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PhD thesis

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Mobility in older acutely admitted and primary care patients – in-hospital physical activity and simple strength training

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Acknowledgements

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List of papers and manuscripts

This thesis consists of 3 papers and 1 manuscript, which will be referred to with roman numerals.

I. Pedersen MM, Bodilsen C, Petersen J, Beyer N, Andersen O, Lawson-Smith L, Kehlet H, Bandholm T. 24-hour mobility during hospitalization in older medical patients. J Gerontol A Biol Sci Med Sci. 2013 Mar;68(3):331-337. doi: 10.1093/gerona/gls165.

II. Pedersen MM. Petersen J, Bean JF, Damkjær L, Juhl-Larsen HG, Andersen O, Beyer N, Bandholm T. Feasibility of progressive sit-to-stand training among older hospitalized patients. Accepted for publication in PeerJ, November 2015.

III. Pedersen MM, Beyer N, Petersen J, Bandholm T. Supervised progressive in-hospital and post-discharge strength training compared with usual care in older medical patients: study protocol for a randomized controlled trial (the STAND-Cph trial). Submitted to Trials, November 2015.

IV. Pedersen MM, Holt NE, Grande L, Kurlinski LA, Beauchamp MK, Kiely D, Petersen J, Leveille S, Bean JF. Mild Cognitive Impairment Status and Mobility Performance: An Analysis from the Boston RISE Study. J Gerontol A Biol Sci Med Sci. 2014 Dec; 69(12):1511-1508; doi: 10.1093/gerona/glu063

Papers I-II and Manuscript III represent Studies I, II and III, which were performed at Clinical Research Centre, Copenhagen University Hospital, Hvidovre from November 2012 to December 2015. In the initial plan for the PhD, Study III should have been reported as an RCT, but due to slow inclusion the last patients are currently being recruited. To keep the study blinded, data analyses will await completion of the data collection. Consequently, only the methods of Study III are presented, in the form of a trial protocol-manuscript currently submitted for publication. Paper IV represents Study IV, which was performed at the Department of Physical Medicine and Rehabilitation, Spaulding Rehabilitation Hospital (SRH), Boston, Massachusetts, in the spring of 2013. Paper IV was not originally a part of the PhD plan. It has been included in the thesis because it reflects work performed at SRH during the PhD study, and because it provides information about the association between mobility and cognition in older adults, which is of importance when designing rehabilitation for older medical patients.

The following papers are not included in the thesis, but reflect work done while being a PhD student:

1) Bodilsen C, Pedersen MM, Petersen J, Beyer N, Andersen O, Lawson-Smith L, Kehlet H, Bandholm T. Acute hospitalization of the old medical patient: changes in muscle strength and functional performance during hospitalization and 30 days after discharge. Am J Phys Med Rehabil. 2013 Sep;92(9):789-96. Doi: 10.1097/PHM.0b013e31828cd2b6.
2) Buhl SF, Andersen AL, Andersen JR, Andersen O, Jensen JB, Rasmussen AM, Pedersen MM, Damkjær L, Gilkes H, Petersen J. The effect of protein intake and resistance training on muscle mass in acutely ill old medical patients – A randomized controlled trial. Clin Nutr. 2015 Mar 5. pii: S0261-5614(15)00073-4. doi: 10.1016/j.clnu.2015.02.015. [Epub ahead of print]
3) Marla K Beauchamp, Cathy Schmidt, Mette Pedersen, Jonathan F Bean, Alan Jette. Psychometric properties of the Late-Life Function and Disability Instrument: a systematic review. BMC Geriatrics 2014, 14:12. doi: 10.1186/1471-2318-14-12.
4) Schepker CA, Leveille SG, Pedersen MM, Ward RE, Kurlinski LA, Grande L, Kiely DK, Bean JF. The Association of Pain and Mild Cognitive Impairment with Mobility. Submitted.
5) Lawson-Smith L, Petersen J, Jensen PS, Sivertsen DM, Pedersen MM, Ellekilde G, Lindhardt T, Andersen O. Nutritional risk in acutely admitted older medical patients. American Journal of Food and Nutrition, 2015, Vol. 3, No.3, 84-89. doi:10.12691/ajfn-3-3-4
6) Bjerre MCK & Ingstrup L. ActivPAL3™: A valid tool for quantifying slow gait in frail elderly populations? An explorative validity study. (Bachelor Thesis in Danish; role as a study supervisor for MCK Bjerre and L Ingstrup).

List of abbreviations

ADL	Activities of Daily Living
aMCI	Amnestic mild cognitive impairment
CAS	Cumulated Ambulation Score
DEMMI	The de Morton Mobility Index
DSST	Digit Symbol Substitution Test
F8W	Figure of 8 Walk
HG	Hand Grip strength
HGS	Habitual Gait Speed
HVLT	Hopkins Verbal Learning Test
iADL	Instrumental Activities of Daily Living
ICF	The World Health Organization's International Classification of Functioning, Disability and Health
LLFDI	Late Life Function and Disability Index
mdMCI	Multiple domain mild cognitive impairment
MCI	Mild cognitive impairment
MMSE	Mini Mental State Examination
naMCI	Non-amnestic mild cognitive impairment
NMS	New Mobility Score
No-MCI	No mild cognitive impairment/cognitively intact
RM	Repetition Maximum
SPPB	Short Physical Performance Battery
STS	Sit-To-Stand
VRS	Verbal Ranking Scale

1. Terminology and definitions

The World Health Organization's International Classification of Functioning, Disability and Health (ICF) provides a framework for classification of disability and health and for the description of health and health-related conditions across populations (Figure 1)(1,2). The ICF was developed to be a scientific basis for understanding and studying health and for standardizing data on health and disability (1,3) and the concepts of the ICF will be used throughout this thesis.

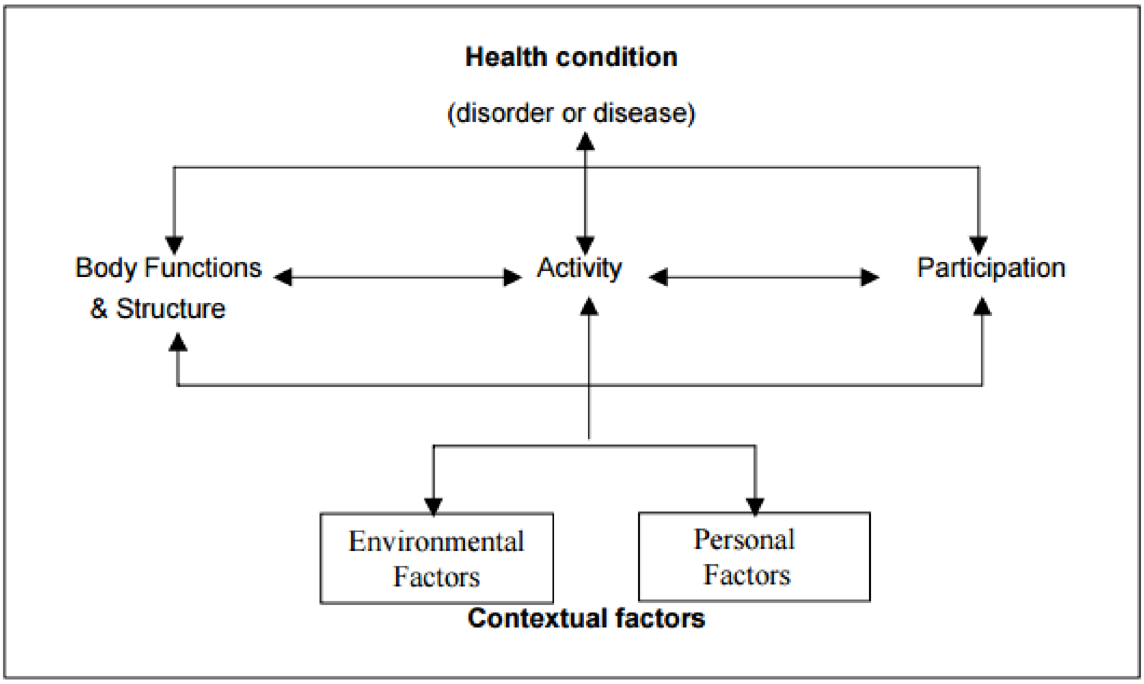


Figure 1. The International Classification of Functioning, Disability and Health (2).

In the ICF, functioning is an umbrella term for human functioning on three levels: the body (all body functions and structures), the whole person (activities), and the person in a social context (participation). Body functions and structures cover the physiological functions of body systems and anatomical parts of the body, activity covers how the individual performs a task or an action, and participation covers how the individual is involved in a life situation (2,3). Like functioning, disability is an umbrella term for dys-functioning on the three levels: impairments (in body functions), limitations (in activities) and restrictions (in participation). Both functioning and disability result from interactions between health conditions and contextual factors that can influence an individual's level of functioning and disability (1–3). Contextual factors cover environmental factors, e.g. the social and physical environment, and personal factors, e.g. age, gender, background, behavior (1–3).

Different nomenclatures have been used to describe the disablement process, amongst others Nagi's disablement model from the 1960's and the precursor of the ICF, the WHO's International Classification of Impairments, Disabilities, and Handicaps (ICIDH) from 1980 (1,3). Moreover, in the WHO classification, a shift has taken place from focusing on disability to focusing on health and functioning. This use of different nomenclatures is reflected in a great variation in the use of concepts like disability, impairment etc. throughout studies. Thus, in the ICF model disability is used as an umbrella termt for dys-functioning, in the ICIDH disability is used to describe lack of ability to perform an activity (individual level), and in the Nagi-model disability describes a limitation in performing social roles and tasks (1,3). When referring to the results of the included studies in this thesis, the terminology used by the authors will be used even though the terminology does not correspond with the terminology of the ICF model. Instead, wherever possible an ICF definition will be added in parenthesis, e.g. functional impairments (ICF: activity limitations). Also, in research literature "mobility", which is a sub-dimension of both the Activities and Participation components of the ICF (1,3), is used to describe abilities on all levels of the ICF, i.e. mobility disability, mobility impairments, mobility limitations, and mobility restrictions. Mobility is described by Drs. Brown and Flood as "more than a person's physical ability to walk or move and encompasses considerations of a person's environment and his or her ability to adapt to it" and mobility disability as "the gap between an individual's physical ability (e.g., muscle strength or balance) and environmental challenges such as walking outdoors on uneven surfaces" (4). Throughout this thesis, the term mobility will be referenced as used in the literature, with the terms "disability", "impairments", "limitations" and "restrictions" as indicators of the corresponding level of the ICF, and will not be followed by a parenthesis with corresponding ICF definitions. The terms "level of mobility", "mobility level" and "24-hour mobility" will be used to denote time spent active and "mobility" to describe abilities as mentioned above, that is the ability to climb stairs, walk, transfer, rise from a chair etc.

Rehabilitation is defined as "a set of measures that assists individuals who experience, or are likely to experience, disability to achieve and maintain optimal functioning in interaction with their environments" (5).

Basic mobility is defined as the ability to get in and out of bed, sit and stand from a chair and walk, as measured by the Cumulated Ambulation Score (CAS)(6).

2. Introduction

2.1 The aging population

In Denmark, as in the rest of the world, the population is aging (7,8) and the number of adults ≥65 years is expected to double over the next 30 years (9). Today, older adults ≥65 years constitute 18% of the population (1 million) in Denmark (10) and this number is estimated to increase to 25% in 2040 (11). The prevalence of disability increases with age (5,8), which along with increasing life expectancy, challenges the health care system (7,8) due to increasing expenses for health related services like hospitalization, medications, public health insurance, and home care (12). Among older Danes (≥65 yrs) in 2005, 37.4% reported mobility limitations, i.e. difficulty walking 400 meters, climbing a flight of stairs without rest or carrying 5 kg (13), compared to 17.4 % in the younger population.

2.2 Age related changes – functioning and disability

2.2.1 Muscle mass and aging

Aging is associated with loss of muscle mass, -strength and -power (14–16) increasing the risk of adverse outcomes like falls, mobility limitations, and disability (14,16,17). From the age of 20 to 80, muscle mass declines by 30% as a result of normal aging processes (18). This decline results from a loss of both slow (Type I) and fast (Type II) muscle fibers (14,19), combined with a conversion of Type II fibers to Type I fibers, due to an accelerated loss of fast motor units (14,18). This is reflected by a shift in activities favoring activities of daily living and submaximal exercises like walking, requiring primarily Type I fibers (18).

The maintenance of skeletal muscle mass requires a balance between muscle synthesis and muscle breakdown (14,20,21), and the decline in muscle mass seen with age is due to a reduction in the rate of protein synthesis, e.g. due to decline in growth hormone (14,22), or a rise in breakdown due to increased levels of inflammatory markers (e.g. inflammatory cytokines), and increased levels of catabolic hormones (e.g. cortisol) (14,21), or a combination of the two (20,22,23). This imbalance can be explained by anabolic resistance, i.e. a decreased ability of diet and exercise to stimulate muscle protein synthesis (21–24), which can possibly be reversed by the intake of protein or performing exercise (18,20,21,24,25). Therefore, older adults depend more on exercise than young to maintain a balance between breakdown and synthesis (25).

2.2.2 Muscle mass, muscle strength and functioning

The age-related change in muscle mass and loss of fast muscle fibers, along with infiltration of fat in the muscle and impairments in neural activation, can explain the loss seen in muscle strength and the loss of ability to generate the strength needed to perform everyday activities like rising from a chair, climbing stairs, or maintaining balance (14,26). From the age of 30, a decline in muscle strength of 10-15% per decade is seen (27). It is well recognized that muscle mass is related to muscle strength (14,17,19,27–29), and that the decline in strength goes beyond the decline in mass, suggesting a change in muscle quality (28–32). The Health ABC study, a large cohort study following 1880 initially well-functioning older adults, evaluated changes in muscle mass and muscle strength in the knee extensors over three years (28). The loss of muscle strength was three fold greater (3% per year) than the loss of muscle mass (1% per year), indicating a decline in muscle quality (28). In the same cohort study, both lower muscle mass and lower muscle strength were found to be associated with increased risk of mobility limitations (17), and lower muscle strength was associated with greater risk of hospitalization and death (33,34). A review on the influence of muscle mass and muscle strength on physical performance (26) found that a higher proportion of studies on muscle strength, than studies on muscle mass, found an association with physical performance.

Several studies have evaluated characteristics associated with disability and other adverse events. The InCHIANTI study has evaluated risk factors for mobility disability in old age (16) in a cohort of 1030 adults (20-102 yrs) living in Tuscany, Italy. Independent of age, they found low muscle strength and -power to be associated with poor mobility defined by a gait speed below 0.8 m/s and inability to walk 1 km (16). Similarly, a systematic review investigating physical performance characteristics related to disability in older adults (35) found an association both between upper and lower body strength, lower gait speed and a sedentary lifestyle, respectively, and a higher probability of disability. Furthermore, the relationship between muscle strength and self-reported Activities of Daily Living (ADL) performance has been elucidated. A prospective study in 567 older adults (≥75 yrs), independent in ADL at baseline, showed muscle strength to be associated with future (5 years) ADL dependence (36). Also, in the EPESE study (37), a longitudinal study of 4588 community-dwelling older adults (≥65 yrs), who initially reported no disability in ADLs, walking a half mile, and climbing stairs, physical performance measures (gait speed, balance, sit-to-stand) were found to be significant predictors of developing mobility disability and ADL disability up to 6 years later (37), as well as institutionalization and death (38). Also, a systematic review by Cooper et al (39) found that those who performed less well on four measures of physical capability

- grip strength, gait speed, chair rise time, and balance – were at higher mortality risk. Taken together, this indicates that maintaining muscle strength, physical performance and activity is important in older adults to avoid disability, dependence, hospitalization and death.

2.2.3 Functional reserve capacity

The age-related decline in muscle strength and mobility implies that older adults do not possess the same functional reserve capacity as younger adults (16,40–43) putting them at risk of falling beneath a threshold for muscle strength where functioning is limited (44). Functional reserve capacity has been defined as ”the difference between a person’s maximal capacity and the minimal capacity required to perform a specific task or maintain a specific level of activity” (45). Thus, older adults with low functional reserve capacity are at greater risk of developing disability and loosing independence (45,46). This risk of losing independence when having a low reserve capacity, is illustrated in a study examining the role of strength in rising from a chair in both young adults and functionally impaired (ICF: activity limited) older adults, characterized by inability to descend stairs without using the handrail and inability to rise from a 33 cm chair (47). The study showed that the older adults required 78% of their available knee extension strength, compared to 34% in the young, to successfully rise from a chair at knee height, and up to 97% to rise at the lowest possible chair height, compared to 39% in the young (47). Thus, in these older adults knee extension strength was a limiting factor in functional performance (i.e. chair rise ability) and additional loss of strength could lead to disability and reduced functional reserve capacity inducing a risk of falling beneath a threshold for independence. Especially maintaining independence and mobility are considered important health outcomes by older adults (48,49).

A greater functional reserve capacity may provide the individual with more resistance towards disability, e.g. as a consequence of disease (36). Indeed, the increase in disability with age is closely related to the occurrence of various diseases, including hypertension, osteoarthritis, cardiovascular disease, lung dysfunction, diabetes and stroke (50), and additionally these diseases are given as self-reported causes of onset of disability in older adults (51).

2.2.4 Factors associated with disability – cognition and physical inactivity

Cognition

As mentioned, loss of muscle strength and the onset of disease are some of the factors associated with disability. Research has pointed to a range of other determinants including cognition and inactivity. Similar to a decline in muscle mass and -strength, a decline in brain weight of about 2-3% per decade is seen (52). A decline in cognitive function is part of the normal aging process and co-exists with decline in physical function (53–56). Thus, in community-dwelling older adults, cognitive impairments as well as mobility limitations, and the accumulation of both, can affect the ability to live independently (57–59). The relationship between cognition and functioning remains to be fully elucidated, but there is a growing body of literature on the subject. A systematic review (54) has found baseline physical functioning to be associated with future changes in cognition, whereas baseline cognition was only marginally associated with future physical functioning - according to the authors possibly due to a limited number of studies examining this association. However, in older adults bidirectional associations between cognition and functioning have been found, with signs of onset of ADL disability as an indicator of the rate of cognitive decline (60) and cognitive level as a predictor of incident mobility impairment (61). Also, functional decline and slowing of gait have been found to coexist with (56) or precede (62,63) cognitive decline in older adults.

It is estimated that among older adults (≥65 yrs) the prevalence of mild cognitive impairment (MCI) is between 10 and 20% (64). MCI is defined as cognitive decline greater than that expected for one's age and education level, but which does not interfere appreciably with daily function (64,65). Thus, MCI is considered a subclinical state, which may remain unreported or undetected for a period of time (66). MCI is a well-known risk factor for dementia (66,67), and people with MCI are at increased risk of gait impairments (ICF: gait limitations), and falls (68). Thus, older adults with MCI may be an especially vulnerable group, why it may be essential to better understand the association between cognitive status and mobility performance.

Physical inactivity

The level of physical activity decreases with age (69,70). In 2005, in Denmark, the percentage of adults who did not engage in leisure-time physical activity was 12.7% for those aged 65-74, compared to 10.6-11.2% for younger age groups, and 27% for those aged 75-84 (13,70).

As mentioned earlier, in older adults a sedentary lifestyle contributes to increased levels of inflammatory markers (71) known to increase muscle protein breakdown (14,21,71). Equally, studies in healthy older adults have shown that restricted activity and bed rest are associated with reduced protein synthesis and a decline in muscle mass and -strength (72–76) as well as a decline in instrumental Activities of Daily Living (iADL), mobility, and physical- and social activity (77). Even merely reducing the daily amount of steps to ≤1500 over a fortnight (≈76% reduction from 3500 steps/day) in 10 healthy older adults led to a 4% reduction in leg muscle mass, a 26% reduction in postprandial muscle protein synthesis, and a 43% reduction in insulin sensitivity (78), indicating that even less extreme forms of inactivity can have negative effects on skeletal muscle. Furthermore, older adults seem more sensitive to bed rest inactivity than younger adults (72,73,79,80) with an impaired ability to fully recover (72,79). In addition, it seems that in older adults episodes of bed rest are accompanied with a decline in physical activity (74,77), creating a possible vicious circle of inactivity.

The lower extremities are especially sensitive to bed rest and reduced activity (73,76,78,81). A study in 12 healthy older adults undergoing 10 days of induced bed rest found an average loss of 1.5 kg lean mass in the whole body, of which 0.95 kg were lost in the lower extremities (73). Also, reduced daily activity has been found to significantly affect lower extremity lean mass, but not upper extremity lean mass (78). This focus on loss of lower extremity muscle strength and –mass in bedrest and inactivity studies is possibly due to the importance of lower extremity strength on functional performance (e.g. mobility and the ability to perform ADL) (82–86). Also, in a study of 1462 older women (≥75 yrs), lower knee extension strength relative to body weight was associated with limitations in self-reported mobility, chair rise ability and usual and fast gait speed (86). Similarly, Manini et al. (87) found knee extensor strength to be indicative of future risk of mobility limitations.

Taken together, this illustrates that in older adults, inactivity and bed rest are associated with loss of muscle mass, muscle strength and functioning with the lower extremities being especially sensitive. Therefore, it seems reasonable to seek to avoid inactivity and maintain lower extremity strength to prevent disability. Indeed, a link has been shown between inactivity (88), lower muscle strength and functioning (i.e. gait speed and repeated chair stand time) (34) and increased risk of hospitalization.

2.3 Older medical patients

In Denmark, older adults (+65 yrs) are hospitalized more often than the rest of the population. In 2010, 90% of older Danes above the age of 90 were admitted to the hospital, compared to 40% between the age of 65 and 74 and 20% between the age of 15 and 64 (11).

The older medical patient (≥65 yrs) is characterized by one or more of the following: severe illness, co-morbidity, functional disability, cognitive impairments, polypharmacy, low self-care capacity, and a need for assistance from the municipality (9,89). In 2009, older medical patients accounted for 34% (115.000) of all hospital admissions, 53% of all admissions to Danish medical wards, and 66% of all in-patient days in Danish medical wards (9). More than 80% of the older medical patients were admitted acutely (90) and 18% of the acute admissions were re-admissions (9). Also, more than one third was hospitalized for one day or less (90).

2.3.1 Consequences of hospitalization

Inactivity and functional decline during hospitalization

In older adults (+65 yrs) a low level of mobility (91–96) and episodes of bed rest (91–94) are common during hospitalization, and a low in-hospital mobility level has been shown to be associated with a decline in ADL during and after hospitalization (92–94), new institutionalization (92) and increased risk of death (92,97). Moreover, associations have been found between pre-admission decline in ADL function and low in-hospital activity (96), which was low whether or not the patients were independent in ADL and walking ability before and on admission (91–96,98). Also, in healthy older adults episodes of bed rest have been shown to be associated with a subsequent decline in physical activity (74,77) - which is likely to be the case in hospitalized older adults as well - and may create a risk of re-admission within 30 days (99).

Throughout the last decade, a change has occurred in how the level of mobility is measured in older hospitalized adults. There has been a shift from assessing the level of mobility via hallway observations (98) and nurse reports (92) to objective measures like step counts (96) and accelerometer-based assessments of mobility level (91,95,100,101), enabling a more accurate assessment of mobility level throughout the entire hospital stay. However, by the time of designing Study I for this thesis, only one study had used accelerometers in assessing mobility level continuously throughout hospitalization in older adults (91), and none had compared the level of mobility with a daily assessment of basic mobility (ability to get in and out of bed, sit and stand from a chair and walk). Since then, more studies have evaluated in-hospital mobility level in older adults using accelerometers (95,97). Common to these studies in hospitalized older adults is a picture of a low mobility level during hospitalization and an association between a low mobility level and adverse events like new institutionalization and death (91,95,97).

In two prospective cohort studies in 498 (92) and 684 (93,94) older medical patients, mobility level was assessed during hospitalization via nurse reports based on identical mobility index'. In both studies, 80% were independent in ADL before admission. Also, corresponding levels of in-hospital mobility were seen: sixteen percent and 18%, respectively, were classified with a low mobility level (bed rest or bed to chair transfers), 32% and 30.1% with an intermediate mobility level (ambulation one or two times per day with total assistance), and 52% and 51.9% with a high mobility level (ambulation two or more times with partial or no assistance). What is more, Brown et al. (92) found low and intermediate levels of mobility to be associated with an increased risk of decline in ADL, new institutionalization and death, even after controlling for illness severity and comorbidities (92). Zisberg et al. (93,94) found that 42% percent of the included patients reported decline in ADL function at discharge, and 46% at 1 month follow-up. Further, those who experienced decline in ADL before hospitalization were less likely to be highly mobile during their hospitalization than those who did not (45% vs 84%), and in-hospital mobility level was highly related to both ADL decline at discharge and at 1 month follow-up (94).

Self-reported functional decline (ADL function) is commonly reported in older adults before and during hospitalization (92,93,102–106). Moreover, a study investigating the effect of hospitalization in older adults not restricted to bed, who were not admitted with acute illness, but for diagnostic investigation (107), found that during 5 days of hospitalization, significant declines in functional capacity, i.e. upper extremity muscle strength, and 6-min walk test, were seen. Studies in older medical and geriatric patients have discovered that 43-64% experience a decline in ADL function in the two weeks prior to hospitalization (103,104,108), 1-17% experience a decline during hospitalization (103,104,106,108,109), and 39-40% are discharged with worse ADL function than two weeks before admission (102,104,108,110). This self-reported decline is seen even after short hospital stays (105). Moreover, it seems that more than 20% of older medical patients report new disabilities in ADL and iADL 3 months after discharge (102,110), which can increase the risk of institutionalization (111). Also, lack of ability to regain function during hospitalization is independently associated with 3-month mortality (112).

In a study by Boyd et al. (102) in 2279 older medical patients, evaluating independence in ADL 2 weeks prior to hospitalization, at admission, and 1,3,6 and 12 months post discharge, 35% were discharged with worse ADL than 2 weeks before admission, and had poorer functional outcomes at follow-up than those discharged without additional disability. Also, 41.3% of those who were discharged with additional disability had died within 1 year and barely one third of the patients returned to their pre-admission level within the first year after discharge. Also, those who had recovered to their baseline level within the first month after discharge had better long term outcomes than those not recovering by one month (102). However, those who decline in ADL before and during hospitalization have been reported to be less likely to recover within the first month after discharge, compared to those remaining stable in ADL (106), stressing the importance of avoiding functional decline during hospitalization. In addition, the significance of the first month after discharge is highlighted by the fact that in Denmark, 18% of admissions of older adults are readmissions (within 30 days after discharge) (89). Interestingly, older adults with cognitive impairment have been shown to have higher risk of functional decline during hospitalization (109,113,114) and after discharge and to be less likely to recover compared to patients without cognitive impairment (113,115), making them an especially vulnerable group.

Hospitalization has been linked with a general loss of functional reserve capacity, and thereby an increased risk of losing independence (46,116). Several risk factors for loss of function during and after hospitalization have been identified, amongst others age (103,104,114,117), cognitive impairment (104,109,113,117), functional status before hospitalization (104,114,117), co-morbidity and polypharmacy (114,117), mobility level (92,93,117,118), a history of falls (104) and nutritional status (93,117,118).

2.3.2 Rehabilitation

Functional status by the time of discharge from hospital seems important, as it has been shown to be associated with the ability to fully recover (102), readmission rate (119), and mortality (102). Moreover, in a cohort of older adults, hospitalization was associated with a subsequent loss of muscle strength (120), putting hospitalized older adults at a higher risk of losing independence as a consequence of their hospitalization, and in greater need of rehabilitation (46). Maintaining independence is considered the most important health outcome by many older adults (48). Therefore, preventing inactivity as well as loss of muscle strength and functional performance during hospitalization may well be a way of preventing adverse events including re-admissions, loss of independence, institutionalization, and death. Moreover, regaining function within the first month after discharge seems especially important as one-month status can be indicative of functional status one year after discharge (102).

According to the Danish Healthcare Quality Programme (DDKM) (121), the functional level and nutritional status of hospitalized patients must be described within 24-48 hours after admission (89) and treatment planned accordingly. No standards exist for in-hospital training (89), but patients needing recovery (e.g. rehabilitation) should be identified and provided with a rehabilitation plan targeting the patient’s impairments and limitations (122). In spite of this, of 4611 older medical patients admitted to Hvidovre Hospital in 2012, only 252 (5.5%) were discharged with a rehabilitation plan, indicating rehabilitation potential.

Exercise programs (strength training)

Systematic strength training has been shown to improve muscle strength and functional performance in healthy and frail older adults, and nursing home residents (23,123–126). However, only few studies have investigated the effect of strength training during (127) and after hospitalization (128) in older medical patients. Two of these studies found positive effects of 10 weeks of lower extremity strength training on leg muscle strength and functional performance in older patients recovering from acute illness on a geriatric ward (127) and older medical patients newly discharged from a geriatric ward (128). However, one study encountered recruitment problems and concluded that an in-patient exercise program for acutely admitted older medical patients was not feasible (129). Positive effects on strength and functional performance have been found in community-dwelling older adults performing at-home lower extremity strength training (130).

However, most exercise programs for older hospitalized or community-dwelling adults cover a range of exercises including upper- and lower body strength training, balance- and walking exercises and stretching exercises (129–136). Few have examined the effect of a program initiated during hospitalization and continued after discharge (129,135), and these studies have experienced problems with compliance. However, a recent systematic review suggests that “the recovery of patients could further benefit from a community based or an in-home intervention program which build on in-hospital programs” (137). In addition, acutely hospitalized older adults express that initiating exercise in the hospital or shortly after discharge is a good idea (129,138). Also, exercise than can be undertaken close to or at home is more likely to be taken up by older adults with mobility-related disability (139). The challenges with compliance might be reduced by ensuring supervision and information about the importance of physical activity (137,140,141) as well providing recommendations for activity from a physiotherapist (142). Supervision may also be beneficial on the effect of training (143). This emphasizes the likely importance of supervision from trained staff both in the hospital and in the home setting.

A meta-analysis concludes that physical exercise therapy has a positive effect on mobility and physical functioning in mobility limited and physically disabled older adults, but that it is unclear which type of intervention is most effective although strength training seems important (144). Also, according to recent systematic reviews and meta-analyses, information is lacking about the appropriate dose of strength training in different settings for older adults as well as detailed descriptions of exercises and dosage (123,145,146). However, it seems that higher intensities are superior to lower intensities (144,145,147,148), but that research is required to elucidate the effect of higher intensities on older adults with chronic health conditions (147).

When constructing an exercise program for hospitalized older adults, it seems reasonable to focus on counteracting loss of strength and functional performance in the lower extremities thereby addressing the impairments (low muscle strength) and limitations (poor functional performance) seen in these patients (149,150). Especially since the lower extremities are sensitive to bed rest (73,81) and lower extremity strength is associated with functional performance, i.e. mobility, chair rise ability, and the ability to perform ADL (17,82–87,151,152), future risk of ADL and mobility limitations (35,87), hospitalization and death (17).

Combining strength training with protein supplementation may be even more beneficial than strength training alone as it may stimulate muscle protein synthesis and thus increase the exercise response on muscle mass and strength as seen in healthy older adults (153–155). In healthy adults, both strength training and amino acids have been shown to be potent anabolic agents, and the administration of amino acids and carbohydrates after strength training may induce a greater increase of muscle protein synthesis than either of the two (156). However, a consistent effect of protein supplementation on muscle mass and function is lacking (157).

A well-described, supervised and simple cross-continuum strength training program including repeated sit-to-stand exercises was chosen for Study III. The program was designed to: focus on the lower extremities and comply with the importance of both supervision and location (home) for adherence; be described in detail and ensure high intensity training; investigate if a minimum treatment approach is sufficient; be feasible to perform within a busy care setting and in a home setting after discharge, requiring only minimal equipment; and be combined with protein supplementation to enhance the exercise response on muscle.

2.4 Summary

In summary, aging is associated with declines in muscle mass and –strength, physical performance and mobility, increasing the risk of adverse events like disability, hospitalization and death. Also, a decline in cognitive function is part of the normal aging process, and can affect the ability to live independently, why it may be important to better understand the association between cognitive status and physical performance. The increase in disability with age is related to the occurrence of various diseases, and older adults (+65 yrs) are hospitalized more often than the rest of the population. A low level of mobility during hospitalization is commonly reported in older adults and associated with adverse events; e.g. functional decline, institutionalization, and death. In-hospital levels of mobility have previously been assessed subjectively, but in the last decade objective measures have taken over. However, only few have assessed in-hospital mobility continuously throughout hospitalization in older adults, and combined this assessment with a daily assessment of basic mobility. Functional decline before and during hospitalization is often reported in older adults, and barely one third seem to return to their pre-admission level within the first year after discharge. Also, functional status by one month after discharge has been shown to be an indicator of long term outcome. Besides, hospitalization seems associated with a subsequent loss of muscle strength and functional performance putting hospitalized older adults at a higher risk of losing independence as a consequence of their hospitalization. Therefore, reducing inactivity and loss of muscle strength and functional performance in connection with hospitalization may be a way of preventing loss of independence. Older hospitalized adults have been shown to display poor muscle strength and functional performance. Systematic strength training can possibly prevent further loss of muscle strength and functional performance, but few studies have examined the effect of a cross-continuum exercise program initiated during hospitalization and continued after discharge. In addition, details are lacking regarding the appropriate nature and dose of training. Higher intensities seem superior to lower intensities, and supervision seems critical in enhancing compliance to training. Moreover, combining strength training with protein supplementation may enhance the muscular response to training (i.e. muscle mass and strength). Additionally, the lower extremities are most sensitive to bed rest and inactivity, why a strength training program focusing on the lower extremities may be the right choice in counteracting hospital-associated inactivity and functional decline.

3. Objectives and hypotheses

The main objectives of the studies included in this thesis were: to investigate 24-hour in-hospital mobility of older medical patients acutely admitted to Hvidovre Hospital, Denmark; to validate the accelerometers used; and to test the feasibility and effect of simple, supervised, cross continuum strength training aiming at avoiding mobility decline in connection with acute hospitalization. In addition, a secondary objective was to describe the association between mobility performance and MCI in older community-dwelling primary care patients.

3.1 Study I

3.1.1 Objectives

To quantify 24-hour mobility and the daily level of basic mobility during hospitalization both in a group of older medical patients who were able to walk independently before admission and in a reference of patients who were unable to walk independently, and to develop and validate an algorithm to quantify in-hospital mobility using accelerometers (Augmentec Inc., Pittsburgh, PA, USA).

3.1.2 Hypotheses

During hospitalization older medical patients spend the majority of their time sitting or lying. Accelerometers can validly quantify in-hospital mobility in older medical patients.

3.2 Study II

3.2.1 Objective

To test the feasibility of a model for progressive sit-to-stand training (STAND) in older medical patients in the hospital and in the patients' own homes.

3.2.2 Hypothesis

The STAND model can be used as a progression model for sit-to-stand strength training in older medical patients.

3.3 Study III (protocol manuscript for ongoing study)

3.3.1 Objective

To investigate if a simple, low technology, supervised strength training program for the lower extremities, combined with post-training protein supplementation initiated during hospitalization and continued for 4 weeks after discharge is superior to usual care on change in mobility 4 weeks after discharge.

3.3.2 Hypothesis

Strength training and protein supplementation will be superior to usual care on change in mobility 4 weeks after discharge.

3.4 Study IV

3.4.1 Objective

To examine the association between MCI and MCI subtypes and mobility in older primary care patients.

3.4.2 Hypothesis

Patients with MCI and all subtypes of MCI are more limited in performance-based and self-report measures of mobility than patients without MCI, and patients with non-amnestic MCI perform worse than those with amnestic MCI.

4. Methods

Inclusion of patients for Studies I-III took place in the Emergency Department at Copenhagen University Hospital, Hvidovre, Denmark. Patients were included by random sampling based on a computer-generated list using the patients' social security numbers. Patients for Study IV were recruited through primary care practices at the medical centers of Massachusetts General Hospital (MGH) and Brigham and Women's Hospital in Boston, Massachusetts, USA. An overview of the study designs in the four studies is presented in Table 1.

Table 1. Overview of study designs for Studies I-IV.

STUDY AIM	DESIGN	INVESTIGATORS	INCLUDED PATIENTS	STUDY SAMPLE	MAIN OUTCOMES
I. To quantify 24-hour mobility and the daily level of basic mobility during hospitalization both in a group of older medical patients who were able to walk independently before admission and in a reference of patients not able to walk independently, and to develop and validate an algorithm to quantify in-hospital mobility using accelerometers.	Prospective cohort study. Patients assessed on admission and daily throughout hospitalization.	Two skilled physiotherapists.	68 patients who gave written informed consent. 49 patients consented to wear accelerometers.	42 ambulatory and 6 non-ambulatory patients.	• In-hospital 24h mobility level assessed by accelerometers (Augmentec Inc) • The Cumulated Ambulation Score Explanatory variables: • The New Mobility Score • The Charlson Index • The Mini Mental State Examination • The Verbal Ranking Scale
II. To test the feasibility of a model for progressive sit-to-stand training (STAND) in older medical patients in the hospital and in the patients' own homes.	Prospective cohort study conducted as a feasibility study. Patients assessed once on admission and once in their own homes after discharge.	Two skilled physiotherapists.	24 patients who gave written informed consent.	23 tested on admission. 19 tested at home.	• Feasibility of STAND • Training load and level • The Borg Scale • The Verbal Ranking Scale Explanatory variables: • The de Morton Mobility Index • The Short Orientation-Memory-Concentration test
III. To investigate the effect of a simple, low technology, supervised strength training program for the lower extremities, combined with post-training protein supplementation, during hospitalization and continued for 4 weeks after discharge (protocol-manuscript).	Randomized, controlled, investigator-blinded trial.	Four skilled physiotherapists.	Aim: 80 patients giving written informed consent. Study still ongoing and data collection not completed.	Aim: 54 patients with complete data sets.	Primary outcome: • The de Morton Mobility Index Secondary outcomes: • 24h mobility level assessed by accelerometers (PAL Technologies Ltd) • Isometric knee extension strength. • Handgrip strength. • Habitual gait speed • 30-sec chair stand
IV. To investigate the association between mild cognitive impairment (MCI) and MCI subtypes and mobility in older primary care patients.	Prospective cohort study. Patient assessments at baseline.	A nurse practitioner and a research assistant.	430 patients who gave written informed consent.	430 with baseline data.	Dependent variables • Habitual gait speed • The Figure of 8 Walk • The Short Physical Performance Battery • The Late Life Function and Disability Index Explanatory variables • The Trail Making test • The Digit Symbol Substitution test • The Hopkins Verbal Learning test, revised

4.1 Inclusion and exclusion criteria

The inclusion and exclusion criteria for Studies I-IV are presented below (Table 2).

Table 2. Inclusion and exclusion criteria for Studies I-IV.

Common inclusion criteria for Studies I-III	**Common exclusion criteria for Studies I-III**
• ≥65 years of age • Acute medical admission from own home	• inability to give informed consent to participate • inability to co-operate in measurements • inability to understand or communicate in Danish • diagnosis of chronic obstructive pulmonary disease (COPD) and participation in a COPD rehabilitation program • isolation-room stay • transferal to intensive care • terminal illness
Additional inclusion criteria	**Additional exclusion criteria**
Study I • co-morbidity	Study I • an expected hospitalization of 2 days or less • inability to walk with or without a walking aid Studies II-III • an expected hospitalization of 1 day or less • inability to rise from a chair with assistance • in treatment for diagnosed cancer Study III • living outside the municipalities of Copenhagen, Broendby or Hvidovre • assigned to physical rehabilitation in the municipality by the time of admission
Inclusion criteria Study IV	**Exclusion criteria Study IV**
• ≥65 years of age • Community-dwelling • Ability to understand and communicate in English • self-reported difficulty with walking half a mile or climbing one flight of stairs	• inability to give informed consent to participate • terminal disease • significant visual impairment • uncontrolled hypertension • amputation of a lower extremity • use of supplemental oxygen • myocardial infarction or major surgery in the previous 6 months • planned major surgery • planned move from the Boston area within 2 years • Mini Mental State Examination (MMSE) score <18 • Short Physical Performance Battery (SPPB) score < 4

All patients gave written informed consent before participating in the studies. In Studies I-III a template from the National Committee on Health Research Ethics, Denmark, was used (available at: www.cvk.sum.dk). Studies I-III were approved by the Ethics Committee of the Capital Region of Denmark (numbers 06072010-1631 and H-2-2012-115) and by the Danish Data Protection Agency (2007-58-0015). Study III was registered at ClinicalTrials.gov (NCT01964482). All procedures in Study IV were approved by the Institutional Review Board of Spaulding Rehabilitation Hospital, Cambridge, Massachusetts.

4.2 Assessments and main outcome measures

All assessments followed standardized testing protocols to ensure assessment consensus. For Studies I-III the admission assessments were performed at the Emergency Department or an internal medicine ward at Hvidovre Hospital within the first 48 hours after admission. For Study I follow-up assessments were performed in the patient's bedroom at the hospital, and for Studies II-III follow-up assessments were performed in the patients' own homes. For Study IV the assessments took place at the Clinical Research Center of MGH and at Spaulding Rehabilitation Hospital Cambridge, Massachusetts. For all studies, descriptive data and self-report outcome measures were assessed via patient registries and by questionnaire based interviews (see Papers I-II+IV and Manuscript III for further details). Table 3 provides an overview of the main outcome measures.

4.2.1 Study I

Forty-nine patients were included in this prospective cohort study aiming at evaluating 24-hour mobility and basic mobility during hospitalization, and developing and validating an algorithm for quantifying mobility using accelerometers. Forty-three patients were ambulatory on admission (median age 84.7 (IQR 78.6; 87.2); 45% women) and 6 were non-ambulatory (median age 82.8 (IQR 79.9; 88.0); 76% women). The patients underwent a structured baseline interview during the initial 48 hours of the hospital stay, including explanatory variables: the self-reported New Mobility Score (NMS) (158) to assess functional independency (in retrospect two weeks before admission and in retrospect over the day of admission); the Charlson Index (159) as a measure of co-morbid conditions on admission; the Mini Mental State Examination (MMSE) (160) to assess cognitive function on admission; and the Verbal Ranking Scale (VRS) (161) as a measure of pain. The mobility level during hospitalization was assessed by two wireless accelerometers (Augmentec Inc., Pittsburgh, Pennsylvania, USA). An algorithm-identification of lying, sitting, and standing/walking was developed based on pilot data. The algorithm was cross-validated on six older medical patients, not included in the primary study, who wore the accelerometers under supervision, following pre-defined behaviors. Basic mobility was assessed by the Cumulated Ambulation Score (CAS) (6,162) within 48 hours of admission, and repeated daily throughout hospitalization.

Table 3. Overview of main outcome measures.

OUTCOME	STUDY	METHODS	PROCEDURE	DATA REDUCTION
Mobility				
24h mobility	I+III★	I: Patient-worn accelerometers 24h/d during hospitalization. III: Patient-worn accelerometers 24h/d during hospitalization and for 1 week following the three follow-up assessments*.	I: Two wireless monitors (Augmentech Inc., Pittsburgh, PA) attached 15 cm above the patella and 15 cm above the ankle joint, respectively, anteriorly on the patient's right leg. III: One activPAL3™ wireless monitor attached to the patient's right thigh.	I: Hours per day spent lying, sitting and standing/walking. III: Hours per day spent lying, sitting/standing and walking.
Basic mobility	I	The Cumulated Ambulation Score. Evaluated on admission and daily throughout hospitalization.	Investigator administered score sheet followed. Quantification of ability to get in and out of bed, sit-to-stand from a chair, and walk.	Total score in points (0-6).
Assessor observed mobility	III★	The de Morton Mobility Index. Evaluated at all four assessments**.	Investigator administered score sheet followed. Quantification of ability to perform 15 hierarchical mobility challenges.	Total score in points (0-100).
Feasibility				
Feasibility of the STAND progression model	II	Sit-to-stand strength training exercise tested in the hospital and at home.	Standard chair 45 cm. Aim to perform 1-3 sets at 8-12 RM following the model.	Level of exercise (STAND), number of sets performed, and repetitions in each set.
Pain	II	The Verbal Ranking Scale. Evaluated before, during, and 10 minutes after the exercise.	Investigator administered score sheet. Quantification of pain.	Score in points (0-5) for 8 different body regions.
Perceived exertion	II	The Borg Scale. Evaluated after each set of the exercise.	Investigator administered score sheet. Quantification of exertion.	Total score in points (6-20).
Functional perf.				
Isometric knee-extension strength	III★	Externally fixated handheld dynamometer. Evaluated at all four assessments**	Standard chair 45 cm. Right leg.Four maximal contractions.	Highest value (Nm/kg).
Handgrip strength	III★	Handheld dynamometer. Evaluated at all four assessments**	Standard chair 45 cm with armrests. Dominant hand. Between three and five maximal contractions.	Highest value (kg).
Lower body strength	III★	30-second chair stand test. Evaluated at all four assessments** Alternative: Modified 30-second chair stand test.	Standard chair 45 cm. Arms folded across chest. One stand for familiarization. Repetitive chair stands in 30 seconds. If unable to stand with arms folded over chest then use of armrests. Repetitive stands in 30 seconds.	Number of full stands (no).
Habitual gait speed	III★+IV	4-meter gait speed test. III: Evaluated at all four assessments** IV: Evaluated at baseline.	Habitual speed with or without habitual walking-aid on a 4-meter course. Start from standing position. Two trials.	Fastest (sec) of two trials.
Curved path walking	IV	The Figure of 8 Walk. Evaluated at baseline.	Walk in a figure of 8 around two markers at habitual speed. Start from standing position in the middle between the markers.	Time to complete the figure of 8 walk (sec).
Lower extremity performance	IV	The Short Physical Performance Battery. Evaluated at baseline.	Composed of three tests: • Timed balance: side-by-side stand; semi-tandem stand; full tandem stand • Habitual gait speed on 4-meter course. • Five repeated chair stands preceded by one test stand.	Total score (0-12).
Self-reported perf.				
Activities of Daily Living	III★	Barthel 20 index. Evaluated at all four assessments**.	Investigator administered questionnaire. Quantification of ability to perform 10 activities of daily living.	Total score (0-20).
Self-reported activity limitation	IV	The Late Life Function and Disability Index – the Basic Lower Extremity subdomain (BLE) and the Advanced Lower Extremity (ALE) subdomain. Evaluated at baseline.	Investigator administered questionnaire. Quantification of ability to perform pre-defined activities.	Total BLE score (0-100) and total ALE score (0-100).

★Data collection for Study III is still ongoing. Hence, data reduction has not yet been performed; *discharge, 4 weeks after discharge and 6 months after discharge; **admission, discharge, 4 weeks after discharge and 6 months after discharge.

4.2.2 Study II

Twenty-four patients (mean age 77 (SD 7); 50% women) were included in this prospective cohort study to test the feasibility of a model for progressive sit-to-stand training in the hospital and in the patients' own homes. The patients were assessed within 48 hours of admission to the hospital and in their own homes shortly following discharge. On admission the patients underwent a structured baseline interview including functional independence (measured by the NMS in retrospect 2 weeks before admission and in retrospect over the day of admission) and explanatory variables: the Short Orientation-Memory-Concentration test (OMC) as a measure of cognition (163,164); and the de Morton Mobility Index (DEMMI) (165) to quantify the patient's mobility level before performing the exercise. The DEMMI was also assessed at the home visit. A progression model for sit-to-stand as a strength training exercise (STAND) was developed (Figure 2). At two time points the patients were tested for their ability to perform the exercise for 1-3 sets at a relative load of 8-12 repetition maximum (RM) for 8-12 repetitions: in the hospital within 48 hours of admission, and shortly following discharge in their own homes. The exercise was considered feasible if three criteria were met: 1) 75 % of the assessed patients could perform the exercise at a relative load of 8-12 RM at both time points (1 set in the hospital; 2 sets at home); 2) no ceiling or floor effect was seen; 3) no adverse events were observed. For each set of training at both time points the level of the model, the extra load added (kg), the number of repetitions performed, and perceived exertion using the Borg Scale (166) were recorded. Pain was assessed with VRS (167) before and after the DEMMI test and before, during, and 10 minutes after the exercise.

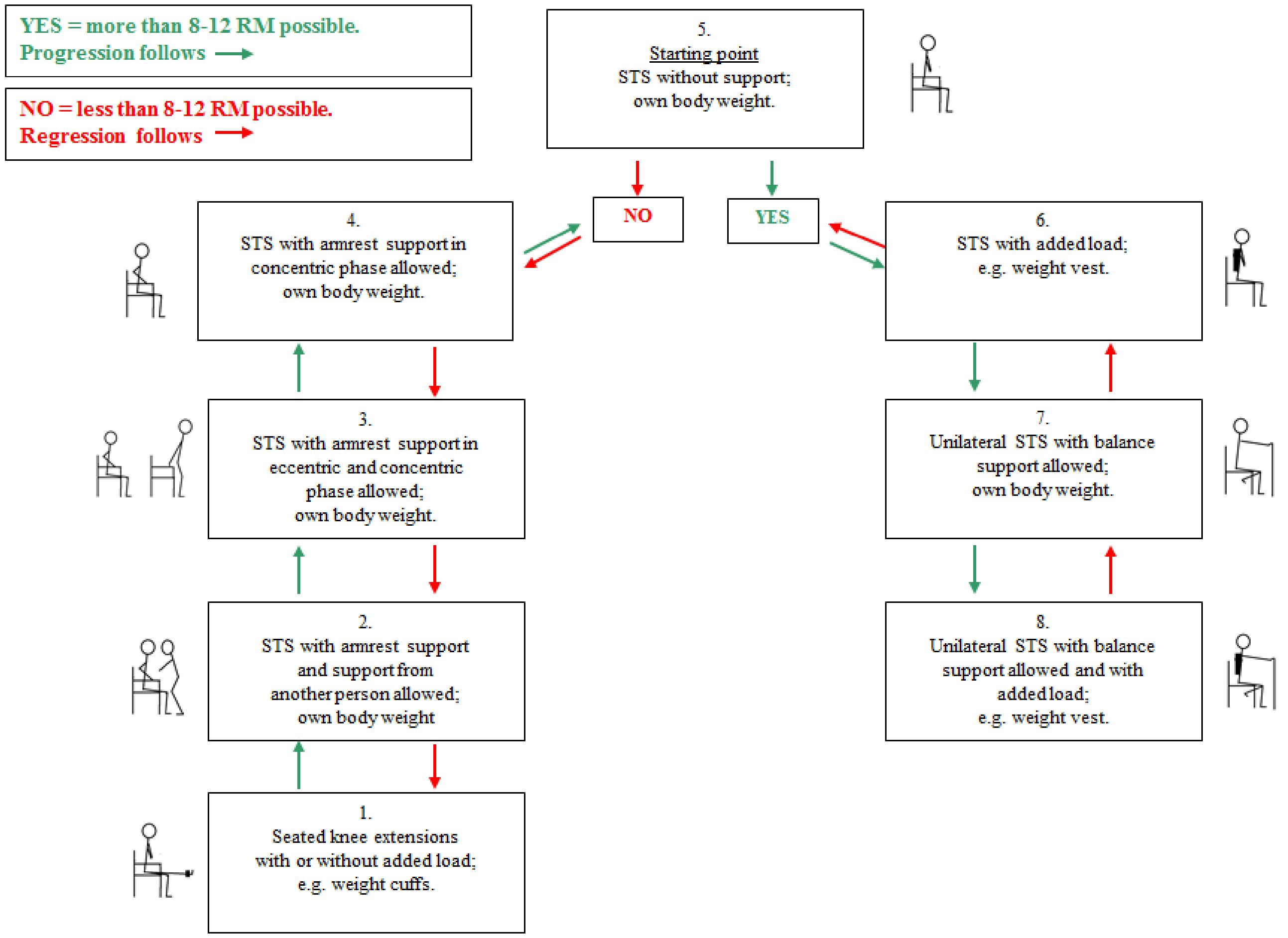


Figure 2. Progression model for loaded sit-to-stand exercise (STAND).

STS: Sit-to-stand; 8-12 RM: 8-12 repetitions maximum (a zone in which muscular fatigue should be reached.)

4.2.3 Study III

In total, 80 patients (≥65 yrs) will be included in this ongoing randomized, controlled, investigator blinded trial to investigate the effect of a simple, low technology, supervised strength training program for the lower extremities, combined with post-training protein supplementation, during hospitalization and 4 weeks after discharge. Patients are randomly allocated to one of two groups: 1) strength training during hospitalization (training every day), and for 4 weeks after discharge (3 training sessions per week); 2) usual care. Prior to study start, physiotherapists in the hospital and in the involved municipalities have been trained in the intervention, and all training sessions are supervised on a 1:1 basis. Each training session starts with a 5-min warm up program. After the warm-up the patients are asked to perform two strength training exercises (sit-to-stand and heel-raise) for 3 set of 8-12 repetitions at 8-12 RM following models of progression based on the STAND model (see Study II). Training loads are adjusted for each set to reach the aimed relative load (RM). The total duration of each training session is approximately 10-15 minutes. Protein is

considered an integrated part of strength training why the patient is asked to consume an oral protein supplement (Nutridrink Compact Protein from Nutricia A/S), containing 18 g milk-based protein and 300 kcal, immediately after each training session. During each training session the supervising physiotherapist completes an exercise diary containing information on level and load of the exercise, the number of sets performed, experienced pain, and the amount of protein consumed.
Trained investigators, blinded to the randomization, perform structured interviews and assessments in the hospital within the first 48 hours of admission (baseline), and at three time points in the patient's own home: shortly after discharge, 4 weeks after discharge (primary end point), and 6 months after discharge. The same investigator performs all assessments of the same patient whenever logistically possible.

The primary outcome is change in the DEMMI score from baseline to 4 weeks after discharge (end of intervention, primary end point) (165). The secondary outcomes are 24-hour mobility measured by an *activ*PAL3^{TM} activity monitor (PAL Technologies Ltd, Glascow, UK), isometric knee extension strength (IKE) in the dominant leg using a handheld dynamometer (Power Track II Commander; JTech Medical, Utah, USA) (168,169), the 30-sec sit-to-stand test using a standard arm chair with a seat height of 45 cm (170), habitual gait speed (HG) on a 4-meter course (37,38), hand-grip strength (HGS) in the dominant hand using a handheld dynamometer (Digi-II; Saehan) (171), and the Barthel Index 20 (BI) (172). In addition, a range of possible confounders and modifiers are assessed, including cognitive function, depression, health status, nutritional status, physical activity level, pain, use of medication, and history of training.

Validation of the ActivPal activity monitor

For Study III we chose to change from the accelerometers used in Study I (Augmentec.com) to the ActivPal activity monitors (PAL Technologies Ltd., Glasgow, UK). This was chosen since the ActivPal monitors can record activity continuously for 7 days as opposed to 2 days for the Augmentec monitors. The aim in Study III was to monitor the patients for one week periods after discharge to get a picture of post-discharge activity. Seven days were chosen since 7 days has been shown to provide a good measure of usual physical activity in community dwelling older adults (173). Because of possible limitations using the ActivPal monitors (which will be elaborated in the discussion) we chose to perform a validation study on the ActivPal monitors, which are delivered with an inbuilt algorithm for distinguishing between lying/sitting, standing, and walking. Six healthy adults (28-48 yrs) were included in the study to examine the precision of the ActivPAL activity monitor in measuring step counts and gait at different gait speeds. The participants were asked to walk on a threadmill at 7 different speeds in a random order of 2 minute intervals wearing an ActivPAL™ on the upper right thigh (0.28 m/s; 0.45 m/s; 0.50 m/s; 0.56 m/s; 0.61 m/s; 0.67 m/s and 0.89 m/s). During each 2 minute interval, steps were counted via direct observation. Data from the ActivPal monitors were compared with direct observations for agreement.

4.2.4 Study IV

Four hundred and thirty community-dwelling primary care patients (mean age 76.6 (SD 7); 58% women) were included in this cross-sectional study investigating the association between MCI and mobility based on baseline data from the Boston Rehabilitative Impairment Study in the Elderly (Boston RISE). The patients underwent a structured baseline interview including neuropsychological testing, physical performance testing and questionnaires on functional ability. Neuropsychological tests were used to characterize patients with MCI, and further sub-classify these patient according to their impaired cognitive domain in amnestic MCI (aMCI; memory impairment), non-amnestic MCI (naMCI; non-memory impairment), and multiple domain MCI (mdMCI; memory and non-memory impairment). The cognitive tests included were: 1) the Trail Making Test (TMT), consisting of two sub-tests (Trails A and Trails B) (174,175), 2) the Digit Symbol Substitution Test (DSST) (174,176), 3) and the Hopkins Verbal Learning Test, revised (HVLT-R), consisting of three subtests (total recall, delayed recall, and recognition discrimination) (177,178). MCI was defined as impairment on two sub-tests within the neuropsychological test battery (179). All patients were identified as either cognitively intact (No-MCI) or as having cognitive impairment (MCI). The subtest scores of the HVLT-R were used to define memory impairment, whereas the subtest scores of the TMT and the DSST were used to define non-memory impairment. Performance-based and self-reported mobility was assessed by habitual gait speed (HGS) on a 4-meter straight course (37,38), the Figure-of-8-Walk (F8W) around two cones 1.5 m apart (180), the Short Physical Performance Battery (SPPB) (37,38), and the sub-domains of basic lower extremity function (BLE) and advanced lower extremity function (ALE) of the Late Life Function and Disability Index (LLFDI) (181). Both self-report and performance-based mobility measures were used to investigate the association between MCI domains and mobility.

4.3 Statistical analyses

The main statistical analyses are presented below (for further details, please see Papers I-II+IV and Manuscript III). For all studies descriptive data are presented as means with standard deviations, medians with inter-quartile ranges, or frequencies with percentages depending on variable type. Comparisons between groups (Studies I, III (to be performed), and IV) were analyzed with the χ^2 test for categorical variables, the Student's t-test for normally distributed continuous variables, and the Mann-Whitney U-test for non-normally distributed continuous variables. To compare change in performance measures from pre-admission to admission (Study I) and from admission to at home (Study II) the Wilcoxon Signed Rank test or the paired t-test were used depending on variable type. All data for Studies I-II were double entered and validated in EpiData Entry, version 3.1 (The EpiData Association, Odense, Denmark). For Study IV all data were collected using electronic data collection forms coded with ID numbers, and validated in a technical review by a research team member before being transferred to a master file. For all studies the level of significance was set at $P \leq 0.05$, and all tests were two-tailed. All statistical tests were performed using the Statistical Analysis System (SAS) version 9.2 (Studies I and IV), and version 9.3 (Study II), SAS Institute, Gary, NC, USA.

4.3.1 Study I

To compare hours spent lying, sitting, and standing/walking between days with an independent CAS score (CAS = 6) and a dependent CAS score (0-5), both an unadjusted and an adjusted (adjusted for individual levels of CAS) linear regression were used. Also, a Kruskal-Wallis test was used for associations with potential explanatory variables.

4.3.2 Study II

Linear regression analyses were used to evaluate if the level of STAND depended on mobility (DEMMI) and cognition (OMC), respectively.

4.3.3 Study III

In this randomized controlled trial the estimated sample size for the primary outcome is based on previous research from our hospital (182), where a random sample of 25 older medical patients had a mean change in the DEMMI score of 1.8 from baseline to 30-days follow-up, and a standard deviation of 12.8. In order to detect a minimal clinically important difference of 10 points (183) in the between-group change in the DEMMI score at the four week assessment (primary end point), a sample size of 27 patients per study arm is needed with 80% power and a type I error rate of 5%. A maximum of 80 patients are expected to be included.

4.3.4 Study IV

An analysis of variance (ANOVA) and an analysis of co-variance (ANCOVA) were used to determine associations between each mobility measure and cognitive status comparing MCI vs. No-MCI. First, we adjusted for gender, race and education. Then, cognitive status was entered into the adjusted model as a categorical variable (aMCI, mdMCI, naMCI, and No-MCI) to calculate estimates for differences in mobility measures between all MCI sub-types. In a post hoc analysis further adjustment was made for current health status and chronic conditions. Also, an additional analysis included baseline MMSE status as a categorical variable to explore whether MMSE <24 modified the association between the respective MCI subtypes and mobility.

5. Results

A summary of the main results are listed below. For further details please consult Papers I-II+IV. Since Manuscript III is a trial protocol no results from the study will be reported in this section. However, a status concerning the ongoing inclusion will be given.

5.1 Study I

24-hour mobility during hospitalization in older medical patients.

Sixty-eight patients met the inclusion criteria, 49 of whom agreed to wear accelerometers during their hospitalization. Forty-three patients were able to walk independently (ambulatory patients), and six patients were unable to walk independently (non-ambulatory patients). One of the ambulatory patients was excluded due to lack of accelerometer data. The patients wore the accelerometers for 4.4 days on average. The ambulatory patients were lying in bed 17.0 hours (IQR: 14.4-19.1), sitting 5.1 hours (IQR: 2.9-7.1), and standing/walking for 1.1 hours (IQR: 0.6-1.7) per day. They were significantly more active than the non-ambulatory patients ($p<0.001$) (Figure 3). On days with a CAS score of 6 (independence in basic mobility), the ambulatory patients were lying 4.1 hours less compared to days with a CAS score of 0-5 (dependency in basic mobility) (15.4 versus 19.5 hours; $p<0.001$), they were sitting 2.4 hours more (6.0 versus 3.6 hours; $p<0.001$), and standing/walking 0.9 hours more (1.6 versus 0.7 hours; $p<0.001$).

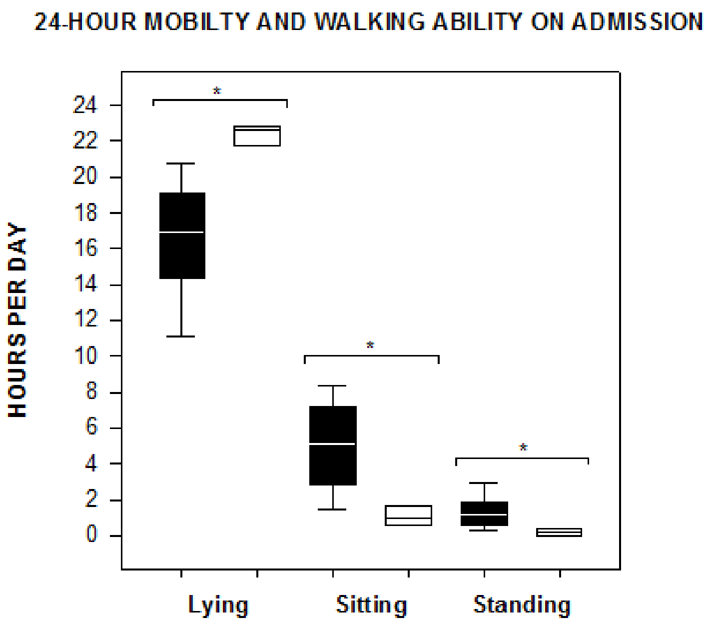


Figure 3. Hours per day spent lying, sitting and standing/walking during hospitalization.

■= *ambulatory patients*

□= *non-ambulatory patient*

Data are given as median (IQR) and 5/95 percentiles.

** denotes statistically significant between-group differences.*

The in-hospital mobility level was independent of pre-admission and admission NMS, co-morbidities and pain. However, patients with a MMSE score >24 were standing/walking significantly more hours during a day than patients scoring <24 (p=0.02). When cross-validating the algorithm based on data from six older medical patients, the algorithm classified time spent lying, sitting, and standing and/or walking with <9.2%, <4.7% and <10.4%, respectively.

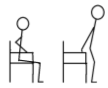
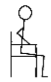
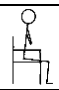
5.2 Study II

Feasibility of progressive sit-to-stand training among older hospitalized patients.

Twenty-four patients consented to participate in the study. A total of 5 patients (20.8%) dropped out of the study; one patient dropped out during the initial examination, leaving 23 patients to be tested at the hospital, and four patients dropped out before the home test, leaving 19 patients to be tested at home. A statistically significant decline in NMS was seen from two weeks prior to hospitalization to admission (from 9 (IQR 5.5;9) to 3 (IQR 2;9); p=0.03); at the home visit the median NMS score was 6.5 (IQR 3;9), but this numerical difference was not statistically significant.

Twenty patients (83%) were able to perform at least one set of 8-12 RM at a given level of STAND in the hospital, and 15 patients (79%) were able to perform two sets of 8-12 RM at home. Half of these could perform three sets of 8-12 RM. The mean Borg score when performing the highest level possible was 14.2 (±1.9) in the hospital and 14.1 (±1.6) at home. Table 4 shows the distribution of patients on the different levels of STAND in the hospital and at home, respectively.

Table 4. Overview over the distribution of patients on the 8 levels of STAND according to the highest level performed in the hospital and at home, respectively.

Level in STAND	Description of level	Illustration	In hospital (n)	At home (n)
1	Seated knee extensions with or without added load, e.g. weight cuffs.		2	0
2	STS with armrest support and support from another person allowed; own body weight.		0	0
3	STS with armrest support in eccentric and concentric phase allowed; own body weight.		2	3
4	STS with armrest support in concentric phase allowed; own body weight.		2	1
5 Starting point	STS without support; own body weight.		6	4
6	STS with added load; e.g. weight vest.		6	4
7	Unilateral STS with balance support allowed; own body weight		1	1
8	Unilateral STS with balance support allowed and added load; e.g. weight vest.		1	2

STS: sit-to-stand

For all patients progression or regression of the exercise was possible, indicating no floor or ceiling effect. Also, no patients reported an increase in pain during or after performing the exercise.

Those scoring higher on the DEMMI performed the exercise at the most challenging levels of STAND (on admission, β=0.10(CI:0.07;0.13), P<0.0001; at home, β=0.07(CI:0.03;0.12), P=0.004), whereas the level of STAND did not depend significantly on OMC (on admission: 0.07(-0.12;0.26), P=0.45; at home: -0.01(-0.42;0.41), P=0.96) (Figure 4).

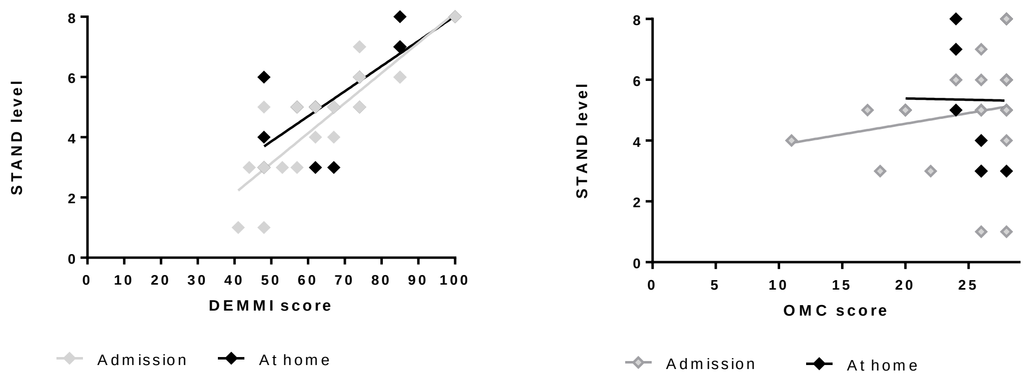


Figure 4. The association between STAND and DEMMI score (Panel A) and OMC score (Panel B), respectively.

STAND level: indicates the level of the model (1 to 8); DEMMI score: score on the de Morton Mobility Index (0-100); OMC score: score on the Short Orientation-Memory-Concentration test (0-28). The higher the score the more difficult level of STAND, the better mobility (DEMMI) and the better cognition (OMC), respectively.

5.3 Study III

Supervised progressive in-hospital and post-discharge strength training compared with usual care in older medical patients: study protocol for a randomized controlled trial (the STAND-Cph trial).

By the time of writing this thesis, inclusion of patients for Study III is still ongoing (December 2015). Seventy-six patients have been included in the study. Of these, 20 have dropped out (26%) – 12 before the discharge assessment, eight before the 4-week assessment, and 1 before the 6 month assessment. Also, five have been excluded from the study (7%) – one was discharged to a rehabilitation unit, two were hospitalized due to apoplexia cerebri at the time of assessment, one was diagnosed with an aortic aneurysm and was to avoid high intensity exercise, and one was enrolled in a pilot project including sit-to-stand training in the municipality at discharge. Thus, 51 patients are enrolled in the study of which 35 have completed all assessments (except for one missing out on the discharge assessment), 13 have completed all but the 6-month assessment, and three have completed the admission and discharge assessments. Due to a higher attrition rate than expected (33% vs. 25%) patients are still being enrolled to ensure a sample size matching the sample size calculation of 54 patients with 4-week assessments (primary endpoint).

Validation of the ActivPal activity monitor

The ActivPAL categorized walked time on gait speeds of 0.56-0.89 m/s with <0.1% error. For speeds of 0.28 m/s, 49.6% of the time was categorized as walking, and for 0.45 m/s and 0.50 m/s, respectively, 88.8% and 86.7% of the time walked was categorized as walking. The ActivPal counted steps with <1% error for gait speeds of 0.61-0.89 m/s. For 0.28 m/s, 43.6% of the steps were registered, for 0.45 m/s, 90.5% of the steps were registered, and 0.50 m/s, 97.2% of the steps were registered by the ActivPal.

5.4 Study IV

Mild Cognitive Impairment Status and Mobility Performance: An Analysis from the Boston RISE Study

In total, 430 participants were included in the study. Of these, 42% were classified as having MCI; 15.8% had aMCI, 22.7% had mdMCI and 3.5% had naMCI. MCI participants performed significantly worse in tests of mobility performance and self-reported functional performance than participants without MCI (e.g. HGS: $\beta=-0.13$, $p<0.01$; SPPB: $\beta=-1.39$, $p<0.01$) even when adjusting for sex, race and education ($p<0.01$) (Table 5).

Table 5. Mean difference given as betas, 95%-confidence intervals and p-values from multiple regression models demonstrating the difference in mobility between those with MCI and without MCI among Boston RISE participants.

	Unadjusted model; β(CI); p-value		Adjusted model 1*; β(CI), p-value	
HGS (m/s)	-0.13 (-0.17;-0.10)	<0.001	-0.12 (-0.16;-0.07)	<0.001
F8W (sec)**	1.19 (1.13;1.27)	<0.001	1.19 (1.13;1.27)	<0.001
SPPB (4-12)	-1.39 (-1.80;-0.98)	<0.001	-1.35 (-1.80;-0.90)	<0.001
BLE	-4.55(-6.84;-2.25)	<0.001	-4.06(-6.48;-1.65)	0.001
ALE	-5.97(-8.74;-3.20)	<0.001	-5.57(-8.43;-2.71)	<0.001

*MCI: mild cognitive impairment; CI: 95% confidence interval; HGS: Habitual gait speed; F8W: Figure of 8 walk; SPPB: Short Physical Performance Battery; BLE: basic lower extremity function; ALE: advanced lower extremity function. * Adjusted for sex, race, and education; **F8W was log2-transformed. Results are given as 2^{β} –coefficients.*

All MCI subtypes performed significantly worse than No-MCI on all mobility measures in the adjusted analysis ($p<0.05$), except for aMCI versus No-MCI on F8W and BLE. Moreover, naMCI patients performed more poorly on a number of mobility tests than aMCI (e.g. SPPB ($p=0.01$) and BLE ($p=0.04$)) (Figure 5). Similarly, patients with mdMCI performed worse on F8W (2^{β} =1.21; $p<0.001$) and SPPB (β=1.07, $p<0.01$) than aMCI (for further details see Paper IV). Adjustment for current health status, chronic conditions and MMSE, respectively, did materially alter the findings.

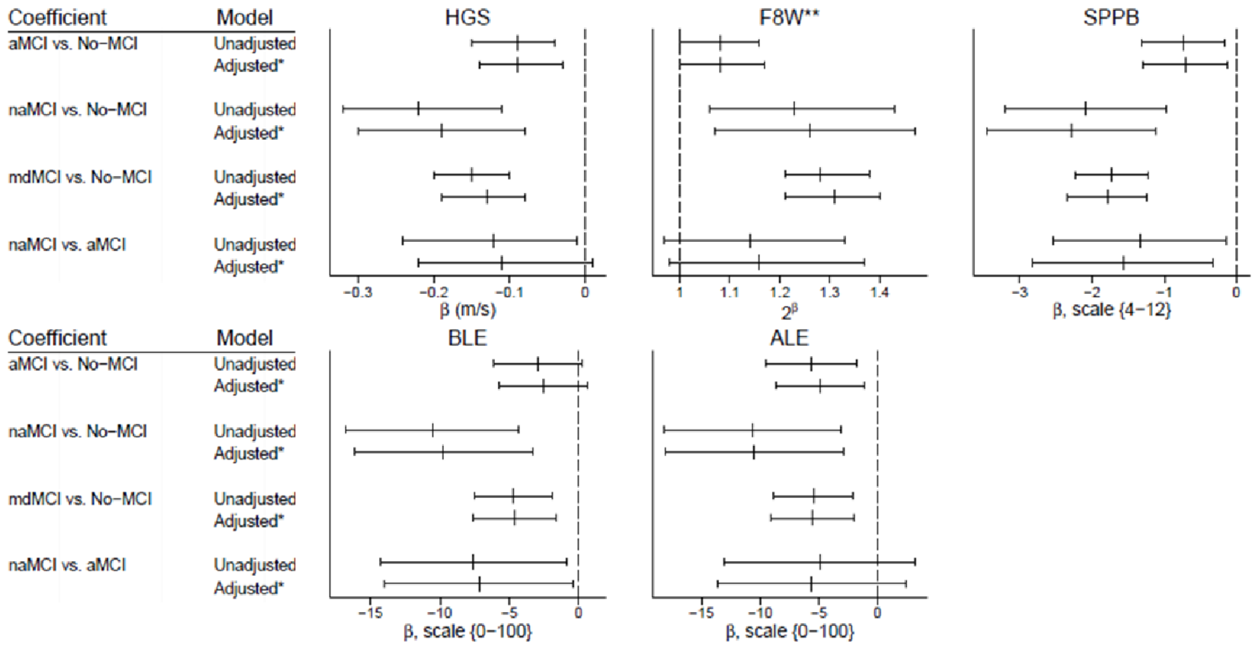


Figure 5. Mean difference given as betas and 95%-confidence intervals from multiple regression models demonstrating the difference in mobility between MCI- subtypes and No-MCI for 5 performance measures among Boston RISE participants. Confidence intervals not crossing the vertical dotted line represent statistically significant values.

*MCI: mild cognitive impairment; No-MCI: No MCI; aMCI: amnestic MCI; mdMCI: multiple domain MCI; naMCI: non-amnestic MCI; HGS: habitual gait speed; F8W: Figure-of-8 walk; SPPB: Short Physical Performance Battery. *adjusted for sex, race, and education;**F8W was log2-transformed. Results are given as $2^β$ –coefficients.*

6. Discussion

This thesis has evaluated 24-hour mobility during hospitalization (Study I), and the feasibility of a progression model for sit-to-stand based strength training (STAND) in the hospital and at home (Study II) in acutely admitted older medical patients. This model is currently being tested in a confirmatory randomized controlled study, for which the study protocol has been submitted for publication and outlined as Study III. Also, the association between different types of MCI and mobility was evaluated in community-dwelling primary care patients (Study IV).

6.1 Key Findings

The key findings of this thesis are:

- A cohort of acutely admitted older medical patients, who were able to walk on admission, were assessed with accelerometers throughout their hospitalization and were found to spend a median of 17.0 hours per day in bed, 5.1 hours per day sitting, and 1.1 hours per day standing or walking. Also, their in-hospital mobility level seemed to depend on their basic mobility (ability to independently get in and out of bed, rise from a chair, and walk), and on cognition.
- An algorithm to measure mobility level in older medical patients was developed and validated for two accelerometers (Augmentec.com) placed on the thigh and lower leg, respectively. The algorithm could discriminate between time spent lying, sitting and standing and/or walking, with a misclassification of 4.7-10.4% of the seconds measured.
- A simple progression model (STAND) for loaded sit-to-stand exercise was found feasible in acutely admitted older medical patients in the hospital- and home setting. STAND could be used to reach a strength-training intensity of 8-12 repetition maximum, with no ceiling or floor effect observed, and with no reported pain as a consequence of performing the exercise. Moreover, no association was found between level of STAND and cognition.
- Among a cohort of primary care patients, performance-based and self-reported mobility was associated with MCI. Those with MCI, and different sub-types of MCI, had worse mobility than those without MCI (also when adjusting for sex, race, and education). Also, mobility appeared to be poorest among those with non-amnestic MCI.

6.2 24-hour mobility

Low levels of in-hospital mobility are commonly reported in older medical patients. In Study I, we found that the included older medical patients, who were independently walking on admission, spent most of their in-hospital time being inactive (17h/day lying). The level of in-hospital mobility corresponded well with levels seen in other studies evaluating in-hospital mobility levels based on accelerometers (95,101) and step counts (96) – i.e. Brown et al. (91) found older medical patients (45 men; age 74±6.5 yrs; mean stay 5.1 days) to spend an average of 20 hours per day in bed, 3.1 hours sitting and 0.9 hours standing or walking; Villumsen et al. (95) found a cohort of geriatric patients (100 patients; 84±6.3 yrs; median stay 13.5 days) to spend 83 minutes per day standing and walking; and Fisher et al. (96) found a cohort of geriatric patients (239 patients; 76±6 yrs; average stay 4.9 days) to spend 57 minutes per day walking, taking 739 steps, and the remaining time being non-mobile. Similar levels of daily steps have been reported by Ostir et al. (97), who found an association between the number of steps taken in the last 24 hours of hospitalization and risk of death within 2 years (for each 100-step increase the hazard ratio decreased by 3%). Likewise, low in-hospital mobility levels have been shown to be associated with increased risk of decline in ADL, new institutionalization and death (92,94), and in older adults with mobility limitations, an association between sedentary behavior and higher odds of metabolic syndrome has been found (184). To the author's knowledge, no studies have evaluated post discharge mobility on a 24-hour basis or the association between in-hospital mobility and post discharge mobility, so whether post discharge levels correspond with those seen in community-dwelling older adults (185) is unknown. This knowledge, however, will be obtained from Study III in which 24-hour mobility will be assessed by accelerometers three times for one week after discharge (at discharge, 4 weeks and 6 months). Nevertheless, the levels of activity seen in hospitalized older adults call for attention in order to avoid the negative consequences seen with low in-hospital mobility levels (e.g. decline in ADL, risk of institutionalization and death) (92–94,97). Study I provides new knowledge about the association between 24-hour mobility and basic mobility (ability to get in and out of bed, sit and stand from a chair and walk), which was assessed daily throughout hospitalization. Independence in basic mobility was found to correlate with daily levels of 24-hour mobility. Thus, it seems that working on solutions to better basic mobility may be one way of improving in-hospital mobility levels. One way of achieving this goal will be evaluated in Study III.

6.3 Assessing 24-hour mobility

Due to the previously mentioned negative effects of low in-hospital mobility, gaining knowledge about in-hospital mobility levels and the characteristics of those with low mobility levels is important. By the time of conducting Study I, only one study had used accelerometers in assessing mobility levels in older medical patients continuously throughout hospitalization (91). Accelerometers can provide an uninterrupted measure of activity as opposed to nurse reports (92), mobility index' (93) and hallway observations (98), and can overcome issues of over- or underreporting by clinicians (92,186), as well as lack of ability to cover every hour of the day (98).

Consistent with Dr. Brown and colleagues (101), in Study I, we found the accelerometers used (Augmentec Inc., Pittsburgh, Pennsylvania, USA) valid in assessing time spent lying, sitting, and standing/walking using a two-accelerometer approach. Our study added to this validation by using a two-axis solution with measurements every second as opposed to a one axis solution with measurements every 20 seconds (101). Nevertheless, consistent with Brown and colleagues we were unable to differentiate between standing and walking. Thus, despite the ability to measure continuously on a 24-hour basis obstacles were encountered in obtaining an image of all activity performed. Moreover, the accelerometers used could measure a maximum of 24 hours before re-charging was necessary, making it logistically difficult to use the accelerometers in the home setting.

Different types of accelerometers for measuring mobility exist. Therefore, in Study III the ActivPal accelerometer was chosen (PAL Technologies Ltd, Glascow, UK), since it can measure continuously for 7 days, and should be able to distinguish standing from walking. However, this differentiation has shown to be difficult at very slow walking speed, why underestimation of time spent walking might occur. When discriminating between standing and walking, previous studies in healthy adults have found a percentage error of <1% for speeds from 0.67–1.56 m/s (187) and 3.7% for 0.45 m/s (188). Our validation study showed similar results for faster walking speeds, but higher percentage errors for lower walking speeds - the ActivPAL categorized walked time on walking speeds of 0.56-0.89 m/s with <0.1% error, 0.28 m/s with a 50.4% error, and 0.45 m/s and 0.50 m/s, respectively, with an 11.2% and 13.3% error. This limit of the ActivPal in assessing time spent walking is worth considering, since it is likely to underestimate time spent walking in older hospitalized patients. In older hospitalized adults (≥65 yrs) mean walking speeds of 0.43 m/s have been reported (189), and in a study from Hvidovre Hospital in 317 older medical patients, 46% walked at a speed below 0.67 m/s, and 34% at a speed below 0.56 m/s (182). Thus, measurements of one third of older medical patients are likely to underestimate time spent walking. However, underestimation is probably less critical than overestimation as slow gait speed (self-selected) has been shown to be associated with daily ambulatory activity, with slow walkers being less ambulatory than faster walkers (190). This calls for particular attention on slow walkers, since gait speed has been shown to be a predictor of adverse events (e.g. disability, cognitive impairment, institutionalization, falls, and/or mortality) (191).

6.4 Functional decline before and during hospitalization

Decline in ADL function is commonly reported by older medical patients both before hospitalization (in retrospect) and during hospitalization (92,93,102–105), and studies have found that around 40 % are discharged with worse ADL function than two weeks before admission (102,104,108,110). Consistent with previous studies, patients in Study I declined in functional independence from two weeks before hospitalization to admission, estimated by the NMS (in retrospect). Similarly, in Study II a decline in the NMS was seen from two weeks before hospitalization to admission (from 9 (IQR 5.5;9) to 3 (IQR 2;9); p=0.03). However, in a subsample of 33 patients (149) from Study I, with functional assessments of muscle strength (hand-grip strength, knee-extension strength) and functional performance (Timed Up and Go) on admission, discharge and 1 month after discharge, functional decline during hospitalization, as previously reported in studies using self-report measures (102,104,108,110), could not be found. Instead, an improvement was seen in the Timed Up and Go test during hospitalization (149). In-hospital improvement in functional performance measures, i.e. walking speed, grip strength (150) and SPPB (192), has also been reported in other studies, while de Buyser et al. (150) did not find a significant change in ADL scores. However, both data from the Study I subsample and from de Buyser et al. showed the patients to have poor performance at discharge – knee extension strength (149) was at the threshold level for independent ability to perform ADL (84) and increased risk of future mobility limitations (87), and hand grip strength and walking speed (150) were at levels indicating mobility limitations (16). Thus, a discrepancy between self-report measures commonly used to describe functional changes and performance-based functional measures seems present and are well in line with studies reporting that performance based and self-reported measures of physical function assess different, partially overlapping, aspects of physical functioning (193,194). Also, community-dwelling older adults have been shown to recalibrate their self-report of functional limitations based on recent health problems (195). That is, people who had experienced illness during the last week and pain or stiffness on the day of assessment had an inflated perception of limitations, i.e. greater self-reported disability on a given level of observed function, than people without these problems. However, when a performance test was administered before self-report assessments, associations between self-report and performance based measures improved (195). Thus, psychosocial and health factors seem to influence self-report measures of disability (193,195), suggesting that both self-report and performance based measures should be used in evaluating populations over time (195). This has been done in Study III, but the associations are yet to be analyzed.

The lack of decline seen in functional performance measures during hospitalization (149,150) is speculated to be due to suppressed performance on admission as a consequence of the acute illness, with stabilization of the medical illness during hospitalization overshadowing the possible negative consequences of in-hospital inactivity (149). This argument is in accordance with the results of a study in older adults admitted for diagnostic investigation, who declined significantly in functional capacity, i.e. upper extremity muscle strength, and 6-min walk test, during 5 days of hospitalization (107). The change in 6-min walk test was beyond a minimal important difference reported in patients with arterial hypertension (196). Another reason for the lack of decline seen in functional performance measures could be that further decrease is difficult to identify during hospitalization, due to an already low functional level on admission. However, despite the lack of change in functional performance seen in the Study I subsample, the low levels of functional performance at discharge are worthy of concern, since functional performance has been linked with future risk of falls and functional decline (197), mobility- and ADL disability (35–37), hospital readmissions (119) as well as death (38,39,197). Furthermore, the need for help in ADL's before admission has been shown to correlate with low ADL scores after discharge (105). Also, a study in older medical patients (≥65 yrs) showed that those who improved or remained stable in self-reported ADL function during hospitalization had lower risk of death in the months following discharge than those who declined (198). This underlines the importance of counteracting functional decline during hospitalization, especially since older adults consider mobility as vital to health and as an indicator of independence, well-being and freedom allowing them to participate in life as they know it, thus not only affecting the physical aspects of life (199). Also, this risk of functional decline associated with hospitalization was the reason for conducting Studies II and III.

6.5 Barriers to mobility and exercise

An association between basic mobility and 24-hour mobility was found in Study I. However, factors other than dependence in basic mobility may foster in-hospital inactivity. Acute illness and inflammation have been linked with lower fatigue resistance as well as poor muscle strength and functional performance in geriatric patients and community-dwelling older adults (200–203), and may affect the urge for being active. Indeed, in one study in older medical patients (≥75 yrs), weakness, need for assistance, potential risk of falling, lack of interest from staff, and structural barriers were mentioned as reasons for being inactive (204). Similarly, the number of steps taken during hospitalization has been found to be associated with a history of falls, age 75 or older, and preadmission mobility impairment (96).

Older medical patients that may benefit from physical rehabilitation during and after hospitalization may have barriers preventing participation. In a study in acutely admitted older medical patients, those declining to participate expressed that they did not feel like exercising or did not believe they could (129). A study in community-dwelling older adults with a history of falls or self-reported mobility disability, found exercise at home, an improvement in the ability to undertake daily tasks, and no need to use transportation to be the three most important attributes for engaging in physical activity among participants 66 years or older (139). In Denmark, physical rehabilitation after discharge is undertaken by the municipalities, and most often rehabilitation takes place in rehabilitation centers, thus requiring transportation to and from the center, and most likely extra time waiting for transportation before and after the rehabilitation session. This can be a barrier for some older adults (139) and may affect compliance with rehabilitation. Also, for older adults discharged with a rehabilitation plan, initiation of rehabilitation is most likely to be between two and four weeks after discharge, thus creating a treatment gap between hospitalization and rehabilitation. Besides, acutely hospitalized older adults may prefer for exercise to be initiated in the hospital or shortly after discharge (129,138). Therefore, initiating exercise training during hospitalization and continuing the exercise training in the patients' own homes after discharge (Study II and III), seems rational.

6.6 Feasibility

To try to overcome the previously reported lack of knowledge regarding the optimal nature and dose of exercise in older adults (123,145,146), we chose a minimal time-consuming treatment approach taking implementation in a busy care setting into account. According to a recent review

(205) low intensities are often the first choice among physiotherapists, as this is perceived to be safer. Low intensities, though, may be inadequate to achieve optimal effects on functional performance (148), why we wanted to investigate if higher intensities could be performed by older medical patients without inducing adverse events. Since we found few studies investigating the effect of a cross-continuum program initiated during hospitalization and continued after discharge (129,135), and due to problems with compliance in these studies (129,135), we chose a program with full supervision from trained staff.

Study II was conducted as a feasibility study to evaluate important parameters of the full-scale study (Study III) (206), i.e. if the progression model could be used to ensure proper loading (8-12 RM) without inducing adverse events, before using it in Study III. We wanted to ensure, that the exercise could be understood and performed, and that proper loading could be achieved. Study II showed that the progression model could be used in hospitalized older adults, both in those with high and low mobility, as measured by the DEMMI, and in those with and without signs of cognitive impairment. However, the ability to perform strength training following the model was only tested once in the hospital and once in the patients' own homes, leaving us without knowledge about the possible use of the model over time. The lack of observed ceiling and floor effect, though, is a promising finding in this regard.

6.7 Cognition

Older adults with cognitive impairment have been reported to be at greater risk of functional decline before admission (94), during hospitalization (109,113,114) and after discharge (113) and less likely to recover from ADL disability during hospitalization and after hospitalization than non-impaired (113). In Study I, patients with cognitive impairment (MMSE≤24) were found to be standing or walking significantly less than those without cognitive impairment, possibly inducing a greater risk of functional decline during hospitalization. In this regard, it is promising that Study II showed the STAND model to be feasible, and thus a potential means of exercise, for both patients with and without cognitive impairment. The ability of both cognitively impaired and non-impaired hospitalized older adults to perform a strength training program including the STAND model, and the effect of the program, though, are yet to be illuminated (Study III).

Cognitive impairment and mobility limitations have also been found to influence the ability of independent living in community-dwelling older adults (57–59). In Study IV, the association between cognition and mobility performance was evaluated in community-dwelling primary care patients, and those with MCI were found to have worse mobility performance than those without MCI. In addition, those with impairments in non-amnestic cognitive domains, e.g. processing speed and executive function, performed the worst. These findings are consistent with previous studies also linking executive dysfunction with disability (56,207–209). Furthermore, co-existence of cognitive impairment and mobility limitations has been shown to affect the ability of community-dwelling older adults to remain at home (59). Altogether, older adults with cognitive impairment and functional disability, or one of the two, are prone to experience adverse events and need particular attention. There is reason to believe, though, that both cognitively impaired and non-impaired can benefit from training interventions. Results from a meta-analysis on training interventions in cognitively impaired and cognitively intact older adults, showed that cognitively impaired can benefit similarly to non-impaired in strength- and endurance outcomes from both strength- and endurance training (210). Moreover, a recent systematic review found that in older adults with MCI, physical exercise can be beneficial on several cognitive domains including executive function (211). Thus, there is reason to believe that the strength training program to be evaluated in Study III can improve mobility in cognitively impaired as well as cognitively non-impaired.

6.8 Training interventions

Previous studies evaluating strength training during (127) and after hospitalization (128), and in community-dwelling older adults (130) have used 10 week programs, using both weight training machines (127,128), and elastic bands for resistance (130), with programs consisting of 3-5 lower extremity exercises (128,130) or only one exercise (127). Common to these studies is a positive effect seen on leg muscle strength and functional performance. However, problems recruiting acutely admitted older medical patients for in-hospital and post discharge training have also been encountered (129), why the feasibility and effect of cross-continuum training programs remains to be fully elucidated. Study III is based on two lower extremity exercises performed daily during hospitalization and three times per week for four weeks after discharge, and thus providing the participants with a lower volume of strength training than in the studies mentioned above. Since data collection in Study III is still ongoing, it is unclear whether four weeks of strength training after discharge is sufficient to induce effects similar to those seen after 10 weeks. However, four weeks were chosen since it has previously been reported, that recovering function within the first month after discharge is of importance for long term outcomes (102). A previous study in older hospitalized adults has shown positive effects of exercise therapy performed during the first four weeks after discharge (135), leading us to believe, that four weeks might be sufficient in inducing an effect, even though the exercise program in Study III is of a smaller volume (but higher intensity). Also, a study in older home care clients found that structured exercise programs are not the preferred activity of these older adults (212), why a four week program may be more acceptable than a program of longer duration. Siebens et al. (135) evaluated the effect of an exercise program of 12 minimally challenging exercises for flexibility and strength (three exercises for the lower extremities) combined with a walking program, in older medical and surgical patients (≥70 yrs). The exercises were performed twice daily during hospitalization (once with supervision), and three times per week (non-supervised) at home after discharge for one month (28% performed the home program), and an amelioration in iADL was found one month after discharge. Although the program used is not similar to the one used in Study III, it bodes well for an ability to induce a positive effect, even using programs of shorter duration. However, a recent meta-analysis evaluating strength training programs of 8 to 52 weeks of duration on strength gains in adults over the age of 55, found that programs of longer duration were superior to shorter duration (213), which questions the sufficiency of four weeks of training.

Both resistance training and amino acids can stimulate an anabolic response (156), and combining the two has been shown to enhance the muscular response to exercise in healthy older adults (153–155). Therefore, protein was chosen as an integrated part of strength training in Study III. Nevertheless, although the protein supplementation provided in Study III was intended to boost anabolism, it is unclear whether it will merely reduce an existing protein deficit. According to the recommendations of an international study group (214), older adults need a greater amount of daily protein than young adults to maintain muscle mass, and older adults with acute or chronic diseases or marked malnutrition, need even more. In Study II, 79.2% of the patients were considered to be at nutritional risk (based on a low body mass index, decreased appetite, weight loss within the last three months, and severity of disease), which is in line with previously reported lack of adequate nutritional intake among older hospitalized adults (215). Thus, despite provision of protein in connection with strength training, some of the patients might still be undernourished.

6.9 Methodological considerations

The studies have some limitations worth considering, some of which have been mentioned previously. In Study I we were unable to distinguish between standing and walking with the accelerometers used. We attempted to overcome this lack of specificity in the assessment of 24-hour mobility by introducing a novel type of accelerometer in Study III. Nevertheless, similar obstacles were encountered, namely an inability of the accelerometer to correctly assess time spent walking at slow walking speeds – speeds that are commonly seen in older medical patients. Thus, regardless of the accelerometers used, we are likely to underreport the time spent walking, although an assessment of upright time can be obtained.

In Study II, 90% of the patients were either excluded (80%) or declined to participate (10%) in the study, leaving us with a very select group of older medical patients. Similar or lower consent rates, however, have been reported in previous studies in older medical patients (129,135,216), underlining the difficulty of recruiting patients in the acute setting and limiting the generalizability of the results. Similar inclusion rates have been encountered in Study III, in which the main reasons for not wishing to participate have been consistent with reasons found by Dr. Brown and colleagues, namely feeling too ill to participate, feeling incapable of exercising during the hospital stay (129), as well as not feeling a need for exercise.

Study IV was cross-sectional and therefore does not add information about a possible causal association between cognitive impairment and mobility limitations. However, associations were found between cognition and mobility. In Study III, we have included cognitive assessments similar to the ones used in Study IV, and we will therefore be able to extend the investigations from Study IV to older medical patients.

7. Conclusions

In two prospective cohort studies, we found that the included acutely admitted older medical patients (+65 yrs) spent a median of 17 hours per day of their in-hospital time in bed. The level of in-hospital mobility seemed to depend on the patients' levels of basic mobility, i.e. their ability to independently get in and out of bed, rise from a chair, and walk, and on their cognitive level. Accelerometers used in measuring in-hospital mobility could validly assess time spent lying, sitting, and standing and/or walking in these patients. Also, based on a pre-defined criteria for feasibility, we found that a simple progression model for loaded sit-to-stands (STAND) was feasible in acutely admitted older medical patients in the hospital- and home setting, in obtaining a strength-training intensity of 8-12 repetition maximum for 8-12 repetitions with no indication of ceiling or floor effect for load, and no report of adverse events. Moreover, the level of STAND performed did not depend on cognition. The effect of a cross-continuum strength training program is currently being evaluated in a randomized controlled trial, and data are still to be analyzed. Also, in a cross-sectional study in older community-dwelling primary care patients, performance on a range of performance-based and self-reported mobility measures was associated with MCI status. Performance was worse among those with MCI, and appeared to be poorest among those with non-amnestic MCI.

8. Perspectives

The findings presented in this thesis are of relevance for clinicians and researchers encountering mixed populations of older adults, by confirming previously reported concerns regarding in-hospital inactivity in older medical patients and in having proposed a simple model for high intensity strength training as a possible method of training for older medical patients with and without mobility limitations and cognitive impairment.

The low levels of in-hospital mobility and muscle strength (Study I and Study I subsample) and require attention. In order to avoid in-hospital in-activity and the associated negative effects it seems relevant to focus on regaining independence in basic mobility (Study I). In conducting Studies II and III we have proposed a minimally time consuming solution. The fact that the older medical patients were able to perform the sit-to-stand exercise as proposed, both in the hospital and in their own homes, is an important finding. Due to continuous economical cuts in the health care sector in Denmark, we wanted to investigate the effect of a program that could realistically be implemented in a busy care setting and continued after discharge, using only little time and equipment and thus, demanding few resources. The final proof of feasibility of the entire intervention will not be established until data from Study III have been analyzed. Thus, whether our program including the sit-to-stand exercise provides a feasible suggestion for a way of overcoming in-hospital inactivity, loss of muscle strength and function, remains unanswered at the moment.

When outlining suggestions for activity and rehabilitation in older medical patients it is crucial to take possible barriers towards physical activity into account – both in the hospital and in the home setting – and combining this knowledge with what is considered to be important for older adults (e.g. strength training). In most hospital wards in Denmark, patients spend most of their time in their bed room (eating, watching television etc.). Thus, the structure of the hospital wards does not encourage activity. Re-introducing dining rooms, encouraging staff and relatives to facilitate out of bed activity etc., may be other ways of avoiding a negative circle of inactivity. Also, a simple daily walking program seems like a good suggestion for a simplistic in-hospital approach (217), and corresponds well with an activity preferred by older adults (212). Also, it may be that training as proposed in Study III should only be targeted patients at risk of developing mobility limitations and that this differentiation could be made on admission. Bodilsen et al. (182) found that physical performance measures (gait speed, hand grip strength, chair stand, basic mobility) - particularly chair-stand and gait speed - assessed on admission, could identify mobility limitations in acutely admitted older medical patients 30 days after hospital discharge. So, an admission evaluation could potentially be conducted to screen for those who are at risk of developing mobility limitations and thus at need for extra attention during hospitalization. This thesis brings forward a suggestion for a program meeting the requirements of avoiding in-activity and promoting independence in basic mobility during and after hospitalization. However, the effect of the program is still unknown.

9. Summary

Mobility in older acutely admitted and primary care patients – in-hospital physical activity and simple strength training

Older medical patients (≥65 yrs) constitute more than half of the patients seen in Danish medical wards, and low levels of mobility are common during hospitalization and associated with adverse events. Besides, older hospitalized adults display poor muscle strength and functional performance, and risk losing independence as a consequence of their hospitalization. Patients with cognitive impairments seem especially vulnerable. Only few studies have assessed in-hospital mobility and basic mobility continuously throughout hospitalization in older adults, and few studies have examined the feasibility and effect of cross-continuum strength training. Therefore, the main objectives of the studies included in this thesis were to evaluate 24-hour mobility and basic mobility during hospitalization in acutely admitted older medical patients and validate the accelerometers used (Study I), to test the feasibility of a model for progressive sit-to-stand training in the hospital- and home setting (Study II) and the effect of simple, supervised, cross continuum strength training (Study III) in acutely admitted older medical patients, and to describe the association between mobility performance and mild cognitive impairment in older community-dwelling primary care patients (Study IV).

Study I

Forty-three ambulatory older medical patients (≥65 yrs) were included. Cognition was assessed on admission by The Mini Mental State Examination (MMSE), and 24-hour mobility was assessed throughout hospitalization by two wireless accelerometers. An algorithm for identification of time spent lying, sitting, and standing/walking using the accelerometers, was cross-validated on six older medical patients. The Cumulated Ambulation Score was used to assess basic mobility every day throughout hospitalization. The patients were assessed for 4.4 days and were lying in bed 17.0 hours, sitting 5.1 hours, and standing/walking for 1.1 hours per day. On days with independence in basic mobility, the patients were significantly more active that on days with dependence in basic mobility ($p<0.001$). Patients with a MMSE score >24 were standing/walking significantly more per day than patients scoring <24 ($p=0.02$). The algorithm could classify time spent lying, sitting, and standing/walking with a 4.7-10.4% error.

Study II

Twenty-four older medical patients were included. Cognition was assessed on admission by the Short Orientation-Memory-Concentration test. A progression model for sit-to-stand as a strength training exercise (STAND) was developed. The model was considered feasible if 75% of the patients could perform the exercise at 8-12 repetitions maximum for 8-12 repetitions at a given level of the model in the hospital and in their own homes after discharge, if no ceiling or floor effect were seen, and if no adverse events were observed. Pain was assessed before, during and after performing the exercise. Twenty-three patients were tested in the hospital, and 19 of these were also tested at home. Twenty patients (83%) were able to perform the exercise following STAND in the hospital, and 15 patients (79%) at home. No floor or ceiling effects were found, and no patients reported an increase in pain during or after performing the exercise. Thus, STAND was considered feasible. The level of STAND did not depend significantly on cognition ($P \geq 0.45$).

Study III

To date, 76 patients have been included in this randomized controlled study. Inclusion is still ongoing, why data are still to be analyzed.

Study IV

Four hundred and thirty community-dwelling primary care patients were included. A battery of neuropsychological tests was used to characterize patients with mild cognitive impairment (MCI) and further sub-classify these patients in amnestic MCI, non-amnestic MCI, and multiple-domain MCI. All patients were classified as either cognitively intact or as having MCI. Performance-based and self-reported mobility were assessed by habitual gait speed, the Figure-of-8-Walk, the Short Physical Performance Battery, and the Late Life Function and Disability Index. Forty-two percent of the patients had MCI. MCI participants as well as MCI subtypes performed significantly worse in tests of mobility than patients without MCI. Moreover, patients with non-amnestic MCI performed most poorly.

Conclusions

In conclusion, this thesis showed that the included acutely admitted older medical patients (+65 yrs) spent a median of 17 hours per day of their in-hospital time in bed, and their mobility level seemed to depend on their basic mobility. Accelerometers could be used to measure time spent lying, sitting, and standing and/or walking in these patients and a model for progressive sit-to-stand training was found feasible to be used in the hospital- and home setting, irrespective of cognitive level of the patients. The effect of simple, supervised, cross continuum strength training is still to be analyzed since the study is ongoing. Also, in the older community-dwelling primary care patients assessed performance-based and self-reported mobility was associated with MCI status, with the poorest performance seen among those with non-amnestic MCI.

10. Resumé (Summary in Danish)

Mobilitet blandt akut indlagte og hjemmeboende ældre patienter – fysisk aktivitet under indlæggelse samt simpel styrketræning

Ældre medicinske patienter (≥ 65 år) udgør mere end halvdelen af de patienter, der behandles på medicinske afdelinger i Danmark, og et lavt aktivitetsniveau er almindeligt under indlæggelse og forbundet med uønskede hændelser. Indlagte ældre fremstår desuden med lav muskelstyrke og dårlig funktionsevne og er i risiko for at miste uafhængighed som følge af deres indlæggelse - patienter med kognitive problemer synes særligt sårbare. Kun få studier har målt aktivitetsniveau og basismobilitet løbende under indlæggelse blandt ældre og få undersøgelser har undersøgt gennemførlighed og effekt af styrketræning gennemført på tværs af sektorer. Derfor var formålene med studierne i denne afhandling, at måle 24-timers aktivitetsniveau og basismobilitet løbende under indlæggelse blandt akut indlagt ældre medicinske patienter og validere de anvendte aktivitetsmålere (Studie I), at teste brugbarheden af en model for progressiv rejse-sætte-sig træning under indlæggelse og i eget hjem efter udskrivelse (Studie II) samt effekten af simpel, superviseret, tværsektoriel styrketræning blandt akut indlagte ældre medicinske patienter (Studie III), og at beskrive sammenhængen mellem mobilitet og mild kognitiv svækkelse blandt hjemmeboende ældre patienter (Studie IV).

Studie I

Treogfyrre ældre medicinske patienter (≥ 65 år) blev inkluderet. Kognition blev vurderet ved indlæggelse via Mini Mental State Examination (MMSE), og 24-timers aktivitetsniveau blev målt under hele indlæggelsen ved hjælp af to trådløse aktivitetsmålere. En algoritme til identifikation af tid brugt henholdsvis liggende, siddende og stående/gående målt med aktivitetsmålerne, blev krydsvalideret på seks ældre medicinske patienter. Cumulated Ambulation Score blev anvendt til at vurdere basismobilitet hver dag under hele indlæggelsen. Patienterne blev mål i gennemsnitligt 4,4 dage og dagligt lå de 17 timer i sengen, sad 5,1 timer, og stod/gik 1,1 time. Patienterne var signifikant mere aktive på dage, hvor de var uafhængige i basismobilitet end på dage med en grad af afhængighed (p <0,001). Patienter med en MMSE score >24 stod/gik signifikant flere timer om dagen, end patienter med en score på <24 (p = 0,02). Algoritmen kunne klassificere tid brugt liggende, siddende og stående/gående med en fejlprocent på 4,7-10,4.

Studie II

Fireogtyve ældre medicinske patienter blev inkluderet. Kognition blev vurderet ved indlæggelse via Short Orientation-Memory-Concentration test. En progressionsmodel for rejse-sætte-sig som styrketræning (STAND) blev udviklet. Modellen blev anset for brugbar, hvis 75 % af patienterne kunne lave 8-12 gentagelser til udtrætning på hospitalet og i eget hjem efter udskrivelse på et givent niveau af modellen, hvis der ikke sås gulv- eller lofteffekt, og hvis ingen uønskede hændelser blev observeret. Smerte blev vurderet før, under og efter udførelse af øvelsen. Treogtyve patienter blev testet på hospitalet, og 19 af disse blev også testet i eget hjem. Tyve patienter (83 %) var i stand til at udføre øvelsen efter STAND-modellen på hospitalet, og 15 patienter (79 %) i eget hjem, der sås ikke loft- eller gulveffekt, og ingen patienter rapporterede om smerter under eller efter udførelse af øvelsen. Således blev STAND anset for brugbar. Desuden var det gennemførte niveau af STAND uafhængigt af den enkeltes kognitive niveau ($P \geq 0.45$).

Studie III

Til dato er 76 patienter blevet inkluderet i dette randomiserede, kontrollerede studie. Da studiet er igangværende, er data endnu ikke blevet analyseret.

Studie IV

Fire hundrede og tredive hjemmeboende patienter blev inkluderet. Et batteri af neuropsykologiske tests blev anvendt til at karakterisere patienter med mild kognitiv svækkelse (MCI), og yderligere sub-klassificere disse patienter i amnestisk MCI, ikke-amnestisk MCI og flerdomæne MCI. Alle patienter blev klassificeret som enten kognitivt intakte eller som havende MCI. Funktionsbaseret og selvrapporteret mobilitet blev vurderet ved habituel ganghastighed, Figure-of-8-Walk, Short Physical Performance Battery og Late Life Function and Disability Index. Toogfyrre procent af patienterne havde MCI. Patienter med MCI og sub-typer af MCI havde signifikant dårligere mobilitet end patienter uden MCI. Patienter med ikke-amnestisk MCI havde dårligst mobilitet.

Konklusion

Denne afhandling har vist, at de inkluderede akut indlagte ældre medicinske patienter (+65 år) brugte 17 timer om dagen i sengen under indlæggelse, og at deres aktivitetsniveau syntes at afhænge af deres basismobilitet. Aktivitetsmålere kunne anvendes til at måle tid brugt liggende, siddende, stående/gående blandt disse patienter, og en model for rejse-sætte-sig træning blev fundet anvendelig på hospitalet så vel som i patienternes eget hjem, uanset kognitivt niveau. Effekten af simpel, superviseret, tværsektoriel styrketræning kendes endnu ikke, da studiet er igangværende.

Blandt hjemmeboende ældre var funktionsbaseret og selvrapporteret mobilitet associeret med mildt kognitivt besvær, og patienter med non-amnestisk mildt kognitivt besvær klarede sig dårligst.

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