be seen as acceptable in this population considering the relatively high intensity achieved. Approval from the participants’ physicians prior to the study was probably important for the participants’ safety as well as the supervision by physiotherapists who were experienced in working with older people with cognitive or physical impairments and multiple diseases. The physiotherapist adjusted the exercises for each session depending on changes in the participants’ health status. However, among people with dementia there was a nonsignificant tendency to experience more adverse events, but no such tendency was observed when correlating adverse events to the MMSE score.
Effect on physical functions
The positive effects on physical functions of the HIFE Program are in accordance with other high-intensity exercise studies targeting older people with moderate cognitive or physical impairments. However, contradictory results were presented in a study by Morris et al. among older people living in residential care facilities including mainly residents with severe cognitive and physical impairments. In that study no improvements in balance and muscle power were seen. One explanation for these results might be that the participants were not offered any specific balance exercises and the strength exercise was not task-specific in relation to the measurement of muscle power. The strength exercises seemed to be performed in isolated muscle groups, whereas muscle power was tested in a functional task.

The long-term effects on physical functions in the FOPANU Study are in accordance with a study that also evaluated the effects of a functional exercise programme but among community-living older people. A study among older people living in residential care facilities that evaluated the effects of an exercise programme, which was one aspect of a multi-factorial falls prevention programme, also found positive long-term effects. Apart from the HIFE Program, the physical tasks that were introduced after the 3-month exercise period might also have a preserving effect on physical function. However, the compliance with these tasks was low.

In contrast to an expected decline in physical functions in the control group during the study there was no decline in function and, actually, at 6-month follow-up there were significant within-group improvements in functional balance. A seasonal effect might be one possible explanation for these results, since the baseline data were collected in late winter and the 6-month follow-up took place directly after the summer season. The control activity programme might also have had a positive impact on physical function. Among people living in residential care facilities physical activity and social interaction are rare. This implies that the control activity may have had a considerable impact on the participants through e.g. increased attention, social stimulation, meaningful activity, or transferring to another location within the facility. The use of this elaborate control activity adds strength to the interpretation that the differences between the exercise and control groups in physical functions were mainly due to physical exercise itself.

Effect of protein-enriched energy suplementation
That the effect of the training on physical functions was not increased by an intake of protein immediately after the exercises is in accordance to a study by Candow et al. but contrasts with a study by Esmarck et al., both of which included healthy older men. One possible explanation for this lack of increased
effect in the FOPANU Study may be that the participants had poor nutritional status, probably indicating a negative energy balance. Thus, the protein might have been absorbed as energy to compensate for this rather than contributing to muscle building. In addition, the majority of the participants had many diseases, which might have affected the absorption or metabolism of the protein. Regarding the positive effect of the protein supplement in the study by Esmarck et al., caution should be taken when interpreting the results since the within-group result indicates that the comparison group did not develop any muscle hypertrophy after 12 weeks of progressive strength exercise, which contradicts other studies among healthy older men.

**Effect on ADL**

The absence of an overall effect on ADL in the FOPANU Study is not in agreement with a study by Morris et al., which showed, in a similar population, that a high-intensity exercise programme reduced ADL decline. The two studies differed in the type of exercises employed and the duration of the exercise intervention, which was shorter in the present study. In contrast to the study by Morris et al., the present study also implemented a control activity in an effort to equalize the attention provided to participants in both groups. This implies that the effect of the exercise programme itself in the study by Morris et al. may be overestimated.

The effect on independence in indoor mobility in the total sample is in accordance with the positive effects on gait ability and balance. The preserved exercise effect for all these outcome measures indicates that people in the exercise group continued to utilize their increased physical capacity in daily life after the 3-month exercise period. Maintaining independence in indoor mobility could, in a longer perspective, prevent further development of disability and diseases related to physical inactivity since an increased dependence in indoor mobility may reduce spontaneous physical activity in daily living. Furthermore, maintaining independence in indoor mobility could also be important for life satisfaction in this group of older people. Evaluation of the effect of the HIFE Program on well-being in the FOPANU Study, showed a positive effect in the subgroup that included people with dementia, but not in the total sample.

Among people with dementia, the HIFE Program prevented decline in overall ADL performance after the 3-month exercise period. A study by Rolland et al., which included only people with Alzheimer’s disease, also evaluated the effect of a functional weight-bearing exercise programme but over a longer period of time (12 months). In that study there was a significant between-group effect on ADL after 12 months but not after 6 months of exercising. This is not in agreement with the present study, which showed an effect of a high-intensity
functional weight-bearing exercise programme after a shorter period (3 months). Explanations for the difference in the effects could be higher intensity of the exercises and higher compliance in the present study. The specific ADL abilities that the effect in overall ADL performance among people with dementia is based on in the present study is unclear, as the analyses for each item showed no significant between-group differences. In addition, whether the effect on overall ADL directly after the 3-month exercise period could partly depend on a positive effect on cognitive functions is unclear, since the effect on cognitive functions was unfortunately not evaluated.

The absence of effect among people with dementia at the 6-month follow-up implies that continuous supervised training in the form of high-intensity functional weight-bearing exercises may be necessary to maintain the effect on ADL. One possible explanation of why exercising seems especially important for older people with dementia may be the fact that some of their ADL decline is due to physical inactivity and not only to the progression of the disease itself. The lack of initiative and a successively more limited social life\(^\text{51,52,53}\) indicate that people with dementia are in particular need of support if they are to stay physically active.

The absence of effect on overall ADL performance in the total sample, together with a significant effect on the mobility indoors-item only, indicate that other strategies might be considered in attempting to optimally affect disability. Exercises for the upper extremities\(^\text{38}\) or multi-factorial interventions\(^\text{56,197}\) may be needed to affect other items in the Barthel ADL Index such as “bowels”, “bladder” or “grooming”, since those items could be less sensitive to change through improved physical function regarding gait and balance ability. However, a longer intervention period with the HIPE Program might have resulted in an overall effect on ADL in the total sample through a greater effect on physical functions compared to the control group.

When considering the size of the effects in the total Barthel ADL Index score it is important to relate it to what it could mean for the individual when performing ADL. The Barthel ADL Index measures what a person actually does in daily life and each point is also clearly separated for each item, in terms of dependence in ADL. Consequently, the size of the effect among people with dementia, a mean difference of 1.1 points, indicates a clinically meaningful effect. However, the scale is limited in that it is rather crude and minor differences are not detectable, such as whether a person is able to perform some activities in daily living faster, more safely, or with less help from someone else. This implies that the exercise programme could have an overall effect on ADL in the total sample but the scale used in the present study was not sufficiently sensitive to detect it.
Effect on functional balance in subgroups
People with dementia seemed to derive benefit from the HIFE Program similar to those without dementia, regarding the effect on functional balance. That the exercises used in the programme mimic movements used in everyday life and were similar to the tasks that the exercises aimed to improve might have been an important prerequisite for achieving a positive effect. This meant that it was possible to perform the exercises with high intensity even for those with e.g. apraxia or aphasia and that the participants did not have to transfer the learned tasks to other similar tasks, an ability that seems to be reduced among people with dementia.133,134

In contrast to a systematic review evaluating the effects of strength exercise,78 the effect of the exercise intervention was not less in people with lower physical functional capacity. This might be a result of the use of the HIFE Program, which was developed to be adaptable for people with different functional levels, including those needing help with all mobility. Hence, the participants with lower physical functional capacity could exercise at an intensity similar to that among those with higher physical functional capacity. Furthermore, people with depression also achieved a similar intensity in the exercises and had a level of attendance similar to those without depression. This seems to contribute to people with depression not deriving less benefit from the exercise programme. Nor did the amount of depressive symptoms have a negative impact on the effects. The relatively high attendance and exercise intensity among people with depression, as well as among the other investigated subgroups, suggest that the exercises suited the participants well and that the physiotherapists in the study, all experienced in working with people with severe physical and cognitive impairments, were able to motivate and stimulate the participants.

One might expect that the presumably reduced ability to increase muscle mass among residents with malnutrition would have negatively influenced the exercise effects on functional balance, since muscle mass is correlated to muscle strength which in turn is of importance when performing physical daily activities.78,80 However, the subgroup interaction analysis regarding the effect on functional balance directly after the 3-month exercise period actually revealed a tendency (p = 0.09) for the exercise to have been more beneficial for people with malnutrition. This trend was also seen when MNA was analysed as continuous variable (p = 0.07). The reason for this tendency in the interaction analysis seems to be that people with malnutrition in the control group, in contrast to the other groups, declined in function. One explanation of why a high-intensity exercise programme did not have a negative effect among those with malnutrition might be that the higher energy expenditure in the exercise group stimulated the appetite with higher nutrition intake as a consequence. Unfortunately, nutrition intake was not measured in this study. Another
explanation might be that the exercise programme mainly affected neuromuscular function, which might be a less nutrition dependent process than achieving muscle hypertrophy. Apart from people with malnutrition, females and those of high age might also have limited muscle hypertrophic responses. That neither of these subgroups derived less benefit from the exercise intervention strengthens the explanation that the improved physical function was achieved, above all, by improved neuromuscular function.

**Physical exercise among people with dementia disorders**

The systematic review that was carried out in this thesis found some evidence of a positive effect of physical exercise on ADL and walking performance among people with Alzheimer’s disease. This is not in agreement with a previous systematic review by Forbes et al. published 2008, which concluded that there was insufficient evidence to say whether or not physical exercise programmes are beneficial for people with dementia. Compared to that review, the present review includes results of the effects on physical functions and is based on ten randomised controlled trials, of which eight are not included by Forbes et al. Contrary to Forbes et al., the present review reports some evidence for a positive effect on ADL. The main reason for this difference is that the results from the analyses in the original paper by Rolland et al. were used in the present review, while Forbes et al. re-analysed the results. Forbes et al. found no statistically significant effect on ADL after the intervention, which is in contrast to the results reported in the original paper. The differences in the results seem to be due to Rolland et al. having included more participants in the analyses compared to Forbes et al., and also adjusting the analyses for baseline values of the outcome measure which is of importance in reducing the risk of bias. Surprisingly, the study by Rolland et al. showed no effect on balance. The reason for the lack of effect seems to be the use of a crude and too challenging outcome measure (able to stand on one leg).

In the two studies in the systematic review that showed positive effects and were of moderate methodological quality, the exercises performed were task-specific and were intended to challenge the individual’s physical capacity. The effects in these two studies are supported by studies by Dick et al., which have shown that people with dementia are able to improve their motor skills but it seems important to exercise in the same or a similar movement pattern to which the improvement is aimed at. Also the results from the FOPANU Study support the view that combined functional weight-bearing exercise programmes that challenge the individual’s physical capacity are a promising method for influencing overall ADL performance among people.
with dementia. In the FOPANU Study the effect on ADL among people with dementia was not sustained three months after the exercise period. Unfortunately, none of the studies with a positive effect in the present systematic review reported whether or not the benefits of the exercise interventions were sustained after the exercise programmes ended. In one of the studies of moderate methodological quality in the systematic review, the physical exercise intervention had no effects on mobility. Compared to the two studies of moderate methodological quality that reported positive effects there are some differences that may explain this absence; the exercise period was shorter (2 weeks compared to 12 months and 16 weeks, respectively), the intervention also included exercises that were not task-specific in relation to the outcome measures, and the intensity of the exercise was unspecified.

In a recently published systematic review by Angevaren et al., aerobic exercise with an intensity that improves cardiorespiratory fitness has been reported to be beneficial for cognitive functions among healthy older people. However, whether physical exercise can improve cognitive functions among people with dementia remains unclear. Four studies specifically evaluated the effects on cognitive functions in the present systematic review, but only one of them reached moderate methodological quality. This study by Eggermont et al. reported no effects after walking exercise at a self-selected speed over six weeks. The apparently low intensity of the aerobic exercise, in addition to the short intervention period, might have been crucial for the absence of effects in this study. Two studies of low methodological quality, evaluating combined exercise including aerobic exercise, also reported the effect on cognitive function. In the study by Kemoun et al. a positive effect was reported which might be explained by the intervention period being longer (15 weeks), use of progression in the physical exercise, and the intensity of the aerobic exercise seemed to be higher compared to the study by Eggermont et al. In the intervention by Steinberg et al., no effect was reported. In that study there was limited data on compliance and use of progression in the exercise, which makes comparison with other studies difficult. Thus, to draw valid conclusions in the future about the effects of aerobic exercise on cognitive functions among people with dementia, more studies of high methodological quality are needed, which report the achieved intensity in the exercise interventions or the effects on cardiovascular fitness.

In general, the studies included in the systematic review did not provide any detailed descriptions of the interventions regarding the exercises in the programmes, intended and achieved intensity level, use of progression in the exercises, and use of individual adjustments. For reproducibility, study comparison and application in clinical practice, these factors in physical exercise
interventions have to be described comprehensively. In addition, before interventions are applied in clinical practice, an estimate must be made as to whether the desirable effect outweighs the undesirable. Unfortunately, only three studies in this systematic review reported the presence of adverse events. None of these three studies, evaluating combined exercise, reported any major adverse events.

**Ethical Considerations**

Physical and cognitive impairments, which contribute to dependence in ADL, are common among people living in residential care facilities. Therefore, there is a great need to develop effective physical exercise programmes that target this group. Despite that, people with physical and cognitive impairments are often excluded from studies and, consequently, there are relatively few studies that have evaluated the effects of physical exercise among people living in residential care facilities. It seems unethical to exclude people living in residential care facilities from evaluations of interventions that are effective for other groups of older people. In this thesis, the effect of a high-intensity functional exercise programme was evaluated among older people living in residential care facilities. However, when performing high-intensity exercise in this group of older people there might be a high risk of adverse events. Before the planning of the FOPANU Study, the research group had experienced two clinical interventions with similar exercise intensity; one study among older people living in residential care facilities and one among older women with residual mobility problems following hip fracture. In neither of these studies, did any severe adverse event occur. To minimise the risk of adverse events in the FOPANU Study, the residents’ physicians had to approve participation in the study and the physiotherapists who supervised the exercise were experienced in working with older people with multiple diseases, including those with severe physical and cognitive impairments. Furthermore, during the exercise intervention the physiotherapists had the possibility to consult the participant’s physician or nurse if there were any questions about the participant’s health and the participants had the possibility of discontinuing the study at any time without giving reason.

In the FOPANU Study there was a high proportion of people with severe cognitive impairment. Among people with severe cognitive impairment, it can be difficult to obtain adequate informed oral consent to participate in a study because this group may have difficulties understanding what the study involves. Therefore, when appropriate because of cognitive impairments, oral consent to participation was also obtained from the residents’ relatives, in order to confirm the will of the resident.
A further problem from an ethical perspective was that half of the residents did not take part of the exercise intervention, but were allocated to a control activity that was held five times during each period of two weeks. Since the residents would spend a lot of time in the research project it was important from an ethical perspective that the control activity should be interesting and stimulating for older people, including those with severe cognitive impairment. The high attendance in the control group indicates that the participants found the activities stimulating.

**METHODODOLOGICAL CONSIDERATIONS**

*The FOPANU Study (Papers I-IV)*

Papers II-IV follow most of the recommended issues that are important for methodological quality in a clinical trial e.g. randomised allocation, concealed allocation, blind assessors, intention-to-treat analysis, and attention control comparability. However, one limitation in Paper III, regarding the assessment of ADL, was that the interviewed licensed practical nurses or nurses’ aide were not blinded to group allocations. However, they were blinded to the study hypotheses and the physiotherapist who asked the questions was blinded to group allocations. These factors may have reduced the risk of bias. Apart from the staff, the participants in the FOPANU Study were also blinded to the study hypotheses. One reason for this approach was to reduce expectations of a negative outcome (i.e. nocebo effect) on e.g. physical functions among the participants who were allocated to the control activity. A limitation in Paper III is that the Barthel ADL Index is a rather crude outcome measure and minor differences are not detectable. Furthermore, no statistical power calculation was made for that outcome measure. The statistical power in the FOPANU Study was calculated on the effects between the exercise and control groups for the BBS. This also implies that the statistical power in interaction analyses might have been low and there is a risk of type II error. Consequently, even though 191 participants were included in the FOPANU Study, larger randomised controlled trials are needed in the future to evaluate whether the exercise programme has an effect on overall ADL performance and to replicate the results that showed that none of the investigated subgroups benefited less from a high-intensity functional weight-bearing exercise programme. Furthermore, a limitation in Paper I was that the scales used to assess the intensity of strength and balance exercises were not tested for interrater reliability. However, the scales were defined before the intervention started, and all physiotherapists were instructed in on how to use them.

For safety reasons, participants who had sustained a hip fracture within the past 6 months or had a hip prosthesis were not assessed for lower-limb strength in a leg press machine in Paper II. This approach contributed to a large loss of
assessments, reducing the statistical power and influencing the possibilities of generalising the positive long-term effect to whole sample. It would probably have been a better strategy to assess the non-affected leg in unilateral 1 RM, where the affected leg could have been placed in a resting position beside the leg press machine.

In the FOPANU Study no specification of type of dementia disorder was reported. The reason for this was that the data for type of dementia disorder were not of sufficiently high quality. Many of the residents included had been diagnosed several years previously. To investigate whether the participants had contracted an additional dementia disease or to specify the type of dementia in participants with a newly detected dementia, a more comprehensive investigation including e.g. neuropsychological tests and assessments with structural imaging (computed tomography or magnetic resonance imaging) would have been necessary. It is a strength in the FOPANU Study that a specialist in geriatric medicine evaluated the documentation of diagnoses, drug treatments, assessments, and measurements for completion of the final diagnoses. Dementia diseases were diagnosed using the DSM-IV criteria. Some degree of under-diagnosing could still be present. However, using the MMSE score to analyse the impact of cognitive function on applicability and effect of the programme provided similar results, in Papers I and IV respectively, as using diagnosis of dementia.

The number of registered adverse events in Paper I seems valid, although participants with severe cognitive impairment were included in the study and the collection was limited to the exercise sessions. However, there may have been adverse events related to the exercises that were not recorded. To improve the quality of data concerning adverse events, information was collected by the physiotherapist in direct connection to the exercise session in order to reduce the impact of memory decline.

The exclusion at baseline of people with an MMSE score of less than 10 or with needing more than one helper to rise from a chair limits the external validity of the FOPANU Study. The reason for only including people with an MMSE score of 10 or higher was based on clinical experience that those people are able to follow simple instructions in exercise and test situations as well as provide reliable responses to uncomplicated questions regarding their current experiences of the exercises. The latter is supported by studies that have shown that people with severe cognitive impairment are able to express a meaningful opinion of their quality of life.202,203 The reason why the participants, to be included in the study, had to be able to rise from a chair with help from not more than one person was that it should be possible for a single physiotherapist to support the participant with the exercises. However, the effect in the
FOPANU Study may be applicable to many older people in residential care facilities since the inclusion criteria were fairly wide, intention-to-treat analyses were used, and the proportion of people who declined to participate in the study was relatively low (27%) and there were no differences between them and those that were included regarding age, sex, and Katz ADL Index score.

The systematic review (Paper V)
In the systematic review, five methodological quality items related to internal validity were developed as a complement to the assessment by the PEDro scale. One limitation was that the validity and the inter-rater reliability of these five items and the rating scale for overall methodological quality were not evaluated. However, the face validity seems reasonable since the rationale for each of the five items was supported in the literature and, regarding the reliability, a consensus method was used to resolve disagreements between raters. In addition, a statistician was consulted when there was doubt among the reviewers about how the analyses were performed. Another limitation of the present systematic review is that neither the size of the effects nor their clinical relevance are discussed. Lack of presentation of the between-group differences in terms of e.g. mean differences (with confidence intervals) in all studies with significant effects makes these estimations difficult. Furthermore, the results from the studies included in this review did not provide any information about whether the effect differed depending on sex, age or type of dementia disorder, or whether the intervention was cost-effective. These remain important areas for future research. An additional limitation is that no systematic estimation was made of whether the tests used in the included studies were reliable, valid, and sensitive to change among people with dementia. However, the four studies of moderate quality have all used established tests and reported references of validation or reliability studies.\textsuperscript{180,183,185,187} The resources only allowed the inclusion of studies published in English or in a Scandinavian language. There could be studies published in other languages that might have affected the conclusion. Data in the systematic review may also be incomplete because of publication bias (i.e. missing studies) or selective reporting bias (i.e. missing data from the included studies).\textsuperscript{189} The authors of the review did not have the resources to assess whether or not publication or reporting bias are present. The assessment of these biases will be easier in the future when more studies and their protocols can be identified from trials registries.
CLINICAL IMPLICATIONS

The main clinical implication of this thesis is that a high-intensity functional weight-bearing exercise programme (the HIFE Program) appears to be applicable and to have clinically meaningful effects in older people living in residential care facilities, especially in people with dementia. This is of great importance, since physical impairments are common among people living in residential care facilities and contribute to dependence in ADL,7,8 which often deteriorates over time.7,21 Based on clinical experience, older people of high age, female sex, with dementia, depression, malnutrition, or severe physical impairment, all common characteristics of people living in residential care facilities, are at higher risk of not being offered comprehensive rehabilitation, including exercise with high intensity. However, according to the results in this thesis, the exercise programme appears to be applicable and beneficial for people with these characteristics.

The HIFE Program can easily be clinically implemented due to the well-described exercises and the fact that the procedure for selecting exercises for each individual is standardized. In addition, all the necessary equipment is portable, thus making it possible to exercise without transfer to a training facility. For people living in residential care facilities, to be able to exercise with high intensity safely, it is probably necessary for their physicians to approve participation and for an experienced physiotherapist to plan and supervise the exercise.

The benefit of task-specific exercise used in the HIFE Program is supported by the systematic review of the scientific literature among people with dementia. Physical exercise may be a useful and important rehabilitation method among people with dementia and there is no support for offering people with dementia less rehabilitation in clinics, as has been reported.9

IMPLICATIONS FOR FUTURE RESEARCH

Future research is needed to determine whether the results of applicability and the effects of a high-intensity functional weight-bearing exercise programme can be replicated among people living in residential care facilities and whether the positive effects are sustained over a longer follow-up period. It is also important to evaluate the cost-effectiveness of the programme. In the FOPANU Study the residents with the most severe physical and cognitive functions were excluded. In the future it is also important to design studies that evaluate the applicability and effects of high-intensity functional weight-bearing exercise in this group. Furthermore, it seems that the capacity of producing muscle power is more strongly associated with functional performance than
muscle strength. In addition, studies among older people that have compared traditional strength exercise with explosive strength exercise have shown greater improvements in functional abilities. Consequently, in future research involving more explosive strength exercise in the HIFE Program is motivated.

One possible explanation for the lack of increased exercise effect from the protein-enriched energy supplement in the FOPANU Study may be that the participants had poor nutritional status, indicating a negative energy balance. Thus, the protein might have been absorbed as energy to compensate for this. Nutritional status was assessed by using the MNA. However, to be able to confirm whether lack of effect was due to a negative energy balance, the participant’s total nutritional intake and energy expenditure need to be measured in future research evaluating protein-enriched energy supplementation.

In future research there is also a need for more exercise studies evaluating the effects on physical and cognitive functions, and ADL among people with dementia, especially among people with dementia disorders other than Alzheimer’s disease and people with dementia living in independent housing. It is important that the exercise interventions are described comprehensively and that the studies are of a high methodological quality, covering aspects related to the type of intervention and sample, and reporting extensive data on applicability and on effects both in the short and long term.
GENERAL CONCLUSIONS

Among older people who are dependent in ADL, living in residential care facilities, and have an MMSE score of 10 or more, a high-intensity functional weight-bearing exercise programme that includes lower-limb strength and balance exercises in standing and walking, is applicable for use with regard to attendance, achieved intensity and adverse events. The exercise programme is also applicable for use among people with dementia. When performed over a period of 3 months, the exercise programme has positive long-term effects on functional balance, gait ability, and lower-limb strength. An intake of a protein-enriched energy supplement immediately after the exercises does not appear to increase the effect on physical functions. High age, female sex, dementia disorder, depression, malnutrition, or severe physical impairment do not seem to have a negative impact on the effect on functional balance. Consequently, people with these characteristics living in residential care facilities should not be excluded from offers of rehabilitation including high-intensity exercises. Furthermore, the exercise programme seems to reduce ADL decline related to indoor mobility and may, in people with dementia, prevent decline in overall ADL, but continuous training may be needed to maintain the effect.

The positive results regarding the applicability and effects of combined functional weight-bearing exercise among people with dementia is confirmed when the scientific literature is systematically reviewed. It seems to be important that exercise interventions among people with dementia last for at least a few months and that the exercises are task-specific and intended to challenge the individual’s physical capacity. Whether physical exercise can improve cognitive functions among people with dementia remains unclear. There is a need for more exercise studies of high methodological quality among people with dementia disorders.
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