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PhD thesis

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Physical activity as intervention for age-related loss of muscle mass and function, the LISA study: A randomized controlled trial

"Age is no barrier. It's a limitation you put on your mind"

Jackie Joyner-Kersee

Principal supervisor: Professor, Michael Kjær

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PhD Thesis

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1. Preface and acknowledgements

The two studies presented in this PhD thesis are the result of my three-year PhD scholarship kindly awarded by the Faculty of Health and Medical Sciences at the University of Copenhagen. The two studies include data from the multidisciplinary LISA study, which was conducted at the Institute of Sports Medicine Copenhagen (ISMC), Department of Orthopedic Surgery M, Bispebjerg Hospital. Nordea Foundation funded the LISA study with a grant from Center for Healthy Aging, University of Copenhagen. The LISA study started in April 2014, and I have since May 2014 been a part of the study. The conduction of the LISA study was only possible with the support and help from many people to whom I am very grateful.

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Anne Theil Gylling, Copenhagen May 27.

2. List of papers

Paper 1:

Anne Theil Gylling, Christian Skou Eriksen, Ellen Garde, Cathrine Lawaetz Wimmelmann, Nina Linde Reislev, Theresa Bieler, Andreas Kraag Ziegler, Kasper Winther Andersen, Christian Bauer, Kasper Dideriksen, Maria Baekgaard, Kenneth Hudlebusch Mertz, Monika Lucia Bayer, Mads Bloch-Ibenfeldt, Carl-Johan Boraxbekk, Hartwig Roman Siebner, Erik Lykke Mortensen, Michael Kjaer.

The influence of prolonged strength training upon muscle and fat in healthy and chronically diseased older adults. Experimental Gerontology, 136, 2020. Doi: 10.1016/j.exger.2020.110939

(Study I)

Paper 2:

Anne Theil Gylling, Mads Bloch-Ibenfeldt, Christian Skou Eriksen, Andreas Kraag Ziegler, Cathrine Lawaetz Wimmelmann, Maria Baekgaard, Carl-Johan Boraxbekk, Hartwig Roman Siebner, Erik Lykke Mortensen, Michael Kjaer.

Maintenance of muscle mass and strength following a one-year resistance training program in older adults. Submitted to Experimental Gerontology, April 2020 (under review).

(Study II)

3. Abbreviations

- ANOVA: Analysis of variance
- BIA: Bioelectrical Impedance
- BMI: Body Mass Index
- CON: Control
- CSA: Cross-Sectional Area
- CT: Computed Tomography
- CV: Coefficient of Variation
- DRCMR: Danish Research Centre for Magnetic Resonance
- DXA: Dual-energy X-ray Absorptiometry
- ES: Effects Size
- HbA1c: Glycosylated Hemoglobin
- HDL: High-Density Lipoprotein
- HRT: Heavy Resistance Training
- ICC: Intraclass Correlation Coefficient
- LISA: Live actIve Successful Aging
- LDL: Low-Density Lipoprotein
- MIT: Moderate Intensity resistance Training
- MRI: Magnetic Resonance Imaging
- RCT: Randomized Controlled Trial
- ROI: Region Of Interest
- RM: Repetition Maximum
- PASE: The Physical Activity Scale for the Elderly
- SD: Standard Deviation
- SE: Standard Error
- SF-36: Short-Form Health Survey 36
- SPPB: Short Physical Performance Battery
- VLDL: Very Low-Density Lipoprotein
- VO_2: Oxygen consumption
- WHO: World Health Organization

4. Abstract

Aging is related to a loss of muscle mass, -strength, and -power, and as those parameters are the dominant determinants of physical function, these age-related losses are associated with a decline in physical function. After the age of 60 years, the age-related decreases in muscle function will accelerate. Additionally, there is an age-related loss of both total brain and hippocampus volume, potentially resulting in impaired cognitive function. It has been demonstrated that strength training over a few months can improve physical function, whereas less is known regarding the effects of long-term strength training upon physical function and hippocampus volume. Further, strength training with a relative high resistance intensity is effective to improve muscle strength and physical function, whereas it is more doubtful as to how effective strength training at a more moderate intensity is. Finally, short-term strength training interventions often result in a disappearance of gained physiological effects quickly after termination of supervised training due to discontinuation of training in the individual. It is unknown to what extent more prolonged training interventions can lead to altered daily routines in the individual, and thus a continued training practice and maintained improved physical and cognitive function.

This thesis investigated the effect of 1-year strength training of two different intensities compared with a non-exercising control group upon physical function and hippocampus volume in older adults (Study I). 451 participants (62-70 years, women 61%, ≈80% with a chronic medical disease) were allocated to either a) supervised, heavy resistance training (HRT, n=149, 3/week), b) moderate intensity resistance training (MIT, n=154, 3/week) or c) non-exercise activities (CON, n=148). Of the 451 randomized participants, 419 completed the 1-year assessment battery (HRT 143, MIT 144, and CON 132). Changes in muscle power (primary outcome), -strength and -size, physical function, body composition, hippocampus volume, and physical/mental well-being were analyzed. The results from Study I revealed that of the participants in HRT and MIT, 83% completed training at least 2/week. In all three intervention groups leg extensor power was unchanged. However, strength training had a positive effect on isometric knee extensor strength in both training groups, whereas only one year of heavy resistance training resulted in an increased muscle mass and cross-sectional area of vastus lateralis muscle (CSA), a decreased whole-body fat percentage and visceral fat content, and improved mental health (SF-36). We also observed that the chair-stand performance was

improved in all groups, whereas hippocampus volume decreased in all groups over time irrespective of strength training.

In addition, we investigated the maintenance (one year after termination of the strength training intervention) of potential gains in muscle mass, -strength, and -function obtained during the 1-year strength training intervention (Study II). We also explored whether one year of organized strength training was enough to implement physical activity in everyday life and if so whether the maintenance was enhanced if strength training was continued during the follow-up year. Of the 419 men and women who completed the 1-year intervention, 398 participants returned for measurements of muscle power, -strength and -mass, physical function, body composition, hippocampus volume, and physical/mental well-being at a 2-years follow-up. Further, participants from HRT and MIT (n=265) were divided into 1) those who on their own continued the strength training program (10-12 months) during the year after termination of the supervised strength training intervention (CONTIN, n=65) and 2) those who did not (STOP, n=200).

In Study II, we observed that out of all the improvements obtained in response to the 1-year strength training intervention, only isometric knee extensor strength in HRT was partly preserved at 2-years follow-up. Even though muscle strength decreased during follow-up, it was still significantly higher than baseline. Additionally, the decrease in muscle strength over the second year was lower in CONTIN than in STOP and of those two groups only in CONTIN was it still higher at 2-years follow-up compared with baseline. The strength training induced improvement in muscle mass in HRT was erased at 2-years follow-up. However, from baseline to 2-years follow-up, CSA in HRT tended to differ compared with CON as it over time was maintained in HRT and decreased in CON. We also observed that waist circumference decreased further and whole-body fat percentage was maintained over the second year in CONTIN, whereas it increased in STOP. Even though leg extensor power was not affected by the 1-year strength training intervention, we observed that participants in CONTIN in fact improved leg extensor power from baseline to 1-year, which was maintained through the second year.

In conclusion, this thesis indicates that strength training in both healthy and chronically diseased older adults can be implemented with good compliance, inducing consistent changes in physiological parameters of muscle and fat, and this to a higher degree with heavy resistance training. Only isometric knee extensor strength was preserved one year after completion of the supervised heavy (but not moderate intensity) resistance training. In addition, the continuation of strength training in the follow-up period resulted in better maintenance of muscle strength and health, which indicates that continued activity is essential for obtaining long-term effects of strength training upon muscle function and health in older men and women.

5. Dansk resumé

Med alderen vil vores muskelmasse, -styrke og -power aftage, hvilket oftest medfører et fald i vores fysiske funktionsniveau. Specielt efter 60 års alderen vil disse aldersrelaterede fald accelere. Ud over den faldende muskelfunktion, mindskes også størrelsen af den totale hjerne og hippocampus med alderen, som potentielt medfører en nedsat kognitiv funktion. Styrketræning over få måneder har tidligere vist at den fysiske funktion forbedres, hvorimod man ikke ved så meget om effekten af længerevarende styrketræning på den fysiske funktion og på volumen af hippocampus. Man ved desuden, at tung styrketræning er effektiv til at forbedre den fysiske funktion, hvorimod det er mere tvivlsomt, hvad effekten er af styrketræning med mere moderat intensitet. Derudover ved man, at interventioner med kortere varighed ofte medfører, at de opnåede fysiologiske forbedringer forsvinder hurtigt, når interventionen ophører. Det er uvist, om længerevarende træningsinterventioner medfører en ændring i de daglige rutiner hos det enkelte individ efter endt intervention. Vedvarende deltagelse i fysisk aktivitet kan potentielt betyde opretholdelse af den fysiske og kognitive funktion.

Denne afhandling undersøger effekten af 1 års styrketræning med to forskellige intensiteter, som sammenlignes med en kontrolgruppe, på den fysiske funktion og hippocampus volumen hos ældre individer (studie I). 451 forsøgspersoner (62-70 år, kvinder 61%, ≈80% med en kronisk sygdom) blev fordelt til enten a) superviseret tung styrketræning (HRT, n=149, 3/uge), b) moderat intensitets styrketræning (MIT, n=154, 3/uge) eller c) kontrol, som ikke blev tilbudt fysisk aktivitet (CON, n=148). Af de 451 randomiserede forsøgspersoner, deltog 419 i 1 års opfølgningen (HRT 143, MIT 144 and CON 132). Ændringerne i muskel power (primære mål), muskelstyrke og -størrelse, fysisk funktion, kropskomposition, hippocampus volumen og det fysiske/mentale velvære blev analyseret. Resultaterne fra studie I viste, at 83% af forsøgspersonerne i de to træningsgrupper (HRT+MIT) gennemførte mindst 2 ugentlige træningssessioner. Der var ingen effekt på muskel power i nogle af de tre interventionsgrupper, men begge styrketrænings interventioner havde en positiv effekt på benmuskelstyrke, hvorimod det kun var tung styrketræning som resulterede i en øget muskelmasse og tværsnitsareal af låret (CSA), en mindre fedtprocent, mindre indhold af visceralt fedt samt en forbedret mental sundhed (SF-36). Vi fandt også, at evnen til at rejse sig fra en stol på 30 sekunder blev forbedret i alle tre grupper, hvorimod vi fandt et fald i hippocampus volumen i alle grupper uafhængig af styrketræning.

Derudover undersøgte vi opretholdelsen (1 år efter endt styrketræningsintervention) af de potentielle forbedringer i muskelmasse, -styrke og -funktion opnået ved 1 års interventionen med styrketræning (studie II). Vi undersøgte desuden, om 1 års organiseret styrketræning var nok til at implementere fysisk aktivitet og i så fald om opretholdelsen var bedre, hvis man fortsatte med at styrketræne i løbet af opfølgningsåret. Af de 419 mænd og kvinder, der gennemførte 1 års interventionen, kom 398 forsøgspersoner igen til 2 års opfølgning til måling af muskel power, -styrke og -masse, fysisk funktion, kropskomposition, hippocampus volumen og fysisk/mental velvære. Derudover blev forsøgspersonerne fra HRT og MIT (n=265) opdelt i to grupper 1) dem som fortsatte med styrketræningsprogrammet på egen hånd (10-12 måneder) i løbet af året efter endt styrketræningsintervention (CONTIN, n=65), og 2) dem som ikke gjorde (STOP, n=200).

I studie II fandt vi, at ud af alle forbedringerne opnået ved 1 års interventionen, var det kun benmuskelstyrken i HRT, som delvist var opretholdt ved 2 års opfølgningen. Selvom muskelstyrken faldt i løbet af opfølgningsåret, var den stadig højere end ved baseline. Derudover fandt vi, at faldet i muskelstyrken fra slutningen af første år til slutningen af andet år var mindre i CONTIN i forhold til STOP, og at det kun var i CONTIN, at muskelstyrken stadig var højere ved 2 årsopfølgningen sammenlignet med baseline. De styrketrænings inducerede forbedringer i muskelmassen var væk ved 2 års opfølgningen, men der var en tendens til en opretholdelse af CSA fra baseline til 2 år i HRT sammenlignet med CON, hvor CSA faldt over tid. Vi fandt ligeledes, at taljemålet faldt yderligere, og at fedtprocenten var opretholdt i løbet af det andet år i CONTIN, hvor begge steg i STOP. Selvom 1 års styrketræning ikke ændrede muskel power, fandt vi, at forsøgspersonerne i CONTIN faktisk forbedrede muskel power fra baseline til 1 år, hvilket var opretholdt til 2 års opfølgningen.

Vi kan konkludere ud fra denne afhandling, at det ser ud til, at styrketræning i både raske og kronisk syge ældre individer kan blive implementeret med høj træningsdeltagelse og medfører forbedringer i både muskelfunktionen og fedtfordelingen, og at disse forbedringer er større, hvis styrketræningen er med høj intensitet. Et år efter den afsluttede superviserede tunge (men ikke moderate intensitet) styrketræningsintervention var det kun benmuskelstyrken, der var opretholdt. Ligeledes så vi, at hvis man fortsatte med styrketræning i løbet af opfølgningsåret, medførte det en forbedret opretholdelse af muskelstyrken og den generelle sundhed, hvilket indikerer, at en fortsættelse af træning er essentiel for at opnå længerevarende effekter af styrketræning på muskelfunktionen og den generelle sundhed hos ældre mænd og kvinder.

6. Introduction and background

“Those who think they have no time for bodily exercise will sooner or later have to find time for illness”

Edward Stanley

”Age is no barrier. It’s a limitation you put on your mind”

Jackie Joyner-Kersee

The quote from the British politician Edward Stanley is a very fitting description of what happens to the body as we age without exercise. If we do not exercise at all as we age, we will lose our functional ability with increased dependency and a need for healthcare as the undesired outcome. The quote by the athlete Jackie Joyner-Kersee reminds us that age is no excuse for not exercising. As the world population is aging and expected to do so rapidly over the next 30 years due to improved healthcare systems and environmental factors, scientific research in this field is important. In fact, the proportion of people above 60 years is expected to increase from 12% of the entire population worldwide in 2015 to 22% in 2050 (World Health Organization 2018). This can raise a socioeconomic challenge since more elderly will be characterized with low muscle mass, which is associated with impaired physical function. An impaired and decreased physical function contributes to functional impairment and physical disability (Janssen, Heymsfield, and Ross 2002; Cruz-Jentoft et al. 2019), affects quality of life as well as increases risk of falls, morbidity, and even mortality in older and frail humans (Beaudart et al. 2014; Kohl et al. 2012; Lee et al. 2012; World Health Organization 2010). All of this will result in an increased need for healthcare.

6.1 Physical function and aging

Physical function is key to healthy aging. The dominant determinants of physical function are muscle mass, -strength, and -power, which, unfortunately, decline with advancing age potentially leading to sarcopenia (Janssen et al. 2000; Lindle et al. 1997; Skelton et al. 1994; Cruz-Jentoft et al. 2019). The term sarcopenia is derived from the Greek words “sarx” (flesh) and “penia” (loss) and was suggested the first time by Rosenberg in 1988 as a progressive loss of skeletal muscle mass that occurs when we age (Beaudart et al. 2016; Rosenberg 1997). It has been demonstrated that an association between low skeletal muscle mass and functional impairment is more pronounced in older individuals with severe sarcopenia compared with individuals with normal skeletal muscle mass (Janssen, Heymsfield, and Ross 2002). Sarcopenia is considered as primary and secondary, where the primary is most likely caused by aging, whereas secondary sarcopenia occurs by e.g. systemic disease or lower physical activity level. In this thesis, I am focusing on primary sarcopenia (Cruz-Jentoft et al. 2019). Since the first definition of sarcopenia, it has been changed some times, and muscle strength and function is now integrated as a part of a more comprehensive definition of sarcopenia (Suetta et al. 2019; Beaudart et al. 2016). Moreover, sarcopenia is now seen as a progressive and generalized skeletal muscle disorder, where the likelihood of adverse health outcomes, e.g. physical disability, is increased (Cruz-Jentoft et al. 2019). The integrated muscle strength is the most reliable measure of muscle function and has been suggested to be better than muscle mass of predicting adverse outcomes (Cruz-Jentoft et al. 2019). For that reason, it is of high importance for the society as well as for each individual to develop prevention and treatment strategies to preserve or even improve muscle mass, -strength, and -function in the elderly population.

6.1.1 Progression of age-related skeletal muscle mass, -strength and -power

The age-related loss of muscle mass are progressive processes already starting slowly from the 4th decade of life, and accelerating after the age of 60 years with a gradually decline by 2% each year (Janssen et al. 2000; Suetta et al. 2019). It has previously been shown that there is an association between low skeletal muscle mass and functional impairment and physical disabilities (Janssen, Heymsfield, and Ross 2002). Further, functional impairment and physical disabilities were found to be greater in elderly with a higher level of sarcopenia than elderly with normal skeletal muscle mass (Janssen, Heymsfield, and Ross 2002). Additionally, a cross-sectional study reported that muscle mass of the thigh decreased by around 0.8% each year from the age of 50-80 years in both men and women (Janssen et al. 2000). Similarly, a decline in thigh cross-sectional area (CSA) by approximately 0.6% each year was observed in a longitudinal study where individuals between 62 and 81 years of age were evaluated twice with 9 years apart (Frontera et al. 2008). Figure 1A illustrates a 60-year old and an 80-year old woman's CSA of the thigh, clearly showing the differences in CSA caused by aging. However, it is important to notice that there is a huge spread of the decrease in CSA and the decrease is for instance not as high in an active older adult as is an adult with e.g. illness. Additionally, as illustrated in figure 1A, the quality of the muscle is also declining with aging, as aging is not only causing a decrease in muscle mass, but also an increase in fat and connective tissue (De Carvalho et al. 2019; Robert 1980). Figure 1B illustrates total skeletal muscle mass with aging, underlining that the decreases occur gradually and slowly.

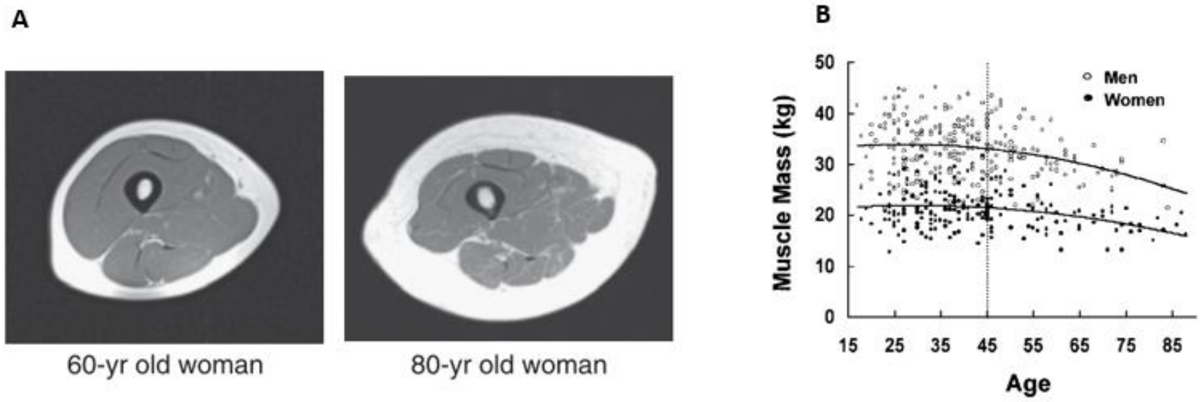

*Fig. 1: **A**) Cross-sectional area of the thigh from a 60-year old (left) and an 80-year old woman (right), and **B**) the development of total skeletal muscle mass with age. Obtained from A) Aagaard and colleagues (Aagaard et al. 2010), and B) Janssen and colleagues (Janssen et al. 2000).*

The loss of muscle mass is also related to a loss of muscle strength (Dey et al. 2009). However, as illustrated in figure 2 the loss of muscle strength is approximately 2% per year already after the age of 40 years, accelerating after the 6th decade of life, and the decline occurs therefore prior to and faster than muscle mass (Suetta et al. 2019; Lindle et al. 1997; Cruz-Jentoft et al. 2019).

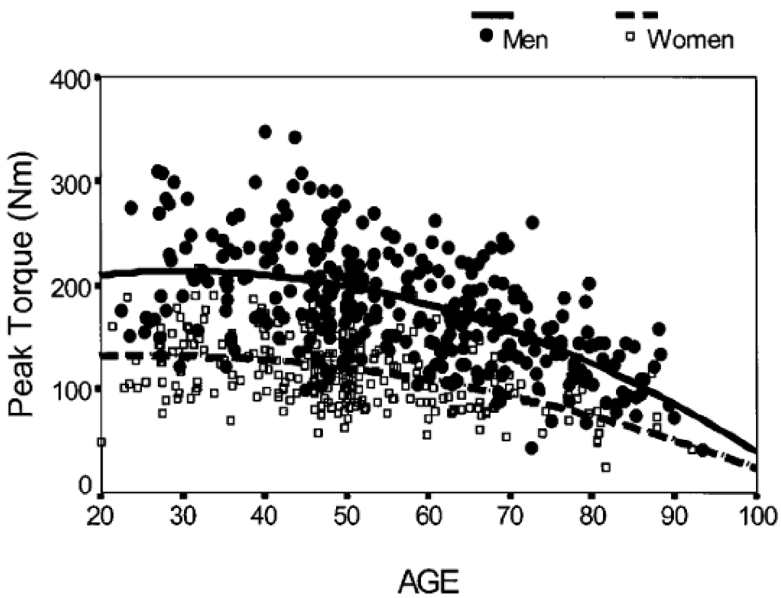

Fig. 2: The development of maximal muscle strength for men and women with age. Obtained from Lindle and colleagues (Lindle et al. 1997).

Moreover, the age-related loss in muscle power is even more pronounced than both muscle mass and -strength, since it already from the age of 50 years declines faster with 3-3.5% each year as illustrated in figure 3A and 3B (Skelton et al. 1994; Suetta et al. 2019).

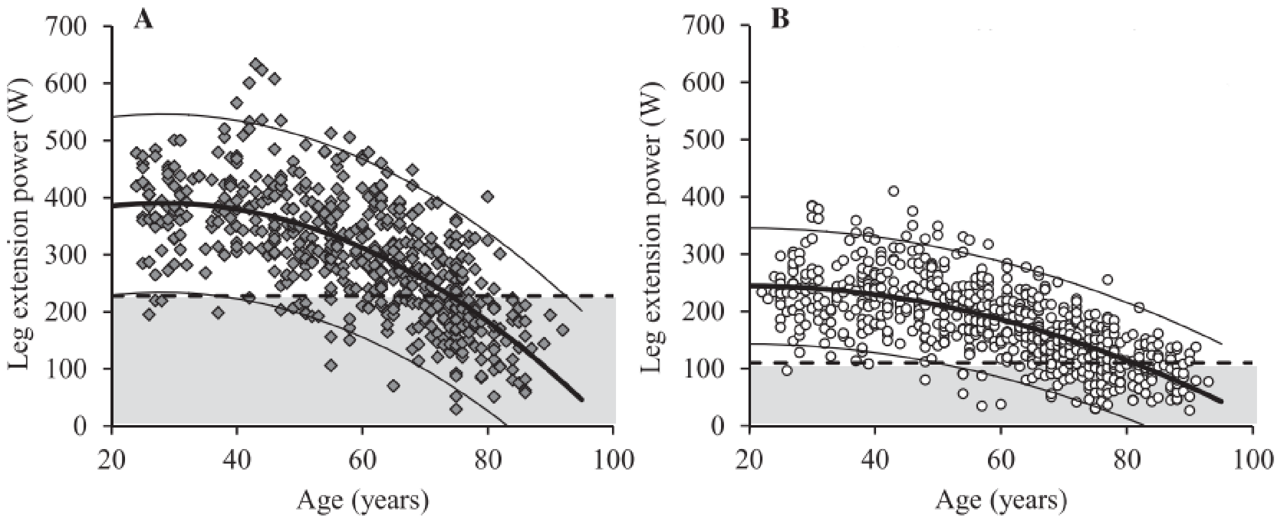

*Fig. 3: The development of leg extensor power for men (**A**) and women (**B**) with age. Obtained from Suetta and colleagues (Suetta et al. 2019).*

As it previously has been shown that muscle power correlates with functional performance, the decline in physical function with aging may be more likely associated with the loss of muscle power than the mere loss of muscle mass and -strength probably due to the earlier and more rapidly decline as we age (Reid and Fielding 2012; Bean et al. 2002; Foldvari et al. 2000; E Joan Bassey et al. 1992). From the presented figures (fig. 1B, 2, 3A, and 3B) obtained from Janssen, Lindle, and Suetta (Janssen et al. 2000; Lindle et al. 1997; Suetta et al. 2019), I have estimated the losses from the age of 45 to 65 years and from 65 to 85 years of age. Table 1 clearly indicates that the loss of muscle power occurs a lot faster than especially muscle mass, but also faster than muscle strength.

Table 1: An estimate of the percentage decrease in muscle mass, -strength and -power obtained from (Janssen et al. 2000; Lindle et al. 1997; Suetta et al. 2019).

	45 to 65 years of age	65 to 85 years of age
Muscle mass	5%	15%
Muscle strength	15%	50%
Muscle power	20%	60%

6.2 The aging brain

In line with muscle mass, -strength, and -function, aging has a negative effect on several areas and functions in the brain e.g. vasculature, morphology and cognition. The brain shrinks in volume as we age with approximately 0.5% per year from the age of 40, and that rate will probably increase after the age of 70 years (Peters 2006). An illustration of the aging brain is presented in figure 4.

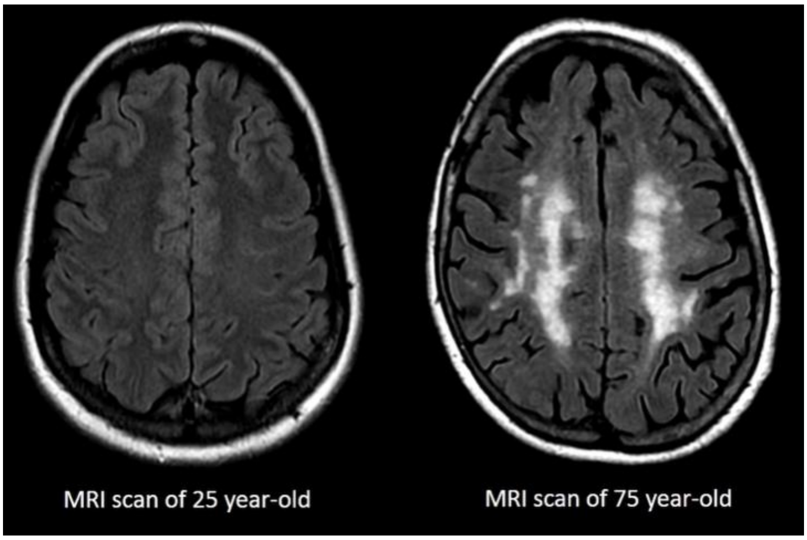

Fig. 4: Two MRI scans from a young (left) and old (right) person, clearly showing the aging brain with a decrease in volume as a result of a degeneration of white matter causing white matter disease (the white color at the picture to the right). Obtained from a video presented at YouTube by Dr. Daniel Mandell, UHN Krembil Neuroscience Centre, Toronto.

Further, it is suggested that one of the most affected regions is hippocampus, which is declining by approximately 1% each year from the age of 50 years (Anderton 2002; Fraser, Shaw, and Cherbuin 2015). As hippocampus is essential for e.g. memory function and mood regulation, in addition to the fact that changes in volume have been associated with several neurological conditions such as dementia, Alzheimer's and Parkinson's disease, it is of high interest to find strategies to counteract or minimize these changes (Fraser, Shaw, and Cherbuin 2015; Erickson et al. 2011).

6.3 Strategies to counteract age-related loss of muscle mass, -strength and -function, health-related quality of life and hippocampus volume

As described above many different aspects are affected by aging. Because of this, different strategies can be suggested to counteract the losses. One strategy could be physical activity as it has been demonstrated that physical activity of various kinds improves muscle function and physical performance. In a randomized controlled trial (RCT), 424 sedentary individuals aged

70-89 years were randomized to either physical activity or a health education intervention for 12 months. The physical activity consisted of a combination of strength, aerobic, balance, and flexibility exercises, where the health education program was weekly group meetings containing sessions of health topics relevant for elderly such as nutrition and medications. The Short Physical Performance Battery (SPPB) score and 400m walking speed were completed before and after the 12 months intervention to evaluate physical performance. Only participants in the physical activity group improved the SPPB after the 12 month (Pahor et al. 2006). In addition, it has been demonstrated that life-long physical activity has a positive effect on several outcomes related to physical function and health. It was found that muscle mass, muscle strength and physical function were superior in older adults with life-long training experience compared with untrained older adults (Mikkelsen et al. 2013; Zampieri et al. 2015). However, strength training appears to be the most effective physical activity to improve muscle mass, -strength and -power. Improving these parameters increases functional performance such as the ability to rise from a chair (Ratamess et al. 2009).

Therefore, this thesis will focus on strength training as a strategy to improve physical function and health as well as to counteract the decline of hippocampus volume. Further, the research in this thesis will consider two different strength training regimes, heavy and moderate intensity, to investigate, which intensity is the most beneficial for counteracting the age-related losses.

6.3.1 The effect of strength training on muscle mass, -strength and -function

Strength training has previously been associated with an effective method to improve muscle strength, -mass and -power in a dose-dependent manner in elderly (Borde, Hortobágyi, and Granacher 2015; Peterson et al. 2010). Strength training programs consist of different variables that can be modulated depending on what the goal of the training is. Variables could be the number of set and repetition, intensity, range of motion, the velocity of lifting, etc. The most effective strategy to improve muscle mass and -strength appears to be with higher intensity (Ratamess et al. 2009; Borde, Hortobágyi, and Granacher 2015). Previous heavy resistance training studies have demonstrated marked increases in muscle strength and more moderate increases in muscle mass after 12-24 weeks of training in both moderately and very old individuals (Leenders et al. 2013; Bechshøft et al. 2017; Fielding et al. 2002; Marsh et al. 2009). In contrast, there are more ambiguous conclusions as to the effect upon muscle strength and -

mass in studies using moderate intensity training (Borde, Hortobágyi, and Granacher 2015; Oh et al. 2017; Martins et al. 2015). However, prior studies have predominantly investigated the effects of short-term training interventions (3-6 months), often used per-protocol analysis, and primarily investigated healthy individuals, which potentially could limit the extrapolation to the general population.

Even though heavy resistance training seems to be most beneficial to increase muscle strength, -mass, and -function, heavy resistance training also requires certain equipment and the risk of injury is higher compared with lower loads of strength training. Further, to achieve the benefits of heavy resistance training, more supervision may be needed to ensure that the progression of the intensity is optimal since self-selected strength training intensities have been shown to be lower than recommended (Ratamess et al. 2009). Besides the lower risk of injury, moderate intensity resistance training requires simple equipment and can easily be performed at home, which could be preferable for elderly individuals who are unwilling or unable to perform heavy resistance training. Therefore, besides the examination of which intensity is most beneficial, we wanted to investigate whether moderate intensity resistance training for one year also has beneficial effects upon muscle strength, -mass, and -function.

6.3.2 Physical activity and its influence on brain function and health-related quality of life

Besides the effect upon skeletal muscle, regular physical activity has also previously been shown to have a positive effect on various mental characteristics including health-related quality of life in older individuals (Rejeski and Mihalko 2001). Further, the review concluded that there was no evidence that the positive effects were limited to specific subgroups, modes of activities, or the experimental settings. However, a study detected a higher response in group-based compared with home-based exercise training, but both groups had increased well-being (Rejeski and Mihalko 2001).

In a population-based cohort study, it was suggested that individuals with life-long higher physical activity score also had stronger functional connectivity, reduced decrease of brain volume, as well as stronger perfusion in one of the most age-sensitive regions of the brain, the posterior cingulate cortex (Boraxbekk et al. 2016). This indicates that good physical shape over decades of life positively influences age-related decreases, potentially influencing the function of the brain. Additionally, training intervention studies also suggest that physical activity has beneficial effects on brain plasticity (Cotman, Berchtold, and Christie 2007; Voss et al. 2013), brain structure, and function (Bherer, Erickson, and Liu-Ambrose 2013; Erickson, Gildengers, and Butters 2013). However, previous studies have primarily investigated aerobic exercise training, and those who have used strength training have investigated the effects of short-term interventions upon brain function and not morphology in moderately old to old individuals (Iuliano et al. 2015; Coetsee and Terblanche 2017; Forte et al. 2013; Ozkaya et al. 2005). The effects of strength training upon mental health and brain structure are largely unknown. In this study, we therefore investigated to what extent long-term strength training influenced health-related quality of life and hippocampus volume.

6.4 Implementation of physical activity habits

As mentioned above strength training is an effective method to counteract the age-related losses in skeletal muscle function. However, it has previously been shown that after termination of a prescribed strength training period, improvements in muscle mass and -strength obtained during this training period are either fully disappeared or only partly maintained (Trappe, Williamson, and Godard 2002; Bickel, Cross, and Bamman 2011; Cleiton S. Correa et al. 2016; Cleiton Silva Correa et al. 2013; Fatouros et al. 2005; Kalapotharakos et al. 2007). To our knowledge, this has predominantly been studied after shorter duration interventions with strength training, all followed by a prescribed detraining period. Only a few studies have investigated older adults in a follow-up period (without any training instructions) after a long-term period with supervised strength training (Snijders et al. 2019; Karinkanta et al. 2009; Uusi-Rasi et al. 2017). In a strength training study, muscle strength was only partly preserved measured one year after termination of the 6-months intervention, whereas improvements in muscle mass were lost (Snijders et al. 2019). This could be explained by discontinuation of training after the intervention. In a few long-term (12-24 months) training studies investigating older women, it was found that the strength training induced improvements in muscle strength were either fully or partly disappeared one or two years after termination of the exercise intervention (Karinkanta et al. 2009; Uusi-Rasi et al. 2017).

It is unknown to what extent one year of systematic strength training leads to a more permanent active lifestyle, or whether strength training (and other types of exercise) is implemented as a part of the daily routine in older adults after one year as well. Therefore, one year after termination of the intervention we wanted to investigate the continuation of unsupervised strength training. Implementation of a more active lifestyle could lead to improved maintenance of gains obtained in a previous exercise training intervention. It has previously been shown that organized strength training 1 day/week for 6 months after a 12-weeks strength training program was enough to maintain the improvements in muscle mass and -strength in older men (Trappe, Williamson, and Godard 2002). In contrast, Bickel and colleagues observed that structured strength training 1 day/week for 8 months after a 16-weeks strength training program could preserve muscle strength, but not muscle mass in older adults (Bickel, Cross, and Bamman 2011). In a study with no given exercise instructions during the follow-up period, it was found that the loss in muscle mass was partly counteracted if some kind of unsupervised strength training was performed (Snijders et al. 2019). In contrast, no further differences were observed for muscle strength between those who continued with strength training and those who did not (Snijders et al. 2019). In the present study, we evaluated whether there was any difference in the maintenance of muscle mass, -strength, physical function, and mental well-being between participants who continued with the same strength training program as during the intervention and those participants who stopped the exercise program.

To summarize, we know that there is an age-related loss of muscle mass, -strength, and -power, resulting in an impaired muscle function and that muscle power has the most pronounced and fastest decline. We also know that strength training is an effective strategy to counteract these age-related losses, and that heavy resistance training favors improvements compared with moderate intensity resistance training. However, prior studies have predominantly used relatively short periods of strength training (3-6 months), often used per-protocol analysis, and primarily investigated healthy individuals, which potentially could limit the extrapolation to the general population, whereas only a few have investigated the effects of long-term interventions. Further, little is known whether one year is enough to implement physical activity as a part of the daily routine in older adults. Therefore, investigating the immediate (1-year) and long-term (2-years follow-up) effects of a 1-year strength training intervention with different intensities including both healthy and chronically diseased older individuals, can aid understanding of what type of training that is the most beneficial in a broad variation of older individuals.

7. Aims and hypotheses

The primary aim of this thesis was to follow the age-related loss of skeletal muscle function and other health-related parameters in older adults (either healthy or with chronic diseases) and to investigate whether these changes could be counteracted with strength training of different intensities. Additionally, we wanted to evaluate whether potential improvements obtained by training could be maintained also after the long-term supervised training intervention. Therefore, the following specific aims were investigated:

Study I:

- To investigate the effects of one year of regular strength training with two different intensities upon muscle mass, -strength, and -function in both healthy and chronically diseased older individuals aged 62-70 years.
- To investigate whether long-term strength training has a positive effect on hippocampus volume and health-related quality of life.

Study II:

- To investigate whether improvements obtained during the 1-year of strength training persisted one year after termination of the intervention.
- To investigate whether the gains obtained during the 1-year of supervised strength training were maintained differently in the two previous training groups at follow-up (2-years follow-up) in all participants who completed the one-year supervised training.
- To investigate whether there was any difference in maintenance between those who continued strength training on their own during the follow-up year and those participants who stopped the regular strength training.

These aims were examined with the following objectives and hypotheses:

In **Study I**, the objectives were to compare the effects of a 1-year intervention with either center-based heavy resistance training (HRT), home-based moderate intensity resistance training (MIT) or a non-exercising control group (CON) on the following parameters: Leg extensor power (primary outcome), muscle strength and -size, functional ability, body composition, daily level of physical activity, health-related quality of life and hippocampus volume. The hypotheses were:

- That compared with a control group, one year of HRT or MIT would improve leg extensor power, muscle strength, and muscle mass.
- That the response in HRT on measured physiological parameters would be superior to MIT.
- That strength training could counteract the age-related decline in hippocampus volume and improve health-related quality of life.

We chose leg extensor power as our primary outcome as we - due to the faster age-related decline - believed that the opportunity to increase muscle power (compared with e.g. muscle mass) was high.

In **Study II**, the objectives were to investigate the maintenance of potential gains obtained during the 1-year strength training intervention, measured one year after completion of the intervention, and whether the maintenance was enhanced if strength training was continued during the follow-up year. The hypotheses were:

- That one year after termination of the strength training intervention, improvements in muscle mass and -strength were maintained in participants in the previous two training groups.
- That the maintenance primarily was due to continuation of strength training and other physical activities on an individual basis.
- That participants in MIT would more likely continue training primarily due to the already implemented training at home.

8. Methodological considerations

This thesis is based on one large RCT, the LISA study, which has generated two papers for the thesis. The LISA study is an abbreviation for Live actIve Successful Aging and investigates the effects of a 1-year strength training intervention upon muscle mass, -strength, and -power as well as physical function and mental well-being in older adults. In the present study, results from the 1-year intervention (paper 1) and from the year after completion of the intervention (2-years follow-up) (paper 2) will be presented. An overview of the study design is presented in figure 5.

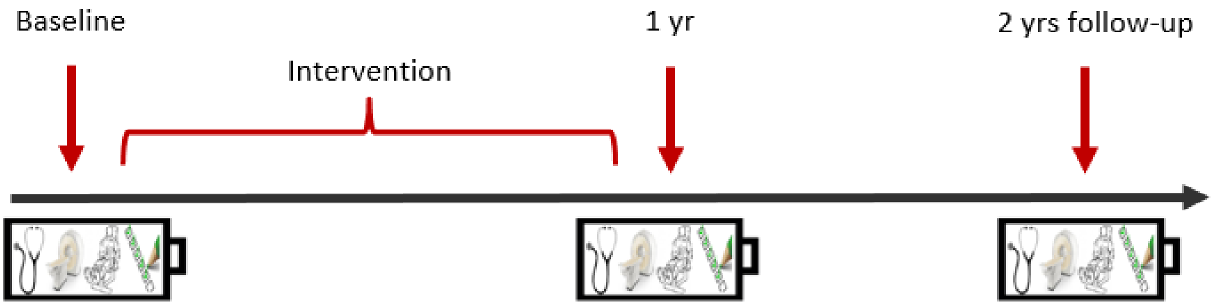

Fig. 5: Study design including measurements at baseline, 1-year and 2-years follow-up.

8.1 Study design

The LISA study included 451 independent healthy and chronically diseased men and women with an age between 62 and 70 years, who were not involved in systematic strenuous exercise or regular strength training for more than one hour/week. The participants were recruited mainly through newspaper advisements in the greater Copenhagen area. Our decision to include both healthy and chronically diseased individuals could potentially contribute to a higher variation in the data. However, we chose to do so to be able to present results that were more applicable to older adults in general than if we had only included healthy participants. Despite that, we excluded individuals with severe or dysregulated medical diseases (e.g. active cancer, or severe heart disease), musculoskeletal diseases impeding training ability, and the use of drugs that may have influenced the training effects (e.g. androgens or antiandrogens). All participants went through baseline assessments including medical screening, physical and cognitive testing, body composition, muscle thigh CSA and brain imaging before randomization to one of three 1-year intervention groups: Heavy Resistance Training (HRT), Moderate Intensity resistance Training (MIT) or Control (CON). Randomization was stratified according to sex (man/woman), functional ability (chair-stand performance ≤11 or >11), and body mass index (BMI ≤28 or >28) to make sure the participants were equally distributed in the three intervention groups. See previous publications for a detailed description of study design, inclusion, and exclusion criteria (Eriksen et al. 2016; Gylling et al. 2020). Of the 451 randomized individuals, 419 completed the 1-year follow-up assessment battery and they were all included in the analysis no matter of compliance to the intervention. At the 2-years follow-up, 21 participants further decided to drop out of the study with 398 participants completing the assessment battery and subsequently included in the analysis to compare baseline, 1-year, and 2-years follow-up. Figure 6 illustrates a study flow chart. After completion of the 1-year intervention, there were no exercise restrictions, leaving participants from all three groups free to perform any kind of exercise on an individual basis without any supervision or exercise instructions.

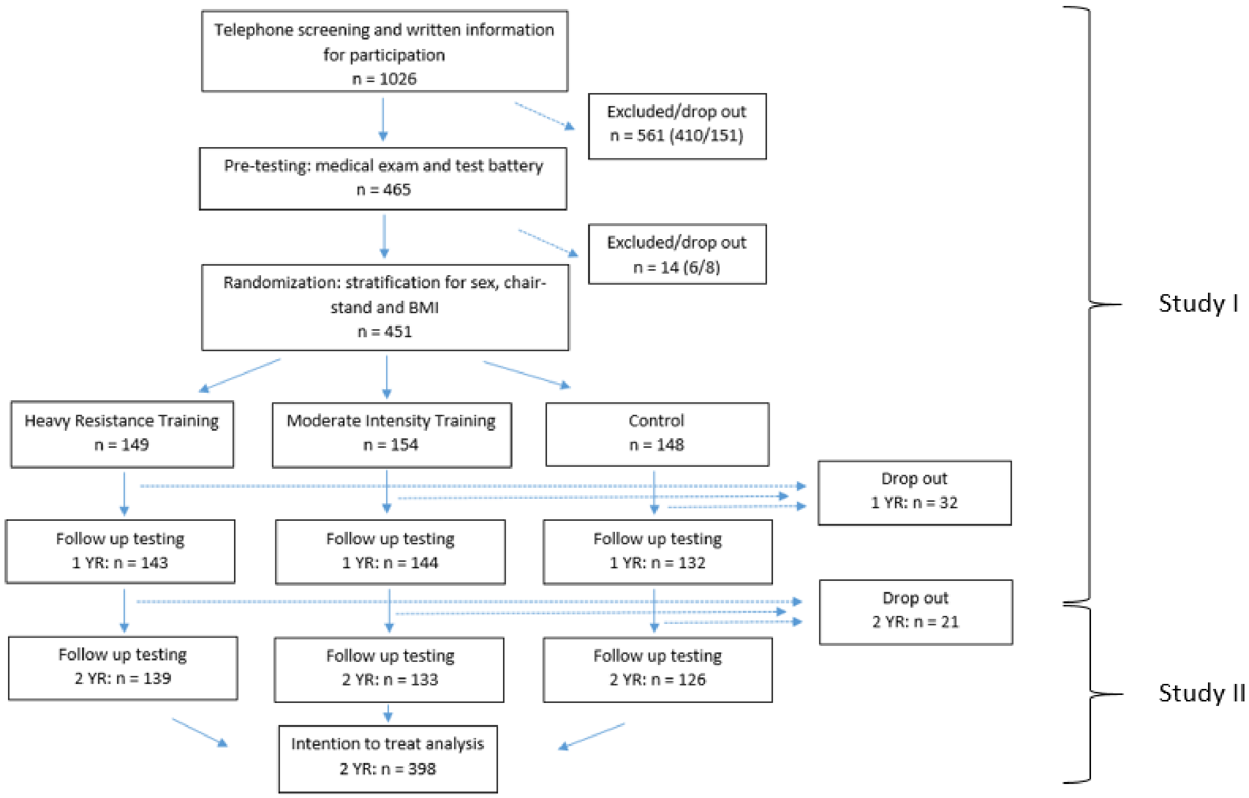

Fig. 6: Study flow chart including the participants' enrolment process, randomization into the intervention and subsequent data from 1-year and 2-years follow-up.

8.2 Interventions

A summarize of the two strength training interventions is presented in table 2. The HRT group consisted of three supervised exercise sessions/week where a whole-body program was performed in a commercial fitness center. The first 6-8 weeks in both strength training groups were a familiarization period at low intensity in order to reduce the risk of musculoskeletal injury and further to familiarize the participants to strength training. Thereafter, a progressive strength training program was performed in both groups with a variety of loads during the entire intervention as it has been suggested to be the most effective way to ensure long-term progression in muscle strength (Ratamess et al. 2009). HRT completed three sets of 6-12 repetitions corresponding to an estimated intensity between 70-85% of 1 repetition maximum (RM) in a linear periodized regime over an 8-week period with increasing workload every second week. After one 8-week periodization there was one week of restitution before the periodization was repeated starting out with 3 x 12 repetitions with a higher workload than during the last period. Thereby the workload would be increased throughout the entire 1-year intervention. We chose a linear periodized strength training program as most previous studies have shown that it is superior to a non-periodized program for increasing e.g. maximal muscle strength and -power if the training period is of longer duration (>6 months) (Ratamess et al. 2009). Both normal and periodized strength training programs are suggested to be equally effective during the initial months of training (Ratamess et al. 2009).

The MIT group consisted of three exercise sessions/week, where one of the sessions was supervised at the hospital and the last two were home-based. The program was also a whole-body program and conducted as circular training, where all exercises were performed once and then repeated for three times. MIT performed three sets of 10-18 repetitions corresponding to an estimated intensity between 50-60% of 1RM with a gradual increase from 10-18 repetitions before the workload was adjusted.

For both groups the last repetition had to be exhaustive, with the workload otherwise adjusted by increasing the number of repetitions (MIT) or the workload (MIT+HRT). In MIT, the workload was adjusted by using a stronger rubber band (red -> green -> blue -> black -> silver -> gold) except for a) push-ups, where the load was increased by gradually decreasing the angle of the body relative to the floor, b) air squats, where the load was increased by putting one foot on a footrest (5–10 cm high), thereby gradually loading the foot on the floor more, and c) calf raises, where the load was increased by changing from a bilateral to unilateral performance and finally by using weight vests (adding 5–10% of the bodyweight).

The training volume between HRT and MIT was not directly matched, but the participants were equally instructed that the exercises had to be exhaustive in both groups. Further, the physical trainers were responsible for adjusting the load continuously to ensure that the intended number of repetitions was reached. A big difference between HRT and MIT was the amount of supervision, which potentially could have affected our results because benefits from supervised exercise training may be higher than unsupervised training. This was chosen to make sure that the participants in HRT exercised with adequate intensity and to ensure that the exercises were performed correctly, hereby lowering the risk of injury. MIT was primarily home-based due to the goal of implementation of the training at home during the intervention, whereby it may be easier to continue the training after completion of the intervention compared with those in HRT where a fitness center was necessary. Consequently, training compliance in MIT relies on self-report. However, we still prioritized to supervise the training once a week to ensure progression in the training as well as proper execution of the exercises. Due to the lower intensity in MIT, their risk of injury was also lower than in HRT.

Participants in the control group were not allowed to do more than one hour of strenuous physical activity per week and the participants were asked not to change their habitual physical activity level throughout the 1-year intervention. Instead of exercise training, the control group was offered to participate in social and cultural activities approximately two times a month throughout the 1-year intervention.

Table 2: Overview of the two strength training interventions.

	HRT	**MIT**
FREQUENCY	3 x per week	3 x per week
REPETITIONS	3 x 6-12	3 x 10-18
INTENSITY	70-85%	50-60%
CONTRACTION VELOCITY	2 s concentric, 2 s eccentric	2 s concentric, 2 s eccentric except for air-squat and calf raises that were 1 s concentric, 3 s eccentric
LOWER BODY EXERCISES	Leg press Knee extension Leg curl Calf raises Hip abduction	Air-squat Knee extension Hip extension Calf raises Hip abduction
EQUIPMENT	Fitness machines	Rubber bands and bodyweight
SUPERVISION	All sessions	Once a week

8.3 Measurements

At baseline, 1-year, and 2-years follow-up, participants went through a comprehensive assessment battery over three days. The three test days are presented in table 3. A detailed description of the measurements is available in previous publications (Eriksen et al. 2016; Gylling et al. 2020).

Table 3: Overview of assessments completed at all three time points.

	BASELINE	1 YR	2 YRS
DAY 1: MEDICAL EXAMINATION	x	x	x
DAY 2: BODY COMPOSITION (DXA)	x	x	x
DAY 2: PHYSICAL TESTING	x	x	x
DAY 3: MRI OF THE THIGH AND BRAIN	x	x	x

8.3.1 Medical examination

On day 1, the participants arrived at the fasted state between 8 and 11 am to the medical examination. After the medical history was noted, measurements of blood pressure and anthropometry were carried out before blood samples were taken.

8.3.2 Body composition

To measure lean body mass, leg lean mass, whole-body fat percentage, and visceral fat content, we chose to use dual-energy-x-ray absorptiometry (DXA) scans. Magnetic resonance imaging (MRI) of the thigh was used to measure CSA of the vastus lateralis muscle. There are many different methods to quantify muscle mass, including e.g. MRI, computed tomography (CT), DXA, bioelectrical impedance (BIA), and ultrasound. Normally, MRI and CT are considered as golden standard to assess muscle mass non-invasively (Cruz-Jentoft et al. 2019). The use of CT is cheaper and faster compared with MRI, but the scans applying radiation, which is why we chose MRI to determine CSA of m. vastus lateralis. Further, MRI is able to identify fat tissue, which can therefore be excluded in the analysis. However, to quantify body composition, these methods would have been too expensive and time-consuming, leading us to choose DXA-scans instead (Lunar DPX-IQ DEXA scanner, GE Healthcare, Chalfont St. Giles, UK). The use of DXA can provide a reproducible estimate of lean body mass and leg lean mass in a few minutes, which is an advantage of using that tool (Cruz-Jentoft et al. 2019). However, the measurement of lean body mass by DXA is not a direct measure but an estimate, where bone and fat mass are subtracted from the total mass to give an estimate of lean body mass including fluid and all other tissues that are not fat and bone. Therefore, the measurement can be influenced by the individual's hydration status (Cruz-Jentoft et al. 2019) or edema, as body water is included in the estimate of lean body mass.

Prior to both DXA and MRI scans, the participants were asked not to perform any strenuous physical activity during the three days leading up to. Participants arrived in a non-fasting state to the DXA scan between 8.30 am and 13.30 pm, and immediately before the scan, they went to the toilet to minimize the aforementioned influence of fluid. The participants were scanned in a supine position with approximately 10cm between the heels to ensure clear separation of the legs in the subsequent analysis. The DXA scan images were assessed to correct and verify the placement of automatic manufacturer-implemented region-of-interests (ROI), ensuring correct body segmentation. Body segmentation was performed with a neckline, lines surrounding the spine, two arm lines at the shoulder joint on the medial side of the head of the humerus, a pelvic horizontal line, and two oblique lines passing through the hip joint and at the lateral edge of os ischium. In addition, all visible artifacts on the body were manually removed, e.g. hip prostheses from hip replacement surgeries and metal objects. The scanner software (Lunar iDXA Forma enCORE vs. 15) automatically calculated body composition based on the scan images. For a very small number of the subjects who could not fit into the defined scan field, being either too tall or big, the scanner software estimated outlying areas. One blinded assessor performed the image analysis for baseline and 1-year DXA-scans and another blinded assessor performed the image analysis for the 2-years DXA-scans. Data were then exported to Microsoft Excel, where it was further organized to the statistical analysis (SAS Enterprise Guide 7.1).

The MRI scans were performed in a 3.0 T TX Philips Achieva scanner allocated at Hvidovre Hospital (DRCMR). From the MRI scans, m. vastus lateralis was manually drawn using the JIM software (Xinapse systems). The mid slice, 20cm above the tibia plateau, was used for the ROI. For ROI delineation, the data was randomized between baseline and 1-year, so the radiographer performing the drawing was blinded to the time of scanning. The MRI scans from the 2-years follow-up were drawn separately and therefore the radiographer was not blinded for time point, but was still blinded to the intervention group.

8.3.3 Physical assessment

The physical assessments were carried out directly after the DXA-scan, explaining why the participants were not allowed to perform any strenuous physical activity three days prior to the examination day. The five different tests were performed in the following order: 400m walking test, leg extensor power, 30 s chair-stand performance, handgrip strength, and isometric knee extensor strength.

8.3.3.1 Strength and power measurements

In the LISA study, our primary outcome was leg extensor power as it has been suggested that the age-related loss in muscle power should be more closely associated with the decrease in functional ability than the loss in muscle mass and -strength (Skelton et al. 1994; Foldvari et al. 2000; E Joan Bassey et al. 1992; Bean et al. 2002). To measure maximal single-leg extensor power (force x velocity), we used Leg Extensor Power Rig (Queen's Medical Centre, Nottingham University, UK), which measures leg extensor power against a fixed load (E J Bassey and Short 1990). The participants were instructed in a seated position with the hands across the chest to kick the pedal as fast and hard as possible accelerating a flywheel, which was used to calculate average power production. The test was repeated at least five times and until two consecutive attempts were lower than the highest one. This test has previously shown excellent reproducibility (ICC=0.92–0.94; CV=8–10%) in healthy older adults (E J Bassey and Short 1990; Bieler et al. 2014). Further, as a secondary measure, we investigated isometric knee extensor strength in a Good Strength device (V.3.14 Bluetooth; Metitur, Finland). In a seated position, the participants were instructed to perform a maximal contraction for at least three times, but the test was repeated until no further improvement occurred to make sure the actual maximum was reached. The reproducibility of the isometric strength test has previously been shown to be good (ICC=0.90–0.94; CV=7–8%) in healthy older adults.

As another measure of muscle strength, we determined handgrip strength with a SAEHAN DHD-1 Digital Hand Dynamometer. Handgrip strength is a valid measure for overall muscle strength, clearly related to functional ability and a valid predictor of mobility limitations (Fragala et al. 2016; Alley et al. 2014; Sallinen et al. 2010; Rantanen et al. 1999). Further, it is a reliable and simple test to carry out (Wang and Chen 2010). The participants were instructed in a seated position to squeeze the dynamometer as hard as possible for about 5 seconds. The measurement was repeated until no further improvement occurred, but at least three times.

8.3.3.2 Functional testing

To investigate the potential conversion of the expected improvements in muscle strength into an improved functional performance as suggested previously (Bean et al. 2009; Christie 2011; Marsh et al. 2009), we chose to determine 400m walking time and 30 s chair-stand performance. Where the 400m walking test assessed walking endurance, the 30 s chair-stand test was a measure for functional lower extremity strength and endurance. Both tests have previously shown excellent reproducibility in healthy middle-aged women and older adults (Pettee Gabriel et al. 2010; Bieler et al. 2014; Jones, Rikli, and Beam 1999) and the 400m walking time provides a valid estimate of peak VO_2 in older adults as well (Simonsick, Fan, and Fleg 2006). Participants were instructed to walk the 400m on an indoor closed circuit as fast as possible and to perform as many chair-stands as possible in 30 seconds.

8.3.4 Physical activity measurement

Overall muscle function could potentially be related to daily physical activity. Therefore, we decided to determine daily physical activity in our participants. On the first test day as a part of the medical examination, an accelerometer (activPAL micro, PAL technologies, Glasgow, Scotland) was mounted on the thigh of the self-reported dominant leg and was worn for five consecutive days including three week and two weekend days measuring daily step count and time spend in sitting/supine position, standing position and time in motion. Data were extracted to Microsoft Excel with ActivPAL software (Research edition, V.7.2.32, PAL Technologies, 2013). In this thesis, the focus will only be on the daily step count as a measure of the level of habitual physical activity.

8.3.5 Measurement of hippocampus volume

MRI of the brain was implemented to assess hippocampus volume and intracranial brain volume using a 3.0 T TX Philips Achieva scanner allocated at Hvidovre Hospital (DRCMR). To estimate hippocampus volume (mm^3) for all time points, we used freesurfer version 6.0 longitudinal stream (Reuter et al. 2012). Radiographers performed initially quality control of the T1-images, and then the hippocampus volume was additionally controlled using the ENIGMA pipeline for quality control. As a covariate, intracranial volume was used to take into account the hippocampus volume change in relation to total brain volume.

8.3.6 Questionnaires

In order to evaluate the participant's health-related quality of life and self-reported physical activity, we chose to use the questionnaires Short-Form Health Survey 36, SF-36, and The Physical Activity Scale for the Elderly, PASE. Further, to evaluate compliance and implementation to strength training the year after completion of the intervention, the participants in HRT and MIT filled out a questionnaire at 2-years follow-up. The questionnaire consisted of 11 different questions concerning their physical activity habits in general and whether they had continued with the same strength training program as they were introduced to during the intervention. Regarding compliance to the strength training program, the participants had five different options to choose from 1) not at all/less than one month, 2) 1-3 months, 3) 4-6 months, 4) 7-9 months, and 5) 10-12 months. Besides the investigation of the ability to preserve muscle mass, -strength, physical function and mental well-being in older adults one year after completion of a 1-year strength training intervention, we wanted to examine whether the preservation was different in the participants who continued with strength training the year after completion of the intervention compared with those who did not. Therefore, we divided the participants into two groups: 1) those who had continued with the exact same strength training program in 10-12 months and 2) those who stopped directly after or during the first 9 months after completion of the intervention.

8.4 Statistical analysis

Previous mean values and standard deviations (SD) for functional muscle measurements on older individuals were used to power calculations and revealed a sample size of n=60 in each group. We chose to include ≈150 participants in each group to detect smaller group differences and consider larger variations. In addition, to be able to detect relevant functional differences at a 10-years follow-up assessment with an estimated 50% loss during the follow-up period, ≈150 participants in each group were necessary. We chose a power level of 80% and significance level of 0.05 for the ANOVA.

For both Study I and II, a two-way mixed model with repeated measures was used to evaluate the overall effects of group and time for all parameters except training compliance and sex distribution. In case of a significant group x time interaction, Tukey post hoc analysis was used to evaluate within group comparisons as well as a one-way ANOVA (a generalized linear model) to detect any group differences between baseline and 1-year in Study I, and further between baseline and 2-years follow-up and between 1-year to 2-years follow-up in Study II. If no significant group x time interaction was detected, the same model but without interaction was used to evaluate effect of time. For sex distribution, a frequency analysis was used. In all statistical models, only participants who came to all assessments were included in the analysis (Study I: baseline and 1-year; Study II: baseline, 1-year and 2-years follow-up), why we have included 419 participants in Study I and 398 participants in Study II. Descriptive statistics will be presented as mean ± SD. All other data are presented as mean ± SE unless otherwise stated. All missing data were removed for the same participant at all time points (e.g. if a participant had one missing data from baseline, data from 1-year and 2-years follow-up were removed). All statistical analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC, USA).

Specific for Study I: To evaluate the magnitude of the mean differences, effects sizes (ES) were calculated for all comparison groups (HRT vs. MIT, HRT vs. CON and MIT vs. CON).
Further, a two-way mixed model was used to evaluate whether there was any differences in the response to the intervention upon muscle strength, -mass, -power or visceral fat content in those who had no chronical disease and those who had one or more if they were analyzed separately. For all analyses, the stratification parameters (BMI, chair-stand and sex) were included in the statistical model. For training compliance, an unpaired t-test was used.

Specific for Study II: To evaluate the effects of unsupervised strength training the year after the intervention, a two-way mixed model with repeated measures was used (group and compliance) to assess the effects of strength training group and compliance on changes from 1-year to 2-years follow-up. We could not detect any group x compliance interaction in changes from 1-year to 2-years follow-up in the two training groups in any parameters, why we only considered main effects of continuation of strength training independent of intensity. Whether there were any differences between CONTIN and STOP at baseline and whether the responses to the 1-year intervention were different as well were evaluated by a one-way ANOVA (a generalized linear model). In these models, only participants in the two strength training groups were included.

9. Results and discussion

In this section, results from Study I, describing the effect of the 1-year intervention, and Study II, describing the maintenance of muscle function and health one year after termination of the intervention (2-years follow-up), will be presented and discussed in themes.

As described earlier, it is well documented that there is an age-related loss of muscle mass, -strength and -function, which partly can be counteracted with strength training. However, previous short-term investigations have shown that gains obtained in muscle mass and -strength either fully disappear or are only partly preserved after a prescribed detraining period. Therefore, it is unknown whether one year of organized strength training leads to a more permanent active lifestyle with strength type exercises (and other types of exercises) is implemented as a part of the daily routine in older adults. The main hypotheses for the present study were that compared with a non-exercising control group one year of HRT and MIT resulted in improvements in muscle function, and that HRT was superior to MIT. Further, we hypothesized that one year after completion of the strength training intervention, participants in the previous training groups had maintained the improvements in muscle mass and -strength, which was primarily due to continuation of strength training and implementation of other physical activities on an individual basis.

9.1 Participant characteristics

A total of 451 participants were included (fig. 6) with an average age of 66 ± 2.5 years and a proportion of woman of 61% (table 4). There were no significant differences between the three intervention groups in any of the baseline characteristics (table 4). During the intervention, 32 participants dropped out and subsequently an additional 21 participants dropped out from 1-year to 2-years follow-up, primarily due to lack of time, lack of motivation or illness (fig. 6). All participants who completed follow-up assessments were included in the data analysis independent of intervention compliance, health status and activity level after inclusion. Therefore, 419 participants (93%) were included at 1-year (143 HRT, 144 MIT and 132 CON) and 398 participants (88%) at 2-years follow-up (139 HRT, 133 MIT and 126 CON) (fig. 6). Of the included 451 participants, around 80% of the participants had at least one self-reported chronic disease. Of all participants, 51% had 1-2 diseases, 27% had three or more diseases, whereas 22% had no diseases. Hypertension, hypercholesterolemia and cardiac diseases accounted for approximately 30%, 25% and 20%, respectively, of all participants. Finally, of the 451 participants 12% reported to be smokers at baseline. As described previously, it could be argued that the inclusion of both healthy and chronically diseased individuals could provide a higher variation in the determined data. From the background data, the two groups did not differ markedly from each other in physiological parameters, so any small group difference is outweighed by the strength of the study to include both healthy and chronical diseased elderly individuals.

Table 4: Participant characteristics at baseline (mean ± SD).

	Total (n=451)	HRT (n=149)	MIT (n=154)	CON (n=148)	Sample size
Age (years)	66 ± 2.5	66 ± 2.6	66 ± 2.5	67 ± 2.4	451
Sex (men/women) %	39 / 61	40 / 60	40 / 60	39 / 61	451
BMI (kg/m²)	26.0 ± 4.2	26.4 ± 4.1	26.0 ± 4.2	25.6 ± 4.3	451
Waist circumference (cm)	93.3 ± 12.2	94.2 ± 11.8	93.4 ± 12.4	92.3 ± 12.3	450
Whole-body fat %	33.6 ± 8.1	34.1 ± 8.0	33.6 ± 7.9	33.1 ± 8.5	451
Lean body mass (kg)	47.3 ± 9.0	47.8 ± 8.9	47.4 ± 9.3	46.8 ± 8.8	451
Leg extensor power (W)	193 ± 67	199 ± 71	192 ± 66	187 ± 63	450
30 s chair-stand (reps)	17 ± 4	16 ± 4	17 ± 4	17 ± 4	451
Total step count (steps/day)	9553 ± 3457	9481 ± 3262	9399 ± 3140	9783 ± 3941	431^

^Missing data due to technical error.

9.2 Training compliance during the 1-year intervention

The overall compliance (total number of completed training sessions) in the two training groups was high and did not differ between HRT (77% ± 21.6% (SD) and MIT (78% ± 24.6% (SD)). When compared with shorter lasting studies the compliance was almost as high (Bechshøft et al. 2017; Marsh et al. 2009; Fielding et al. 2002; Leenders et al. 2013; Oh et al. 2017) and even higher than a in a two year intervention study (Aartolahti et al. 2019). Further, 83% of the participants (HRT and MIT) completed at least two weekly training sessions. Thus, the results indicate that long-term supervised strength training in both healthy and chronically diseased elderly individuals can be implemented with good compliance. Additionally, due to the high training compliance, the results presented in the thesis are reliable and any lack of difference is not a result of low compliance.

9.3 Continuation of strength training during follow-up

In addition to the effects of strength training on muscle mass, muscle strength and physical function, a long-term strength training program could potentially initiate a positive long-term change in physical activity habits in older adults, including implementation of weekly strength training. From the questionnaire completed by the participants in the two strength training groups (n=272), 24% reported (41 HRT, 24 MIT) that they continued with the same strength training program from year 1 to year 2 with 2.3 sessions/week in average (CONTIN). Those participants who decided not to continue the exercise training in the period between 0 and 9 months post intervention (STOP) corresponded to 74% (94 HRT, 106 MIT), of which 114 participants (51 HRT, 63 MIT) reported not to have continued at all (0 months). The final 2% did not reply to the adherence questionnaire (4 HRT, 3 MIT). In contrast to our hypothesis, there were significantly more participants in HRT than MIT that continued the strength training program during follow-up ($p<0.05$). Our results could indicate that even though the MIT was home-based and therefore more applicable to perform also after termination of the initial training intervention, fitness center-based training was preferred. A reason for this could be that our study consisted of participants who apparently were more well-functioning already at the beginning of the intervention. However, the choice of training intensity may change over the 10 years of follow-up and it may be that more participants prefer to perform the moderate intensity training in the long run.

The continuation of 24% of the participants in the present study was less than in a previous study where 45% of the participants continued with some sort of strength training one year after completion of a 24-weeks strength training intervention (Snijders et al. 2019). However, we assessed whether or not the participants continued with the exact same exercise program, and in fact 46% of all participants in our training study continued doing some form of strength training during the follow-up year.

9.4 Muscle power and strength

9.4.1 Leg extensor power

In the present study, leg extensor power was the primary outcome. One year of strength training did not improve leg extensor power (fig. 7A). This was somewhat to our surprise, as a previous study with a similar strength training protocol, demonstrated a 15% increase in muscle power already after 12 weeks (Bechshøft et al. 2017). However, the participants in that study were markedly older than in the present study. As a previous study found a higher response in leg extensor power in very old individuals compared with moderately old individuals (Caserotti et al. 2008), our results support the view that improvements in muscle power is more likely to be observed in older and more functionally impaired individuals than in the age-range (62-70 years) included in the present study. Another explanation for the lack of improved muscle power in the present study could be that the exercises were not performed in an explosive, high-velocity pattern. It has previously been suggesting that to maximize improvements in muscle power, the strength training program should be of higher velocity (Caserotti et al. 2008), which is supported by studies comparing strength training programs with low and high velocity (Fielding et al. 2002; Marsh et al. 2009). In these studies, higher improvements were observed in leg extensor power as a result of high-velocity strength training compared with regular low-velocity strength training. However, compared with baseline also regular low-velocity strength training resulted in improved muscle power in moderately old individuals (Marsh et al. 2009; Fielding et al. 2002), which is supported by the previous mentioned study by Bechshøft and colleagues (Bechshøft et al. 2017).

One year after completion of the intervention, leg extensor power was still unaffected, and we did not observe any significant effect of time in the three intervention groups (table 5). However, the group that continued training during follow-up had an improved leg extensor power of 5% in response to the 1-year training intervention, which was maintained at 2-years follow-up (fig. 7B). In contrast, those who stopped training the year after termination of the 1-year intervention did not change leg extensor power at all over time (fig. 7B). It has previously been suggested that leg extensor power decreases markedly only after the age of 60 years, and differs among individuals dependent upon daily physical activity (Skelton et al. 1994; Suetta et al. 2019). The participants in the present study were already at baseline relatively active walking approximately 10.000 steps/day and therefore they might have had a high leg extensor power level even before participation.

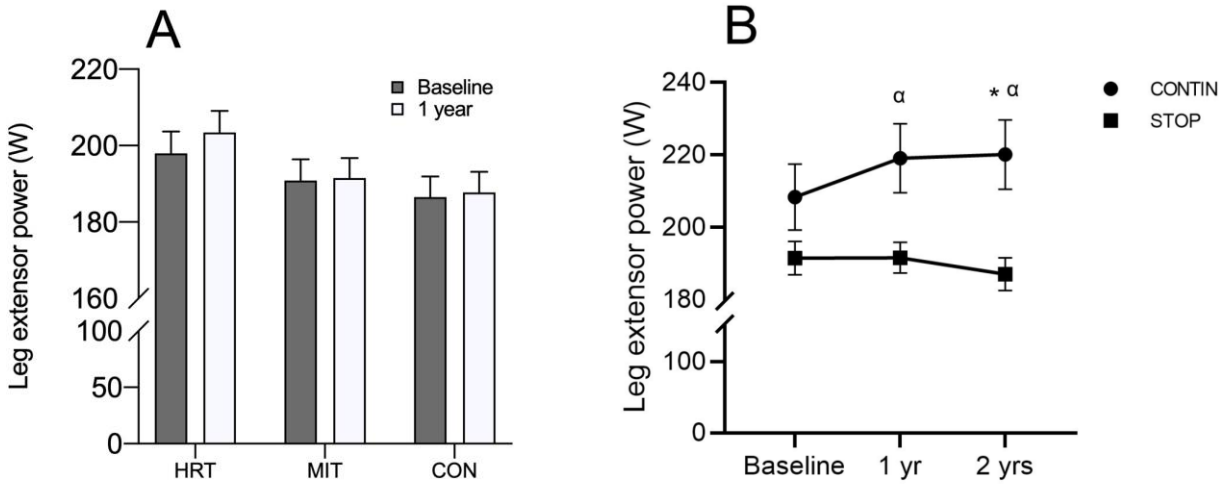

*Fig. 7: **A**) Leg extensor power before (baseline, filled bars) and after one year (open bars) of either heavy resistance training (HRT), moderate intensity resistance training (MIT) or habitual physical activity (CON) (n=417). **B**) Leg extensor power in CONTIN and STOP before (baseline), after one year of strength training (1 yr) and 2-years follow-up (2 yrs) (n=263) (mean ± SE).*

**: significantly different compared with baseline (p<0.05)*

α: change from baseline to 1 yr and 2 yrs significantly different compared with STOP (1 yr p<0.05 and 2 yrs p<0.01)

9.4.2 Muscle strength

In contrast to leg extensor power, isometric knee extensor strength improved in response to both heavy and moderate intensity resistance training compared with the non-exercising control group (p<0.0001, ES: 0.80, and p<0.05, ES: 0.31, respectively) (fig. 8). Further, as expected the response in HRT was higher than the one observed in MIT (with average increases of 11% and 4%, respectively) (p<0.0001, ES: 0.52), which fits well with previous studies comparing high and low-moderate intensity resistance training in healthy older adults (García-Pinillos et al. 2019; Fatouros et al. 2005).

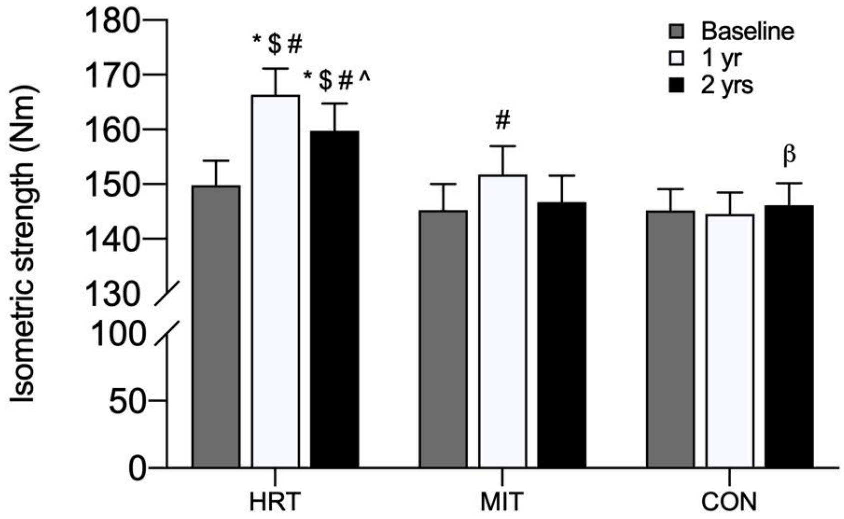

Fig. 8: Isometric knee extensor strength (n=389) before (baseline, grey bars), after one year of either heavy resistance training (HRT), moderate intensity resistance training (MIT) or habitual physical activity (CON) (1 yr, white bars), and one year after completion of the intervention (2 yrs, black bars) (mean ± SE).

**: significantly different from baseline (both p<0.0001)*
^: significantly different from 1 yr (p<0.01)
#: change from baseline significantly different compared with change in CON (HRT 1 yr p<0.0001 and 2 yrs p<0.01; MIT p<0.01)
$: change from baseline significantly different compared with change in MIT (HRT 1 yr p<0.0001 and 2 yrs p<0.01)
β: change from 1 yr significantly different compared with change in HRT and MIT (p<0.01)

The improvement observed in response to HRT was comparable to previous long-term training studies (1-2 years) in older adults (Aartolahti et al. 2019; Sundstrup et al. 2016; Karinkanta et al. 2009; Uusi-Rasi et al. 2017). Interestingly, when comparing studies with shorter duration as illustrated in figure 9 (Marsh et al. 2009; Bechshøft et al. 2017; Fielding et al. 2002; Churchward-Venne et al. 2015), the strength improvement in the present study was not higher (fig. 9, green square) even though we used periodization, which as previously described is suggested to improve muscle strength to a higher degree (Ratamess et al. 2009). It is important to notice that most of the improvements in muscle strength that were higher than in the present study, were using a dynamic 1RM measurement method, whereas the present study measured muscle strength by using isometric peak torque. In the present study, we did not determine 1RM directly. However, when estimating 1RM from the first and last period of 12RM, we found a 52% increase in HRT (fig. 9, blue circle), clearly indicating that improvements obtained by an isometric measurement is lower than by a dynamic measurement. Therefore, it appears to be more difficult to detect an isometric strength improvement after performing a dynamic exercise regime compared with a dynamic 1RM method.

Further, as figure 9 illustrates, it seems that the improvement increases primarily during the first months, after which the curve reached a plateau. Therefore, our results could indicate that weekly training intensity and volume are more important than the total length of a training intervention to gain muscle strength. However, to initiate a positive long-term change in physical activity habits a prolonged training intervention could potentially play an important role.

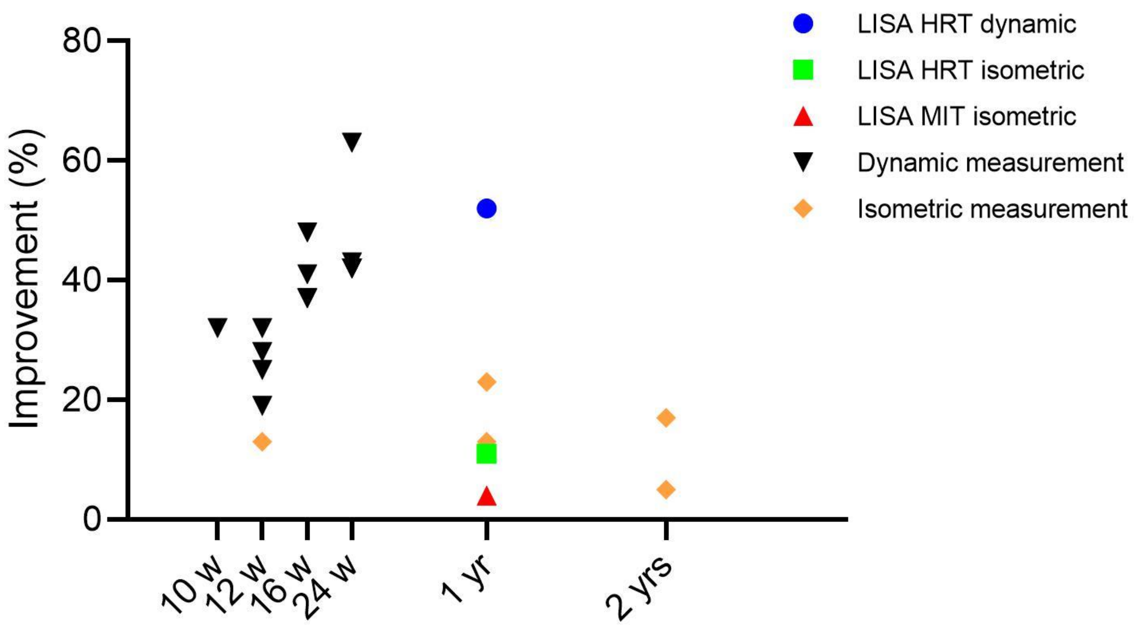

Fig. 9: The figure shows the improvements in muscle strength measured by a dynamic (1RM) measurement (black) or by isometric peak torque (orange) obtained from the literature, and the improvements gained in the LISA study using isometric peak torque (green HRT, red MIT). The blue circle illustrates an estimate of the improvement in dynamic (1RM) muscle strength in response to one year of HRT in the LISA study.

In contrast to previous short-term (8-24 weeks) studies using MIT-like training, where there are ambiguous conclusions as to the effect upon muscle strength (Borde, Hortobágyi, and Granacher 2015; Martins et al. 2015; Oh et al. 2017; Fatouros et al. 2005), we did observe an improvement in muscle strength in response to MIT. This underlines that lower intensity resistance training for one year also seems to be sufficient to improve muscle strength significantly. In individuals who are unable or unwilling to undertake heavy resistance training, this knowledge could be beneficial. Thus, in order to obtain a significant improvement in muscle strength and function with MIT, our findings could indicate that the training should be of a longer duration than a few months.

One year after completion of the strength training intervention (2-years follow-up), the isometric knee extensor strength was partly preserved in HRT, whereas it was lost in MIT and not different from CON anymore (fig. 8). This fits well with findings by Fatouros and colleagues, where muscle strength only was higher compared with baseline in the heavy resistance training group but not after moderate intensity training one year after completion of a 24-weeks intervention (Fatouros et al. 2005). Also a study investigating a moderate intensity resistance training program for 10 weeks followed by a 6-weeks post-intervention measurement found a loss in muscle strength (Kalapotharakos et al. 2007). However, these observations were both after a prescribed period of detraining, whereas the present study had not given any exercise restrictions. Even though isometric knee extensor strength in HRT decreased significantly during the follow-up year in the present study ($p<0.01$), it was still higher than baseline ($p<0.0001$) and the change from baseline to 2-years follow-up was significantly higher compared with both MIT and CON ($p<0.01$) (fig. 8). This finding correlates well with findings by Snijders and colleagues, who also found a higher muscle strength one year after completion of a 24-weeks training study compared with baseline (Snijders et al. 2019). Additionally, a study by Uusi-Rasi and colleagues found that also two years after completion of a strength training intervention muscle strength was higher than baseline (Uusi-Rasi et al. 2017), whereas muscle strength gains were lost after one year in another study (Karinkanta et al. 2009).

Handgrip strength was unaffected by one year of strength training. As the strength training program focused on the lower extremities, it was not a surprise, that we did not find any improvements. However, during the two years of observation, we observed a main effect of time with a significant decrease in handgrip strength ($p<0.01$) (table 5). This fits well with a cross-sectional study showing that unrelated to exercise training, handgrip strength declines with age (Suetta et al. 2019).

Table 5: Body composition, muscle function, physical activity level and total hippocampus volume measured before (baseline), after the 1-year intervention (1 yr), and one year after completion of the intervention (2 yrs) (mean ± SE).

	Baseline	1 yr	2 yrs	Sample size
Waist circumference (cm)ᵗ	92.8 ± 0.6	91.8 ± 0.6	92.3 ± 0.6	395
Leg extensor power (W)	192.2 ± 3.3	194.4 ± 3.2	191.6 ± 2.6	392
Handgrip strength (kg)ᵗ	34.9 ± 0.5	34.6 ± 0.5	34.3 ± 0.4	394
400 m walking time (s)	240 ± 2	236 ± 2	238 ± 2	383
Total step count (steps/day)	9607 ± 174	9641 ± 167	9599 ± 171	379¤
Total hippocampus volume (mm^3)ᵗ	7701 ± 42	7642 ± 43	7583 ± 43	305¤

t: main effect of time (Waist circumference and Handgrip strength p<0.01; Total hippocampus volume p<0.0001)
¤: Missing data due to technical error (total step count and hippocampus volume) or claustrophobia (total hippocampus volume)

9.5 Muscle mass and body composition

9.5.1 Lean body mass, leg lean mass and CSA of m. vastus lateralis

In line with isometric knee extensor strength, one year of heavy resistance training resulted in an increase in lean body mass and CSA compared with both MIT (p<0.01, ES: 0.35 and p<0.05, ES: 0.30, respectively) and CON (both p<0.0001, ES: 0.64 and 0.51, respectively) (fig. 10A and 10C), whereas only lean body mass was different compared with baseline (p<0.0001). One year of moderate intensity resistance training resulted only in a tendency towards a higher lean body mass compared with CON (p=0.06). Similarly, leg lean mass increased more in HRT compared with CON (p<0.01, ES: 0.37), and tended to be higher in MIT compared with CON (p=0.05) (fig. 10B).

The improvement of lean body mass and CSA with HRT were rather small (1.5% and 3%) but significant compared with both MIT and CON. Our findings fit well with findings by previous studies investigating the effects of heavy resistance training in healthy older adults upon lean body mass and CSA (Leenders et al. 2013; Bechshøft et al. 2017; Cleiton Silva Correa et al. 2013). In a 24-weeks strength training intervention, it was found that lean body mass increased by 2.5% and CSA by 7.5%, whereas a 12-weeks strength training intervention resulted in no increase in lean body mass, but a 3% increase in CSA, similar to the present findings (Bechshøft et al. 2017; Leenders et al. 2013). Our findings in lean body mass could be caused by the longer duration of the intervention than the study by Bechshøft and colleagues (Bechshøft et al. 2017). The smaller increase in the present study in lean body mass and CSA compared with Leenders and colleagues could be due to our study sample with approximately 80% chronically diseased individuals, whereas Leenders and colleagues included healthy individuals only (Leenders et al. 2013). In another 12-weeks intervention study, they found a 25% increase in muscle volume (Cleiton Silva Correa et al. 2013). However, the increase cannot be directly compared with the present study and the other described studies, as the method is different.

In studies using moderate intensity resistance training, similar results were found upon lean body mass as in the present study (Oh et al. 2017; Martins et al. 2015). Therefore, it seems that even though the strength training program is of longer duration, it appears that a positive response in lean body mass only occurs if the intensity is high.

The observed increases in lean body mass and leg lean mass as a response to HRT were erased at 2-years follow-up (fig. 10A and 10B). However, the change in lean body mass between baseline and 2-years follow-up was still significantly different between HRT (with a slight increase) and MIT (with a slight decrease) ($p<0.01$), but the change did not differ from CON, and neither HRT nor MIT was at 2-years follow-up different from baseline (fig. 10A). In MIT, both lean body mass and leg lean mass decreased significantly during the follow-up year ($p<0.0001$ and $p<0.001$, respectively) (fig. 10A and 10B). The present findings are in accordance with observations from several previous investigations of muscle mass in older adults after a follow-up period with either a prescribed detraining period or period with no given activity instructions (Bickel, Cross, and Bamman 2011; Trappe, Williamson, and Godard 2002; Snijders et al. 2019; Cleiton Silva Correa et al. 2013).

The observed significant improvement in CSA in response to the one year strength training intervention was no longer significant ($p=0.1$) in the analysis including data from the 2-years follow-up. However, at this time point we did observe a significant effect of time with a decreased CSA ($p<0.01$) (fig. 10C). As with leg lean mass, CSA in HRT returned to baseline values and was no longer different from MIT or CON as was observed after the 1-year intervention. However, there was a tendency towards a higher relative change from baseline to 2-years follow-up between HRT and CON ($p=0.06$). Regarding the control group, the 1-year intervention resulted in a significant decrease in CSA (p<0.01). However, the analysis performed at 2-years follow-up detected no longer a significant difference between baseline and 1-year, but only between baseline and 2-years follow-up (p<0.05) (fig. 10C), probably due to the lower statistically power. Interestingly, the decreased CSA over time in the non-exercising control group could indicate that strength training in some way counteracts and postpones the age-related decrease in muscle mass. A postponing of the otherwise expected declines in e.g. muscle mass and -strength would potentially affect the functional ability later in life, why a postponing is very valuable for each older individual.

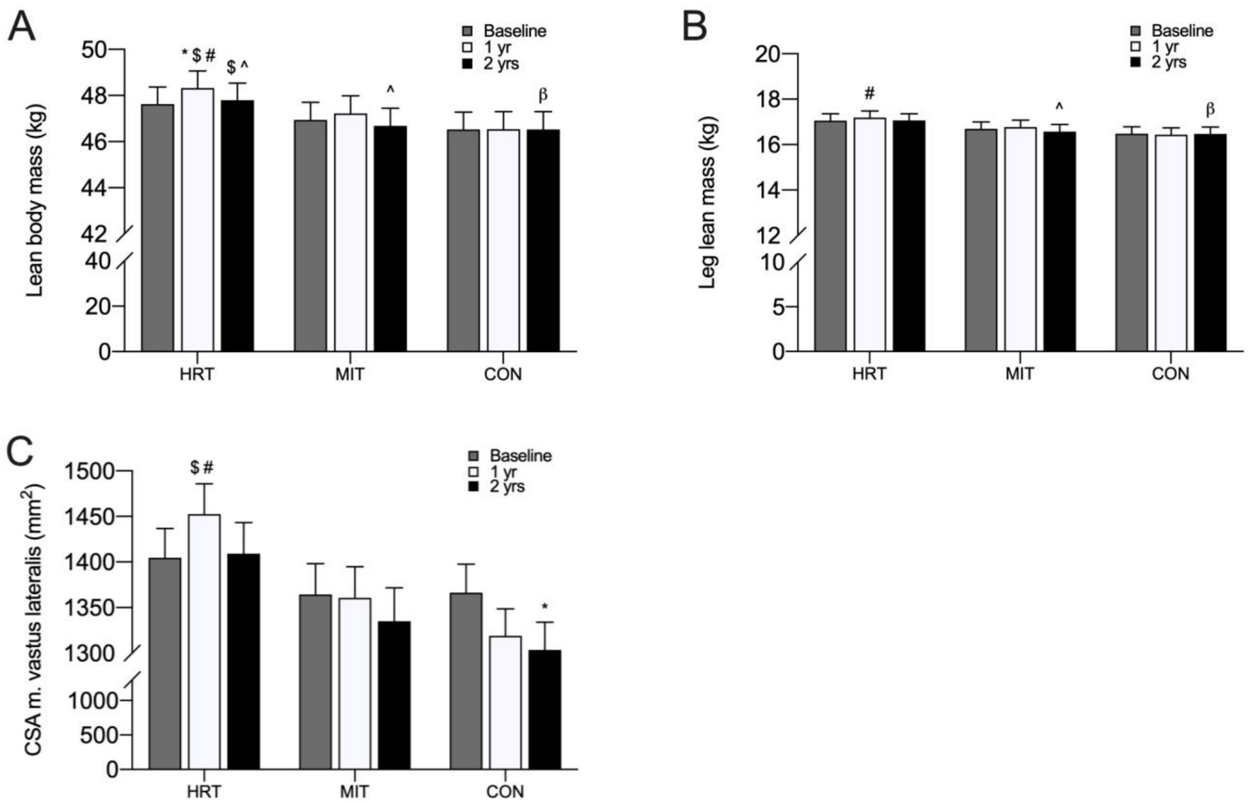

*Fig. 10: **A**) Lean body mass (n=398), **B**) Leg lean mass (n=398) and **C**) CSA of m. vastus lateralis (n=342) before (baseline, grey bars), after one year of either heavy resistance training (HRT), moderate intensity resistance training (MIT) or habitual physical activity (CON) (1 yr, white bars), and one year after completion of the intervention (2 yrs, black bars) (mean ± SE).*

**: significantly different from baseline (A: p<0.0001; C: p<0.05)*
^: significantly different from 1 yr (A: p<0.0001; B: p<0.001)
#: change from baseline significantly different compared with change in CON (A: p<0.0001; B: p<0.01; C: p<0.0001)
$: change from baseline significantly different compared with change in MIT (A: p<0.01; C: p<0.05)
β: change from 1 yr significantly different compared with change in HRT and MIT (A: p<0.001; B: HRT p<0.05, MIT p<0.01)

The discrepancy between the preserved isometric knee extensor strength and the loss in lean body mass and CSA one year after completion of the initial supervised heavy resistance training is in accordance with previous findings (Trappe, Williamson, and Godard 2002; Bickel, Cross, and Bamman 2011; Cleiton Silva Correa et al. 2013; Snijders et al. 2019). Normally you would expect that the decline of muscle strength is faster than muscle mass (Suetta et al. 2019; Lindle et al. 1997; Janssen et al. 2000). However, it appears that after a training intervention the decrease in muscle mass occurs at a faster rate than in muscle strength. The reason for this discrepancy could be that muscle mass is more sensitive to reduced muscle loading, whereas muscle strength persists even after reduced training potentially by a longer-lasting neuromuscular adaptation induced by strength training (Häkkinen et al. 1998).

9.5.2 Whole-body fat percentage and visceral fat content

As a response to the 1-year intervention, whole-body fat percentage as well as visceral fat content were reduced only after HRT when compared with baseline (both $p<0.0001$) (fig. 11A and 11B). The reduction of whole-body fat percentage and visceral fat in HRT was also significantly different compared with both MIT (both $p<0.01$, ES: 0.41 and 0.37) and CON ($p<0.0001$, ES: 0.53, and $p<0.01$, ES: 0.42, respectively) (fig. 11A and 11B). The decrease in whole-body fat percentage as a response to prolonged heavy resistance training is in accordance with a previous study using strength training (Leenders et al. 2013), whereas our decline in visceral fat content is not previously seen that often. The majority of previous training studies in elderly investigating the influence on visceral fat are pointing to aerobic exercises to be the most beneficial to lose visceral fat (Maillard, Pereira, and Boisseau 2018), whereas strength training investigations did not detect any evidence that this type of training should influence visceral fat content (Ismail et al. 2012). However, when comparing the results from the present study with most other strength training studies reporting no beneficial effect upon visceral fat, the duration of our study was much longer (Bechshøft et al. 2017; Phillips et al. 2017). Therefore, our findings indicate that strength training can also provide beneficial effects on visceral fat but the intervention should be of longer duration and with high intensity. The achieved reduction in visceral fat is very important in relation to reduce the risk of developing metabolic diseases (Fox et al. 2007).

One year after completion of the intervention, the improvements in whole-body fat percentage and visceral fat content as a response to the 1-year of heavy resistance training were lost again and both components were not different from baseline anymore (fig. 11A and 11B). For visceral fat content, the significant group x time interaction at 1-year only tended to be significant at 2-

years follow-up (p=0.08). Therefore, we also evaluated the effect of time, which was significant with a decrease from baseline to 1-year (p<0.05) and an increase from year 1 to year 2 (p<0.05). Interestingly, the change in whole-body fat percentage was still improved at 2-years follow-up if the strength training was continued during the follow-up year, whereas it was lost in the ones that did not continue (table 8). The observed increase in fat with the fat mass returning to baseline values was also found by Snijders and colleagues one year after termination of their strength training intervention (Snijders et al. 2019). The present findings of an increase in whole-body fat percentage and visceral fat content during the follow-up year correlate well with our findings of an effect of time upon waist circumference, where the observed decrease in response to the intervention (p<0.001) was replaced with a significant increase during follow-up (p<0.05) (table 5).

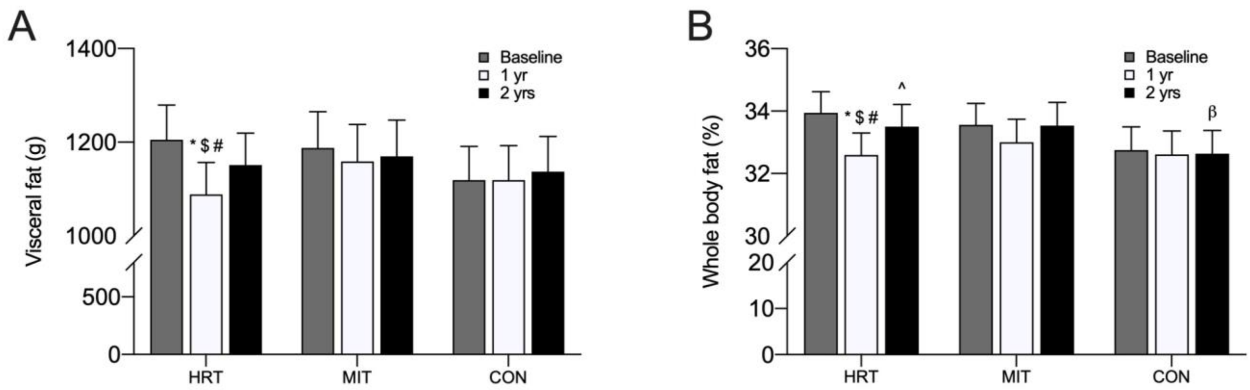

*Fig. 11: **A**) Visceral fat content (n=398) and **B**) whole-body fat percentage (n=398) before (baseline, grey bars), after one year of either heavy resistance training (HRT), moderate intensity resistance training (MIT) or habitual physical activity (CON) (1 yr, white bars), and one year after completion of the intervention (2 yrs, black bars) (mean ± SE).*

**: significantly different from baseline (A: p<0.01; B: p<0.0001)*
^: significantly different from 1 yr (B: p<0.001)
#: change from baseline significantly different compared with change in CON (A: p<0.001; B: p<0.0001)
$: change from baseline significantly different compared with change in MIT (A: p<0.05; B: p<0.05)
β: change from 1 yr significantly different compared with change in HRT (B: p<0.01)

9.6 Functional outcomes

9.6.1 Chair-stand performance and 400m walking test

In response to the 1-year intervention, we did not find any specific effect of strength training upon functional performance measured by 30 s chair-stand performance and 400m walking time (table 7 and 5, respectively). However, we did observe an increase in all three groups (HRT, MIT, and CON) from baseline to 1-year in chair-stand performance (p<0.0001) and also a higher increase in performance in MIT (from 17.1 ± 0.4 to 20.0 ± 0.4) compared with CON (from 17.0 ± 0.4 to 18.7 ± 0.4) ($p<0.01$, ES: 0.37). At 2-years follow-up, there were no differences between the three intervention groups, but we did observe a main effect of time ($p<0.0001$), where the chair-stand performance was further increased from 1-year to 2-years follow-up in all groups ($p<0.01$) (table 7). The 400m walking time was still not affected at 2-years follow-up (table 5).

The increase in chair-stand performance compared with baseline was also seen in response to another 1-year strength training program (Sundstrup et al. 2016). However, this increase was not different from a control group even though there was no improvement in the control group (Sundstrup et al. 2016). The improvement in all three groups could be related to a learning effect from the first to the second trial. Our heavy resistance training was also not specifically targeted towards this type of physical activity and none of the training groups towards walking exercises, which could act as another explanation for not finding a difference in performance compared with the control group. The latter is supported by a previous study, where the strength training program also included walking exercises, which resulted in an improved walking time as an effect of the training intervention (Santanasto et al. 2017). However, the study by Santanasto and colleagues included mobility-limited individuals only, which could also explain the effect of training on the functional outcome. In the present study, we included strength training naive, but well-functioning individuals with a possibly limited potential for conversion of improved muscle strength towards an improved physical function. This is supported by previous findings, where an increase in muscle strength only resulted in improved walking speed in frail elderly (Fiatarone et al. 1994) but not in healthy adults (Buchner et al. 1997). Further, in the present study, 400m walking time was used to evaluate functional ability as the reproducibility is good (Pettee Gabriel et al. 2010) and the measurement provides a valid estimate of peak VO_2 in older adults (Simonsick, Fan, and Fleg 2006). However, it cannot be excluded that we would have found an effect on functional ability as a response to the intervention if we had chosen 10m gait speed instead, as a previous cross-sectional study found that gait speed was the best measure of physical function (García-Pinillos et al. 2019). Additionally, the present findings of daily activity, measured by steps per day and by the PASE questionnaire, showed that even though the intervention did not affect the level of daily activity (table 5 and 6, respectively), the participants were quite active both prior to and after the intervention period walking approximately 10.000 steps/day. This was markedly higher than what was observed in another study investigating older adults (Bechshøft et al. 2017). Even though the lifestyle of our participants was not explored in detail, it cannot be excluded that the entire group of participants maintained a healthy lifestyle in general regarding e.g. food and activity level, although 80% of the included participants had a chronic disease. Therefore, it might have been more challenging to demonstrate further improvements in functional outcomes than in a more average part of the background population.

9.7 Questionnaires

9.7.1 Health-related quality of life (SF-36)

The evaluation of health-related quality of life measured by SF-36 showed that the physical summary score did not differ between or within groups as a response to the 1-year intervention, whereas the mental summary score showed a higher score in HRT (from 56.3 ± 0.6 to 57.5 ± 0.5) compared with MIT (from 57.6 ± 0.4 to 56.8 ± 0.5) ($p<0.05$, ES: 0.29). Together with findings in a systematic review (Hart and Buck 2019) the present observation supports the view that regular physical training also in the form of strength training can improve the mental health-related quality of life in older adults, and that the degree of improvement is related to training intensity. However, at 2-years follow-up the previous observed group x time interaction was no longer significant, and there was no difference between the three intervention groups, but an overall effect of time for both SF-36 physical ($p<0.01$) and mental summary score ($p<0.05$) was observed (table 6). This was caused by a decrease in the score during the follow-up year (table 6), indicating that an improved mental health-related quality of life only occurs during a long-term supervised heavy strength training intervention, which will be lost again during a follow-up period independent of continuation of strength training.

Table 6: Questionnaires; Physical Activity for Elderly (PASE) and Health-related quality of life (SF-36) score measured before (baseline), after the 1-year intervention (1 yr), and one year after completion of the intervention (2 yrs) (mean ± SE).

	Baseline	1 yr	2 yrs	Sample size
PASE (score)	136.0 ± 2.8	142.7 ± 3.2	141.0 ± 3.2	390
SF-36 Physical Summary (score)[t]	53.1 ± 0.3	53.1 ± 0.31	52.1 ± 0.4	389
SF-36 Mental Summary (score)[t]	56.8 ± 0.3	56.9 ± 0.3	56.0 ± 0.4	389

t: main effect of time (SF-36 physical summary $p<0.01$; SF-36 mental summary $p<0.05$)

9.8 Brain

9.8.1 Hippocampus volume

In the present study, we did not observe any positive effect of the strength training intervention upon total hippocampus volume. However, a main effect of time was observed with a significant decrease corresponding to approximately 0.75% during the 1-year of intervention ($p<0.0001$) and a similar decrease during the follow-up year ($p<0.0001$) ending up with an overall decrease corresponding to 1.5% from baseline to 2-years follow-up (table 5).

Our observed decrease in hippocampus volume is in accordance, maybe slightly lower, with findings from a meta-analysis that found an age-related decrease independent of training of approximately 1% per year in the age range of the present study (Fraser, Shaw, and Cherbuin 2015). Unfortunately, in contrast to most previous studies supporting a long-term positive association of hippocampus volume in relation to aerobic training (Jonasson et al. 2016; Erickson et al. 2011), we did not find an effect of 1-year of strength training on hippocampus volume. However, to our knowledge, only few studies have investigated the effect of strength training on brain readouts. In a previous study, it was suggested that one year of strength training was able to improve functional plasticity of response inhibition processes in the cortex, but any changes in hippocampus volume were not reported (Liu-Ambrose et al. 2012). Another study reported that 24-weeks of strength training increased the hippocampus volume compared with a control group (Kim et al. 2017). However, in contrast to the present study, their sample size was small (n=21 participants), all participants were women, and they were generally older (67-81 years). Further, the ability to perform chair-stand for 30 s was much lower in those participants compared with our participants, which could explain the discrepancy to our findings. Future research is necessary to evaluate whether strength training can delay the age-related decline in hippocampus volume or not.

9.9 Effects of participation in a scientific project per se

An interesting observation in the present study was that some health-related parameters independent of strength training had a positive development during the two years of investigation. For the measured blood parameters, we observed a drop in total cholesterol, LDL and VLDL from baseline to 2-years follow-up ($p<0.0001$, $p<0.0001$ and $p<0.05$, respectively), which was also seen for the anthropometric measurements BMI and weight (both $p<0.05$) and for the systolic and diastolic blood pressure measurements ($p<0.0001$) (table 7). During the 1-year intervention, all mentioned parameters, except VLDL, decreased significantly with levels maintained during the follow-up year and therefore still lower than at baseline (table 7). For VLDL, the main effect of time was caused by a significant decline from year 1 to year 2, resulting in a lower value at 2-years follow-up compared with baseline (table 7). As described previous, the 30 s chair-stand performance was also improved in all groups during the two years of investigation ($p<0.0001$). For this parameter, we observed an increase during the 1-year intervention but also a further increase during the follow-up (table 7).

The improvement in all three groups could be related to an unspecific effect of participating in a controlled study potentially related to a change in lifestyle (e.g. food intake), which is then maintained after termination of the supervised intervention. For chair-stand performance, the improvement could additionally be related to a learning effect.

However, it is important to notice that as a response to one year of either HRT or MIT, we did find an effect upon some circulating metabolic factors with an increase in HDL after HRT and a decrease in LDL after MIT both when compared with CON (both $p<0.05$, ES: 0.31 and 0.29, respectively). This was in line with previous findings of several strength training interventions (Tsuzuku et al. 2007; Ihalainen et al. 2019), where it is emphasized that strength training potentially has positive metabolic effects besides the known changes in muscle function and body composition. However, at 2-years follow-up the previous observed group x time interaction was no longer significant, and there were no differences between the intervention groups.

Table 7: Body composition, functional ability, blood parameters and blood pressure measured before (baseline), after the 1-year intervention (1 yr), and one year after completion of the intervention (2 yrs) (mean ± SE).

	Baseline	1 yr	2 yrs	Sample size
BMI (kg/m²)^t	25.8 ± 0.2	25.6 ± 0.2	25.6 ± 0.2	398
Weight (kg)^t	75.5 ± 0.7	75.0 ± 0.7	75.1 ± 0.7	398
30 sec chair-stand (reps)^t	16.9 ± 0.2	19.3 ± 0.3	19.9 ± 0.2	390
Total cholesterol (mmol/l)^t	5.77 ± 0.05	5.61 ± 0.05	5.56 ± 0.05	398
LDL (mmol/l)^t	3.31 ± 0.05	3.15 ± 0.05	3.14 ± 0.05	391
VLDL (mmol/l)^t	0.52 ± 0.01	0.51 ± 0.01	0.49 ± 0.01	393
Systolic BP (mmHg)^t	144 ± 0.9	137 ± 0.9	137 ± 0.9	387
Diastolic BP (mmHg)^t	86 ± 0.5	82 ± 0.5	82 ± 0.5	387

t: main effect of time (Chair-stand, Total cholesterol, LDL, Systolic BP and Diastolic BP p<0.0001; BMI, Weight and VLDL p<0.05)

9.10 Healthy vs. chronically diseased participants

Interestingly, in a sub-analysis of Study I, where the 20% healthy and 80% chronically diseased participants were analyzed separately, we observed no difference in the response of isometric knee extensor strength, leg extensor power, lean body mass, CSA and visceral fat content to the intervention regarding group x time interaction. However, there was some difference in isometric knee extensor strength compared with the overall analysis. The difference between HRT and MIT in the healthy participants or between MIT and CON in the diseased participants was no longer present. Additionally, the change in lean body mass during the 1-year intervention between HRT and MIT was only significantly different in the healthy participants (p<0.05), whereas the differences between HRT and MIT/CON in visceral fat content were only still significantly different in the diseased participants (p<0.01). An important observation was that, there was no significant difference in training compliance between the healthy and chronically diseased (82% ± 23% (SD) vs. 76% ± 23% (SD), respectively). Our findings indicate that the ability of strength training to affect skeletal muscle and visceral fat in elderly is independent of chronic diseases.

9.11 Continuous training during follow-up vs. no-training (CONTIN vs STOP)

When comparing participants who continued with the same strength training program (but without any supervision) the year after termination of the intervention (CONTIN) with those who stopped (STOP), we observed that CONTIN had a significantly lower decline in the training-induced improvement in isometric knee extensor strength compared with STOP ($p<0.05$) (table 8). To our knowledge we are the first to make this observation as a previous investigation did not find any further differences in muscle strength in those who continued with unsupervised strength training during follow-up (Snijders et al. 2019). In contrast, there was no difference between the two groups in the present study regarding lean body mass and CSA preservation. This was a bit surprising, as Snijders and colleagues found better preservation in both lean body mass and CSA in the exercise group compared with the non-exercising group (Snijders et al. 2019). Another study that looked into the maintenance of muscle mass after 12 weeks of strength training followed by a 24-weeks prescribed strength training program found that strength training once a week was enough to preserve the improvement in muscle mass (Trappe, Williamson, and Godard 2002). However, a complete loss of muscle mass returning to baseline values was also seen in another study after a prescribed strength training program for 32 weeks (Bickel, Cross, and Bamman 2011). Our results in muscle strength and -mass again underline that these do not follow each other in time patterns and that a faster loss is seen for muscle mass than for muscle strength in the period following a supervised strength training intervention.

Further, during the follow-up year waist circumference changed significantly differently between CONTIN and STOP ($p<0.05$). In CONTIN, we observed a decrease in waist circumference from 1-year to 2-years follow-up, whereas it increased in STOP (table 8). Unfortunately, for all other measured parameters, we did not observe any differences between CONTIN and STOP from 1-year and 2-years follow-up. For instance, the observed increases in whole-body fat percentage and visceral fat content from 1-year to 2-years follow-up were similar in the two groups.

A very interesting observation was that, when CONTIN and STOP were compared at baseline, isometric knee extensor strength, lean body mass and the SF-36 mental summary score were significantly higher ($p<0.01$, $p<0.05$ and $p<0.05$, respectively) and whole-body fat percentage lower ($p<0.001$) in CONTIN than in STOP (table 8). Additionally, the effects of the 1-year strength training program upon isometric knee extensor strength ($p<0.001$), leg extensor power ($p<0.05$), chair-stand performance ($p<0.05$) and 400m walking time ($p<0.05$) were also higher in CONTIN compared with STOP (table 8). This could be due to the fact that CONTIN had a significantly higher training compliance (88%) during the 1-year of strength training compared with STOP (78%) ($p<0.0001$). This indicates that those participants who continued strength training on their own during the follow-up period were the ones who apparently were more well-functioned from the beginning of the study, and in addition had a higher compliance and response to the strength training intervention. A promising observation at 2-years follow-up was that isometric knee extensor strength ($p<0.0001$), leg extensor power ($p<0.05$), chair-stand performance ($p<0.0001$), whole-body fat percentage ($p<0.01$), and waist circumference ($p<0.05$) in CONTIN were still significantly improved compared with baseline, whereas only chair-stand performance was significantly higher in STOP compared with baseline ($p<0.0001$) (table 8). Further, the changes between baseline and 2-years follow-up were also significantly different between CONTIN and STOP in isometric knee extensor strength ($p<0.0001$), leg extensor power ($p<0.01$), whole-body fat percentage ($p<0.01$), and waist circumference ($p<0.05$), whereas it only tended to be different in chair-stand performance ($p=0.07$) (table 8).

Table 8: Muscle function and body composition before (baseline), after one year of strength training (1 yr), and one year after completion of the intervention (2 yrs) in participants who continued with strength training (CONTIN) and participants who stopped (STOP) during the one year follow-up period (mean ± SE).

	Baseline		1 yr		2 yrs		Sample size
	CONTIN (n=65)	STOP (n=200)	CONTIN (n=65)	STOP (n=200)	CONTIN (n=65)	STOP (n=200)	
Isometric knee extensor strength (Nm)	164.7 ± 6.9£	143.0 ± 3.7	184.5 ± 7.8*α	152.5 ± 3.8*	182.8 ± 7.8*Δα	145.1 ± 3.7^	260
Leg extensor power (W)	208.3 ± 9.0	191.4 ± 4.6	219.1 ± 9.4α	191.5 ± 4.2	220.1 ± 9.5*α	187.0 ± 4.5	263
30 sec chair-stand (reps)	17.6 ± 0.5	16.7 ± 0.3	21.0 ± 0.6*α	19.2 ± 0.4*	21.4 ± 0.7*	19.6 ± 0.4*	261
400 m walking time (s)	235 ± 3	243 ± 2	227 ± 3α	239 ± 3	227 ± 3	243 ± 4	256
Lean body mass (kg)	49.5 ± 1.1£	46.7 ± 0.6	50.2 ± 1.2*	47.1 ± 0.6*	49.7 ± 1.2^	46.5 ± 0.6^	265
Whole-body fat (%)	30.7 ± 1.1£	34.6 ± 0.5	29.2 ± 1.0*	33.8 ± 0.6*	29.6 ± 1.1*α	34.6 ± 0.6^	265
Waist circumference (cm)	91.7 ± 1.5	94.0 ± 0.8	90.3 ± 1.4	93.0 ± 0.8	90.1 ± 1.4*Δα	93.9 ± 0.8^	264
SF-36 mental summary score	58.3 ± 0.6£	56.7 ± 0.4	57.0 ± 0.8	57.3 ± 0.4	57.5 ± 0.8	55.5 ± 0.6	259

**: significantly different compared with baseline (Isometric strength and Chair-stand p<0.0001; Leg extensor power and Waist circumference p<0.05; Lean body mass and Whole-body fat (%) p<0.01)*
^: significantly different compared with 1 yr (Isometric strength, Lean body mass (STOP) and Whole-body fat% p<0.0001; Lean body mass (CONTIN) and Waist circumference p<0.05)
£: significantly different compared with STOP at baseline (Isometric strength p<0.01; Lean body mass and SF-36 mental score p<0.05; Whole-body fat (%) p<0.001)
α: change from baseline to 1 yr and/or 2 yrs significantly different compared with STOP (Isometric strength 1 yr p<0.01, 2 yrs p<0.0001; Leg extensor power 1 yr p<0.05, 2 yrs p<0.01; Chair-stand, Walking time and Waist circumference p<0.05; Whole-body fat (%) p<0.01)
Δ: change from 1 yr to 2 yrs significantly different compared with STOP (p<0.05)

In the present study, it is clear that the 24% of the participants who continued training after ending the supervised training were the ones that maintained their muscle strength and -power improvements as well as some metabolic parameters. Our findings in the maintenance of muscle strength in CONTIN are comparable with previous studies investigating continuous training compared with detraining (Trappe, Williamson, and Godard 2002; Bickel, Cross, and Bamman 2011; Fatouros et al. 2005; Snijders et al. 2019; Cleiton Silva Correa et al. 2013; Uusi-Rasi et al. 2017; Karinkanta et al. 2009). From figure 12A and 12B, it is clear that most studies identified that those individuals who continued strength training were the ones who maintained muscle strength, whereas a markedly decline in muscle strength was observed in response to detraining, indicating the importance of ongoing activity to ensure the maintenance of muscle strength.

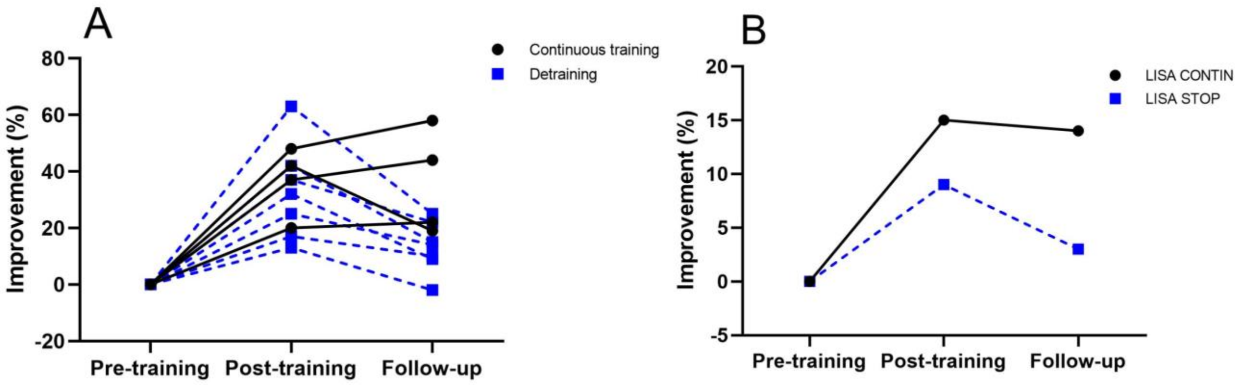

Fig. 12: Muscle strength improvement (%) after a prescribed training intervention (post training) from ***A****) previous strength training interventions following either continuous training (black) or detraining (blue dotted) during follow-up (follow-up) and from* ***B****) The LISA study with either continuous training (CONTIN, black) or no-training (STOP, blue dotted).*

10. Conclusions and perspectives

From Study I, we can conclude that leg extensor power was neither affected by one year of heavy resistance training nor moderate intensity resistance training. However, heavy resistance training improved muscle strength by 11%, lean body mass by 1.5%, and CSA of the thigh by 3%, whereas moderate intensity resistance training only improved muscle strength by 4%, all detected by the intention-to-treat analysis. The present findings indicate that even though the magnitude of the response to heavy resistance training was a lot higher, one year of moderate intensity resistance training also has beneficial effects upon muscle strength. This finding can be useful and helpful for individuals who are unwilling or unable to perform heavy resistance training. The observed improvements in muscle function were not directly translatable to an improved functional ability, as all three intervention groups improved the ability to rise from a chair in 30 s and the time to walk 400m was furthermore not affected in any of the intervention groups. Also, whole-body fat percentage and visceral fat content were affected positively by one year of heavy resistance training. This very interesting finding indicates that not only aerobic training is able to improve metabolic parameters but also long-term strength training if the training is of high intensity. A reduction in whole-body fat percentage and visceral fat content is important to reduce the risk of developing e.g. type-2 diabetes or cardiac diseases. Unfortunately, the present study was not able to counteract the age-related decline in hippocampus volume. This indicates that other types of exercise training or another strength training set-up than the present study are necessary to be investigated in future research. We did observe an improved mental health-related quality of life in response to one year of heavy resistance training only.

In Study I, we observed that both heavy and moderate intensity resistance training had equally high compliance to the strength training intervention (including all participants) and that 83% of the participants in the two training groups completed 66% or more of the training sessions corresponding to at least two sessions per week. Therefore, another conclusion of the present study is that a long-term strength training intervention with two different intensities can be implemented with good compliance in both healthy and chronically diseased older adults.

From Study II, we can conclude that one year after completion of the supervised heavy resistance training, only isometric knee extensor strength (and to some degree thigh muscle area) was partly maintained. During the follow-up year, muscle strength decreased significantly but was still 7% higher than at baseline. In the moderate intensity training group muscle strength was no longer different from the control group. In relation to the thigh muscle area, we observed that the difference between baseline and 2-years follow-up was higher than the one observed in the control group. In the heavy resistance training group, CSA returned to baseline values, whereas the control group had a significant decline during the two years of investigation, leading us to the conclusion that one year of heavy resistance training appears to postpone the age-related decrease in muscle area. Most other muscle, functional and health parameters that responded positively to the strength training intervention had returned to baseline values at 2-years follow-up. Importantly, when analyzing those who continued with the strength training program on their own during follow-up and those who did not, we observed that the training-induced adaptations in muscle strength were maintained only if the strength training was continued. Another very interesting finding of the present study was that leg extensor power was positively affected in the group that continued after the strength training intervention and maintained at 2-years follow-up, whereas no effect was seen in those who stopped. Also, whole-body fat percentage and waist circumference were maintained during follow-up, whereas both parameters increased in those who stopped the strength training. These findings emphasize the importance of ongoing physical activity for ensuring long-term effects of strength training upon muscle function and to some degree other health-related parameters in elderly.

The number of participants who continued the strength training program on their own, could indicate that to successfully implement strength training as a daily routine there is a need for more than one year of supervision or stricter instructions on the importance of performing strength training. From the adherence questionnaire, we can conclude that one year after termination of the initial training intervention a significantly higher number of participants from the heavy resistance training group continued the strength training program compared with participants from the moderate intensity resistance training group. It is very interesting whether this picture will continue or whether it is the opposite way around during the 10 years of follow-up.

From Study II, we can also conclude that there is an unspecific effect of participating in a controlled study. During the two years of investigation, we observed that total cholesterol, LDL, VLDL, blood pressure, BMI, weight, and chair-stand performance were improved in all participants unrelated to exercise training.

Thus, the results from the present study show that long-term supervised strength training in both healthy and chronically diseased elderly individuals can be implemented with good compliance and that the training induces consistent changes in physiological parameters of muscle and fat, and to a higher degree if the strength training is of high intensity. The present findings will be able to contribute to recommendations for retirement-age individuals in order to counteract the long-term decline in physical function, metabolism, and health. This thesis can also back up the current recommendations (Ratamess et al. 2009) of it is never being too late to engage in strength training to improve muscle function, and also that heavy resistance training is superior to strength training performed with more moderate intensity. However, it seems that only prolonged training programs with high intensity are able to maintain muscle strength in older adults after a period with no training instructions. Further, it appears that the continuation of strength training contributes to improved maintenance of several parameters related to overall muscle function and health. As the plan for the LISA study is to follow the participants for 10 years, the study will be able to answer the question, whether one year of organized strength training has a longitudinal effect upon the degree of physical activity implemented in the daily routine. The study will also be able to answer, whether the observed differences in the maintenance of physical function at 2-years follow-up is still the case over an even longer period between those who continued strength training and those who did not. Time will tell and we will eagerly await this.

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12. Papers

Paper 1:

The influence of prolonged strength training upon muscle and fat in healthy and chronically diseased older adults.

Anne Theil Gylling, Christian Skou Eriksen, Ellen Garde, Cathrine Lawaetz Wimmelmann, Nina Linde Reislev, Theresa Bieler, Andreas Kraag Ziegler, Kasper Winther Andersen, Christian Bauer, Kasper Dideriksen, Maria Baekgaard, Kenneth Hudlebusch Mertz, Monika Lucia Bayer, Mads Bloch-Ibenfeldt, Carl-Johan Boraxbekk, Hartwig Roman Siebner, Erik Lykke Mortensen, Michael Kjaer.

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The influence of prolonged strength training upon muscle and fat in healthy and chronically diseased older adults

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ABSTRACT

Background: Physical muscle function and brain hippocampus size declines with age, accelerating after the age of 60. Strength training over a few months improves physical function, but less is known about how long-term strength training affects physical function and hippocampus volume. Therefore, we aimed to investigate the effect of 1-year strength training of two different intensities upon muscle mass, function, and hippocampus volume in retirement-age individuals.

Methods: In this multidisciplinary randomized controlled trial (clinicaltrials.gov: NCT02123641), participants were allocated to either a) supervised, heavy resistance training (HRT, $n = 149$, 3/wk), b) moderate intensity resistance training (MIT, $n = 154$, 3/wk) or c) non-exercise activities (CON, $n = 148$). 451 participants were randomized (62–70 yrs., women 61%, ≈80% with a chronic medical disease) and 419 were included in the intention-to-treat analysis ($n = 143$, 144 and 132; HRT, MIT and CON). Changes in muscle power (primary outcome), strength and size, physical function, body composition, hippocampus volume and physical/mental well-being were analyzed.

Findings: Of the participants (HRT + MIT), 83% completed training at least 2/week. Leg extensor power was unchanged in all groups, but strength training had a positive effect on isometric knee extensor strength in both groups, whereas an increased muscle mass, cross-sectional area of vastus lateralis muscle, a decreased whole-body fat percentage, visceral fat content and an improved mental health (SF-36) occurred in HRT only. Further, chair-stand performance improved in all groups, whereas hippocampus volume decreased in all groups over time with no influence of strength training.

Interpretation: Together, the results indicate that leg extensor power did not respond to long-term supervised strength training, but this type of training in a mixed group of healthy and chronically diseased elderly individuals can be implemented with good compliance and induces consistent changes in physiological parameters of muscle strength, muscle mass and abdominal fat.

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1. Introduction

Good physical function is key to healthy aging, and muscle mass, strength, and power are its dominant determinants. Unfortunately, muscle mass and function declines with advancing age potentially leading to sarcopenia (Cruz-Jentoft et al., 2019; Janssen et al., 2000; Lindle et al., 1997; Skelton et al., 1994). An association between low skeletal muscle mass and functional impairment has been demonstrated to be more pronounced in older individuals with severe sarcopenia compared to individuals with normal skeletal muscle mass (Janssen et al., 2002). Further, a decrease in physical function with aging may affect quality of life as well as increase risk of falls, morbidity, and mortality in older and frail humans (Kohl et al., 2012; Lee et al., 2012; World Health Organization, 2010)..

One way to influence muscle power and strength as well as physical function in older adults is strength training. Many studies have shown that strength training is an effective method to improve muscle strength and power in older individuals in a dose dependent manner (Bechshøft et al., 2017; Borde et al., 2015; Fielding et al., 2002; Marsh et al., 2009). Prior studies, however, have predominantly used relatively short periods of training (3–6 months), often used per protocol approaches, and primarily investigated healthy individuals thus potentially limiting the extrapolation to the general population. In addition to the positive effect on skeletal muscle, it has been shown that regular physical activity in retirement-aged individuals has a positive effect on different mental characteristics including health-related quality of life (Rejeski and Mihalko, 2001). Further, physical activity is also known to have beneficial effects on brain plasticity (Cotman et al., 2007; Voss et al., 2013) as well as brain structure and function (Bherer et al., 2013; Erickson et al., 2013). However, these studies have mostly studied endurance-like training, and those that have used strength training have studied brain function (and not morphology) and had more short-term interventions (Coetsee and Terblanche, 2017; Forte et al., 2013; Iuliano et al., 2015; Ozkaya et al., 2005). It is largely unknown to what extent long-term strength training influences mental health and brain structure.

This randomized controlled trial aimed to investigate the effect of regular strength training for 1 yr to counteract age-related loss of skeletal muscle function in both healthy and chronically diseased older individuals aged 62–70 years. We chose a 1 yr intervention in order also to study the adherence to training over a more prolonged period. Additionally, the study investigated the currently unanswered question, whether long-term strength training has a positive effect on hippocampus volume as well as on health-related quality of life. Furthermore, we have tried to establish a dose-response relationship between training resistance and outcomes by the use of two different training protocols (heavy resistance training (HRT) and moderate intensity resistance training (MIT)) and compared these with a non-exercising control group (CON) on the following parameters: Leg extensor power as our primary outcome, and muscle strength and size, functional ability, body composition, daily level of physical activity, health-related quality of life and hippocampus volume as our secondary outcomes.

We hypothesized that compared with a control group, 1 yr of HRT or MIT intervention would both improve leg extensor power, muscle strength and muscle mass, and that the response in HRT would be superior to MIT. Further, we hypothesized that strength training could counteract age-related decline in hippocampus volume and improve health-related quality of life.

2. Method

2.1. Study design

The detailed methods of this study have been described elsewhere (Eriksen et al., 2016). In brief, the study included 451 home dwelling independent men and women aged 62–70 years out of which 419 completed the 1 yr intervention test-battery and are included in the present intention-to-treat analysis. The participants were recruited in

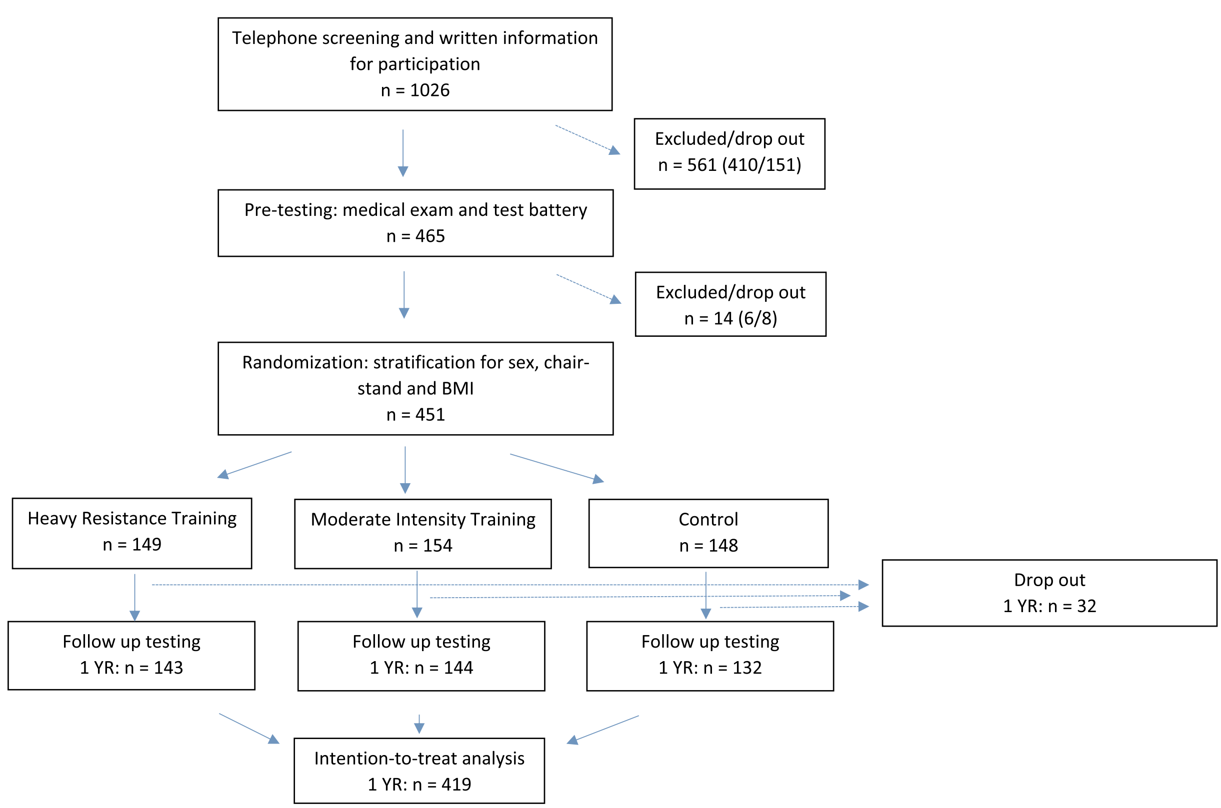

Fig. 1. Study flow chart including the participants' enrolment process, randomization into the intervention and subsequent follow-up data.

the greater Copenhagen area mainly through newspaper advertisements. Following a telephone screening they completed the baseline assessments including a medical screening, physical testing, body composition, muscle thigh cross-sectional area (CSA) and brain imaging, before participation in the study. All participants signed an informed consent before participating in the study. The study was approved by the regional ethical committee (Capital Region, Copenhagen, Denmark, No. H-3-2014-017), complied with the declaration of Helsinki, and the study was approved by the Danish Data Protection Agency and registered on clinicaltrials.gov (NCT02123641). A study flow chart is illustrated in Fig. 1.

The study inclusion criteria were age between 62 and 70 years and independent living. The exclusion criteria were more than one hr/wk. of regular strenuous exercise training, severe unstable medical diseases (e.g. active cancer or severe heart disease), musculoskeletal diseases that inhibited training ability, use of medication that may influence the effects of training (e.g. androgens or antiandrogens), and drugs that caused safety concerns in relation to training. Due to the few exclusion criteria, the participants constituted a sample with a broad range of chronic diseases.

2.2. Randomization and masking

Participants were stratified according to sex (man/woman), functional ability (chair-stand test ≤ 11, or > 11) and body mass index (BMI ≤ 28, or > 28) and randomized through a computer-generated allocation sequence provided by an external statistician. We did not stratify for any other parameters e.g. our primary outcome. The person assigning the allocation was not involved in the recruitment or enrolment of participants. Participants were requested not to inform their group allocation to the blinded outcome assessors.

2.3. Procedures

After baseline assessment, the participants were randomized into one of three 1 yr intervention groups: HRT, MIT or CON. Both training groups consisted of a whole-body strength training program in either weight machines (HRT) or with rubber bands and own bodyweight (MIT). A summary of the exercises is presented in Table 1. The program was performed three times/wk. with at least 48 h between sessions, and the duration of the training program was 1 yr. The HRT was located in a commercial fitness center and was supervised for all training sessions, whereas the MIT was supervised once a week in small groups and home based without supervision the other two times/wk. Experienced physical trainers supervised the training. Both intervention groups had a 6–8-weeks familiarization period at low intensity in order to reduce the risk of musculoskeletal injury. After this period, a progressive training program with increasing load was performed in both groups. All training sessions in HRT began with 5–10 min low-intensity walking, running, rowing or cross training. Thereafter, three sets of 6–12 repetitions corresponding to an estimated intensity between $\approx$70–85% of 1 repetition maximum (RM) were performed in a linear periodized regime over a 9-week period, with an increasing load every second week and restitution in the last week. After the restitution week, the participants started out with 3 × 12 repetitions with a higher load than the last time they performed 3 × 12 repetitions. Thereby the load was meant to increase throughout the 1 yr intervention. The MIT group performed three sets of 10–18 repetitions corresponding to an estimated intensity between $\approx$50–60% of 1RM. For the rubber band exercises, the workload was adjusted by using stronger rubber bands (six different bands starting from red to gold). The load for the other exercises were increased in the following way a) push-ups: the angle of the body relative to the floor were gradually decreased, b) squats: a stool was used to put one foot on, and 3) calf raises: changing from bilateral to unilateral performance or using weight vests (for full description see Eriksen et al., 2016). The participants in the control group were asked to continue their habitual physical activity level (less than one hour of strenuous physical activity per week) and were offered to participate in social and cultural activities approximately two times a month during the 1 yr intervention.

Table 1
Overview of the strength training exercises in each group.

	HRT	MIT
Lower body exercises	1. Leg press	1. Air squat
	2. Knee extension	2. Knee extension
	3. Leg curl	3. Hip extension
	4. Calf raises	4. Calf raises
	5. Hip abduction	5. Hip abduction
Upper body exercises	6. Chest press	6. Push-ups
	7. Seated row	7. Seated row
	8. Crunches	8. Crunches
	9. Back extension	9. Back extension
Equipment	1–7: Fitness machines	2;3;5;7: Rubber bands
	8–9: Own body weight	1;4;6;8;9: Own body weight

2.4. Measurements

Before and after the 1 yr intervention all participants went through a comprehensive assessment battery over three days, which consisted of a wide range of measurements: Day 1: *A medical examination* including medical history, blood samples, measurements of blood pressure, height, weight, waist circumference and auscultation of lungs and heart. The participants were fasting to the examination and it was performed between 8 am and 11 am. At the examination an accelerometer (activPAL) was put on the dominant leg to measure *physical activity* counting the total number of steps performed over five consecutive days. Day 2: Between 8 am and 2 pm in a non-fasting state *body composition (muscle mass, whole-body fat percentage and visceral fat content)* was determined using dual-X-ray-absorptiometry (DXA)-scan. Following the DXA-scan, participants went through *physical testing* including five different measures to determine muscle strength and functional lower extremity strength and endurance in the following order; 1) 400 m walking test, 2) Leg extensor power (primary outcome) measured with Leg Extensor Power Rig, 3) 30 s chair-stand test, 4) Maximal handgrip strength measured with SAEHAN DHD-1 Digital Hand Dynamometer, and 5) Maximal isometric knee extensor strength measured with the Good Strength device. The 400 m walking test and 30 s chair-stand test have previously shown excellent reproducibility in healthy middle-aged women and older adults (Bieler et al., 2014; Jones et al., 1999; Pettee Gabriel et al., 2010). Further, the 400 m walking test provides a valid estimate of peak VO_2 in older adults (Simonsick et al., 2006). Day 3: *Magnetic resonance imaging (MRI)* of the thigh and brain were implemented to determine CSA of m. vastus lateralis and to assess hippocampus volume and intracranial brain volume. M. vastus lateralis was manually drawn using the JIM software (Xinapse systems). The region-of-interest (ROI) was drawn on the mid slice, 20 cm above the tibia plateau. For ROI delineation, the data was randomized between baseline and 1 yr, so the radiographer performing the drawing was blinded to time of scanning. Freesurfer version 6.0 longitudinal stream was used to estimate hippocampus volume (mm^3) for baseline and 1 yr (Reuter et al., 2012). Quality control of the T1-images was initially performed by radiographers, and then the hippocampus volume was additionally controlled using the ENIGMA pipeline for quality control. Intracranial volume was used as a covariate to take into account the hippocampus volume change in relation to total brain volume. Finally, *questionnaires* were used to evaluate health-related quality of life (Short-Form Health Survey 36, SF-36) and self-reported physical activity (The Physical Activity Scale for the Elderly, PASE). Further information about the measurements is available in Eriksen et al., but besides our primary outcome, leg extensor power, all other measurements were secondary outcomes (Eriksen et al., 2016).

2.5. Statistical analysis

Power calculation based upon previous mean values and standard deviations for functional muscle measurements on older individuals revealed a sample size of $n = 60$ in each group. To detect smaller group differences and take larger variations into account we chose to include ≈150 participants in each group. In addition, we wanted to be able to detect relevant functional differences at a 10 yr follow-up assessment with an estimated 50% loss during the follow-up period. We chose a power level of 80% and significance level of 0.05 for the ANOVA.

A two-way ANOVA was used to evaluate the overall effects of group and time for all parameters except training compliance and sex distribution. In case of a significant group*time interaction, Tukey post hoc analysis was used to evaluate within group comparisons as well as a one-way ANOVA to detect any group differences. In addition, to evaluate the magnitude of the mean differences, effects sizes (ES) were calculated for all comparison groups (HRT vs. MIT, HRT vs. CON and MIT vs. CON).

Further, a two-way ANOVA was used to evaluate whether there were any differences in the response to the intervention upon muscle strength, −mass, −power or visceral fat content in those who had no chronical disease and those who had one or more if they were analyzed separately. For all analyses, the stratification parameters (BMI, chair-stand and sex) were included in the statistical model. For training compliance an unpaired *t*-test was used and for sex distribution a frequency analysis was used. All analyses were performed after the intention-to-treat principle. Descriptive statistics will be presented as means ± SD. All other data are presented as mean ± SE unless otherwise stated. All missing data were removed for the same participant at both time points. All statistical analyzes were performed using SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC, USA). For some parameters, residuals were not completely normally distributed. Logarithmic transformation did not resolve the issue and therefore results are presented for the base data with a note indicating the non-normality of the parameters in question.

2.6. Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

3. Results

3.1. Participant characteristics

A total of 451 participants were included from April 1, 2014, to June 30, 2017 (Fig. 1). The average age was 66 ± 2.5 years and the proportion of women was 61% (Table 2). There were no significant differences between the three intervention groups in any of the baseline characteristics. During the intervention 32 participants dropped out primarily due to lack of time, motivation or illness (Fig. 1). As an intention-to-treat study, we have included individuals who completed the 1 yr test-battery - independent of intervention compliance - in the data analysis ($n = 143$, 144 and 132; HRT, MIT and CON, respectively). Around 80% of the participants had at least one self-reported chronic disease. Of these most participants (≈51%) had 1–2 diseases, 27% had three or more diseases, whereas ≈22% of the participants had no diseases. Hypertension, hypercholesterolemia and cardiac diseases accounted overall for approximately 30%, 25% and 20%, respectively. For those who had 2–3 diseases, the most common combination of diseases was hypertension, hypercholesterolemia and cardiac diseases (2 or all 3). Finally, of all participants ≈12% reported to be smokers at baseline.

3.2. Muscle power and strength

3.2.1. Leg extensor power

For leg extensor power (primary outcome), there was a tendency towards a main effect of time ($p = .07$) (Fig. 2A) with higher leg extensor power at 1 yr compared to baseline.

3.2.2. Isometric strength of the quadriceps femoris muscle (IsoQ)

Only participants assigned to the strength training groups showed a relative increase in IsoQ (Fig. 2B), resulting in a significant group*time interaction ($p < .0001$). Changes in IsoQ were significantly different between HRT and MIT (p < .0001, ES: 0.52), HRT and CON (p < .0001, ES: 0.80), and between MIT and CON ($p < .05$, ES: 0.31). Compared to baseline, a significantly higher muscle strength at 1 yr was observed in HRT (p < .0001).

3.2.3. Handgrip strength

We observed no significant within- or between-group differences in handgrip strength after the 1 yr intervention. However, there was a significant decrease in strength over time (p < .05) (Table 3).

3.3. Muscle mass

3.3.1. Lean body and leg lean mass

In line with IsoQ, participants in the strength training groups experienced an increase in lean body mass, resulting in an overall significant interaction (p < .0001). There was no change in the control group. Changes in lean body mass were significantly different between HRT and MIT (p < .01, ES: 0.35), between HRT and CON ($p < .0001$, ES: 0.64) and a tendency towards a higher relative change in MIT than in CON ($p = .06$) (Table 4). Compared to baseline a significant higher lean body mass at 1 yr was observed in HRT ($p < .0001$). For leg lean mass, we found an overall interaction ($p < .01$), resulting in a higher relative change in HRT compared with CON (p < .01, ES: 0.37) (Table 4) and a tendency towards a higher relative change in MIT than in CON ($p = .05$).

Table 2
Participant characteristics at baseline (mean ± SD).

	Total ($n = 451$)	HRT ($n = 149$)	MIT ($n = 154$)	CON (n = 148)	Sample size
Age (years)	66 ± 2.5	66 ± 2.6	66 ± 2.5	67 ± 2.4	451
Sex (men/women) %	39/61	40/60	40/60	39/61	451
BMI (kg/m^2)	26.0 ± 4.2	26.4 ± 4.1	26.0 ± 4.2	25.6 ± 4.3	451
Waist circumference (cm)	93.3 ± 12.2	94.2 ± 11.8	93.4 ± 12.4	92.3 ± 12.3	450
Body fat %	33.6 ± 8.1	34.1 ± 8.0	33.6 ± 7.9	33.1 ± 8.5	451
Lean body mass (kg)	47.3 ± 9.0	47.8 ± 8.9	47.4 ± 9.3	46.8 ± 8.8	451
Leg extensor power (W)	193 ± 67	199 ± 71	192 ± 66	187 ± 63	450
30 s chair-stand (reps)	17 ± 4	16 ± 4	17 ± 4	17 ± 4	451
Total step count (steps/day)	9553 ± 3457	9481 ± 3262	9399 ± 3140	9783 ± 3941	431^

^Missing data due to technical error.

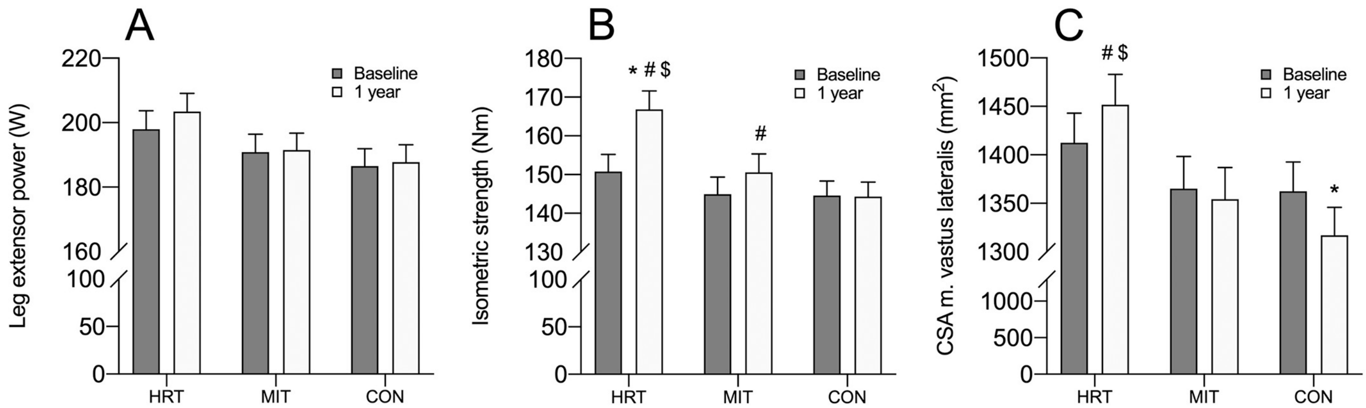

Fig. 2. Leg extensor power (A, $n = 417$), isometric strength (B, $n = 415$) and cross-sectional area (CSA) of m. vastus lateralis (C, $n = 380$) before (baseline, filled bars) and after 1 yr (open bars) of either heavy resistance training (HRT), moderate intensity resistance training (MIT) or habitual physical activity (CON). Bars represent mean ± SE.
*: significantly different from baseline (*B*: $p < .001$ (HRT); *C*: $p < .01$)
#: change from baseline significantly different compared with change in CON (*B*: $p < .0001$ (vs. HRT), $p < .05$ (vs. MIT); *C*: $p < .0001$)
$: change from baseline significantly different compared with change in MIT (*B*: $p < .0001$; *C*: $p < .05$).

3.3.2. Cross-sectional muscle area (CSA)

Fig. 2C illustrates the group data for CSA of m. vastus lateralis, showing a significant interaction ($p < .0001$) with a significant difference in muscle area change between HRT and MIT ($p < .05$, ES: 0.30) as well as between HRT and CON ($p < .0001$, ES: 0.51). Further, there was a significant decrease in cross-sectional area of 3.3% from baseline to 1 yr in CON ($p < .01$).

3.4. Functional outcomes

3.4.1. Chair-stand and 400 m walking test

We detected an overall significant interaction in the 30 s chair-stand test ($p < .01$) with a significant difference between MIT and CON ($p < .01$, ES: 0.37). Further, we observed significant improvements in all three groups from baseline to 1 yr ($p < .0001$) (Table 3). In regard to 400 m walking test, we found no within- or between-group differences in time to walk 400 m (Table 3). There was some non-normality in the residual distribution for both parameters.

3.4.2. Activity monitoring

Total step count data showed no significant changes in response to neither time nor intervention (Table 3).

3.5. Body composition

3.5.1. Whole-body fat percentage

We observed an overall significant interaction in whole-body fat percentage ($p < .0001$) with significant differences in changes between HRT and MIT ($p < .01$, ES: 0.41) as well as between HRT and CON ($p < .0001$, ES: 0.53) (Fig. 3A). In addition, we detected a significant decrease from baseline to 1 yr in HRT only ($p < .0001$).

3.5.2. Visceral fat

In line with whole-body fat percentage, we observed an overall significant interaction in visceral fat ($p < .001$), resulting in significant differences in changes between HRT and MIT as well as between HRT and CON (both $p < .01$, ES: 0.37 and 0.42, respectively) (Fig. 3B). Further, we observed a significant decrease from baseline to 1 yr in HRT only ($p < .0001$). There was some non-normality in the residual distribution for this parameter.

3.5.3. BMI, weight and waist circumference

For BMI, weight and waist circumference, we observed no within- or between-group differences, but there was an effect of time with a decrease in BMI ($p < .0001$), weight ($p < .0001$) and waist circumference observed at 1 yr ($p < .001$) (Table 4).

3.6. Blood parameters

3.6.1. Plasma lipids, HbA1c and c-reactive protein (CRP)

For HDL and LDL, we observed an overall significant interaction ($p < .05$) since the HDL changes in HRT differed from CON ($p < .05$, ES: 0.31), and LDL changes in MIT differed from CON ($p < .05$, ES: 0.29) (Table 5). Total cholesterol, triglycerides, CRP and VLDL did not differ between or within groups, but there was an effect of time with a decrease in VLDL only ($p < .05$) (Table 5). In accordance with the

Table 3
Muscle strength, functional outcomes and spontaneous activity level before (baseline) and after 1 yr of either heavy resistance training (HRT), moderate intensity resistance training (MIT) or habitual physical activity (CON) (mean ± SE).

	HRT		MIT		CON		Sample
	Baseline	1 yr	Baseline	1 yr	Baseline	1 yr	Size
Handgrip strength (kg)^t	36.1 ± 0.9	36.0 ± 0.9	33.8 ± 0.9	33.6 ± 0.9	35.2 ± 0.9	34.5 ± 0.9	418
Chair-stand (reps.)	16.5 ± 0.3	18.9 ± 0.4*	17.1 ± 0.4	20,0 ± 0.4*#	17.0 ± 0.4	18.7 ± 0.4*	416
400 m walking time (s)	243 ± 3	239 ± 3	241 ± 3	237 ± 3	238 ± 2	237 ± 3	410
Total step count (steps/day)	9524 ± 276	9608 ± 253	9522 ± 268	9671 ± 274	9876 ± 351	9687 ± 331	399^

*Significant different from baseline ($p < .0001$).
t: main effect of time ($p < .05$).
#: change from baseline to 1 yr was significantly different compared with change in CON ($p < .01$).
^Missing data due to technical error.

Table 4
Anthropometric data for participants before (baseline) and after 1 yr of either heavy resistance training (HRT), moderate intensity resistance training (MIT) or habitual physical activity (CON) (mean ± SE).

	HRT		MIT		CON		Sample
	Baseline	1 yr	Baseline	1 yr	Baseline	1 yr	size
Lean body mass (kg)	47.8 ± 0.7	48.5 ± 0.7*#$	47.1 ± 0.8	47.4 ± 0.8	46.5 ± 0.8	46.5 ± 0.8	419
Leg lean mass (kg)	17.1 ± 0.3	17.2 ± 0.3#	16.7 ± 0.3	16.8 ± 0.3	16.5 ± 0.3	16.4 ± 0.3	419
BMI (kg/m^2)t	26.3 ± 0.34	25.9 ± 0.33	26.0 ± 0.35	25.9 ± 0.36	25.3 ± 0.36	25.2 ± 0.34	419
Waist circumference (cm)t	94.0 ± 0.98	92.3 ± 0.92	93.3 ± 1.02	92.6 ± 1.03	91.7 ± 1.03	91.1 ± 1.04	416
Weight (kg)t	77.4 ± 1.1	76.4 ± 1.1	76.0 ± 1.2	75.6 ± 1.2	74.1 ± 1.2	73.8 ± 1.2	419

*Significant different from baseline (HRT: $p < .0001$).
t: main effect of time (BMI, weight and waist circumference: $p < .0001$).
#: change from baseline to 1 yr was significantly different compared with change in CON (lean body mass, $p < .0001$; leg lean mass, $p < .01$).
$: change from baseline to 1 yr was significantly different compared with change in MIT ($p < .01$).

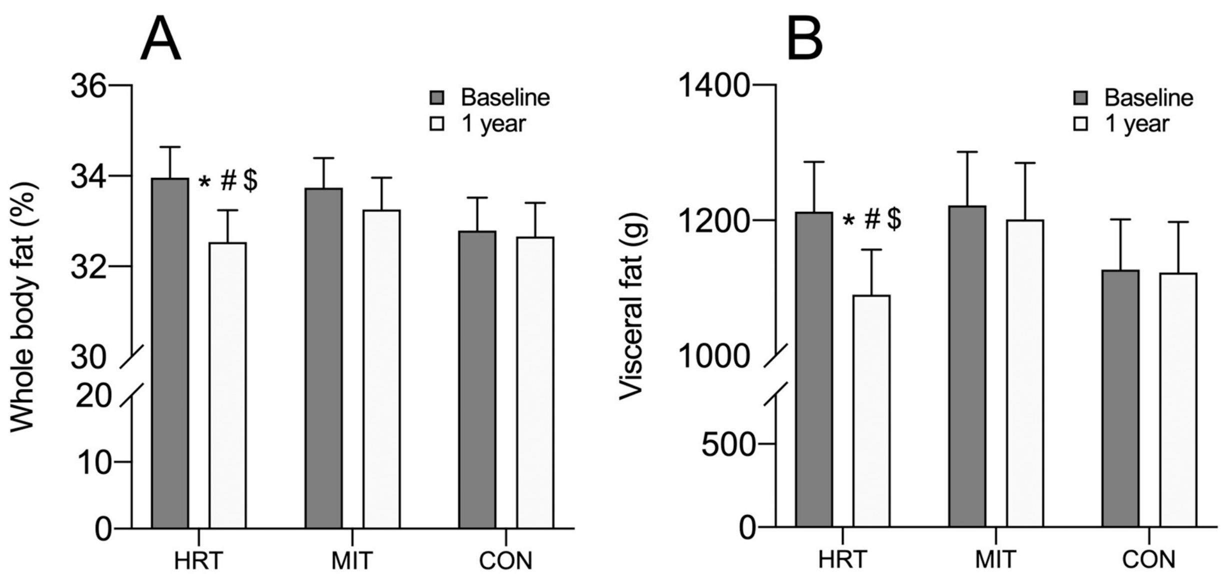

Fig. 3. Whole body fat percentage (A, $n = 419$) and visceral fat (B, n = 419) before (baseline, filled bars) and after 1 yr (open bars) of either heavy resistance training (HRT), moderate intensity resistance training (MIT) or habitual physical activity (CON). All values are given as mean ± SE.
*: significantly different from baseline ($p < .0001$)
#: change from baseline significantly different compared with change in CON (*A*: $p < .0001$; *B*: $p < .01$)
$: change from baseline significantly different compared with change in MIT ($p < .01$).

change measured for VLDL, there was no overall response to the intervention for HbA1c but an effect of time with an increase ($p < .05$) (Table 5). There was some non-normality in the residual distribution for VLDL, triglycerides, CRP and HbA1c.

3.6.2. *Blood pressure*

The analysis detected an effect of time for the systolic blood pressure of −7 ± 1 mm Hg as well as for the diastolic blood pressure of −4 ± 0 mmHg (both $p < .0001$) from baseline to 1 yr (Table 5).

Table 5
Blood pressure and blood parameters before (baseline) and after 1 yr of either heavy resistance training (HRT), moderate intensity resistance training (MIT) or habitual physical activity (CON) (mean ± SE).

	HRT		MIT		CON		Sample
	Baseline	1 yr	Baseline	1 yr	Baseline	1 yr	size
Total cholesterol (mmol/l)	5.7 ± 0.1	5.6 ± 0.1	5.9 ± 0.1	5.6 ± 0.1	5.8 ± 0.1	5.7 ± 0.1	419
HDL (mmol/l)	1.9 ± 0.1	2.0 ± 0.0#	1.9 ± 0.0	1.9 ± 0.0	2.0 ± 0.1	1.9 ± 0.0	418
LDL (mmol/l)	3.3 ± 0.1	3.1 ± 0.1	3.4 ± 0.1	3.1 ± 0.1#	3.3 ± 0.1	3.2 ± 0.1	414
VLDL (mmol/l)t	0.5 ± 0.0	0.5 ± 0.0	0.5 ± 0.0	0.5 ± 0.0	0.5 ± 0.0	0.5 ± 0.0	414
Triglycerides (mmol/l)	1.2 ± 0.0	1.1 ± 0.1	1.2 ± 0.0	1.1 ± 0.0	1.2 ± 0.1	1.2 ± 0.1	419
CRP (mg/l)	1.7 ± 0.2	2.5 ± 0.7	1.4 ± 0.2	1.3 ± 0.2	1.5 ± 0.3	1.3 ± 0.2	216^
HbA1c (mmol/mol)t	36.7 ± 0.4	37.0 ± 0.4	36.4 ± 0.3	37.2 ± 0.4	36.8 ± 0.4	37.1 ± 0.4	419
Systolic BP (mmHg)t	144 ± 1	137 ± 1	143 ± 1	136 ± 1	144 ± 2	137 ± 2	410
Diastolic BP (mmHg)t	86 ± 1	82 ± 1	86 ± 1	81 ± 1	86 ± 1	82 ± 1	410

#: change from baseline to 1 yr was significantly different compared to change in CON ($p < .05$).
t: main effect of time (VLDL and HbA1c: $p < .05$; systolic and diastolic BP: $p < .0001$).
^Missing data are caused by a late analyzing start-up of CRP.

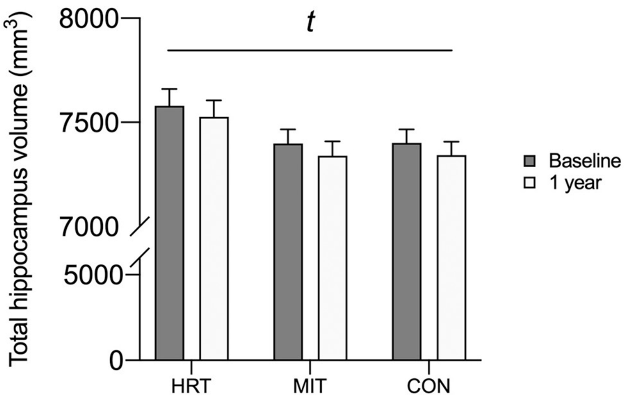

Fig. 4. Total hippocampus volume before (baseline, filled bars) and after 1 yr (open bars) of either heavy resistance training (HRT), moderate intensity resistance training (MIT) or habitual physical activity (CON). All values are given as mean ± SE. For this parameter $n = 332$, missing data due to technical error or claustrophobia.
t: main effect of time ($p < .05$).

3.7. Brain

For hippocampus volume, there was no overall significant group*-time interaction, but there was a main effect of time with a 57 ± 7 mm^3 decrease corresponding to a 0.77% compared to baseline ($p < .05$) (Fig. 4). Similar results were observed for the right and left hippocampus, respectively.

3.8. Questionnaires

3.8.1. Physical Activity for Elderly (PASE)

For PASE, we found no overall effect of intervention (Table 6).

3.8.2. Health-related quality of life (SF-36)

The SF-36 physical summary score did not differ between or within groups and there was no effect of time either (Table 6). However, when looking at the SF-36 mental summary score, we observed an overall significant interaction ($p < .05$) since HRT had a significantly higher relative change compared with MIT ($p < .05$, ES: 0.29) (Table 6). There was some non-normality in the residual distribution for SF-36 mental and physical summary score.

3.9. Training compliance

The overall compliance (total number of completed training sessions) for all participants in the training groups was high and did not differ between HRT (77% ± 21.6% (SD)) and MIT (78% ± 24.6% (SD)). Of the participants, 83% (HRT and MIT) completed 66% or more of the training sessions equivalent to at least two weekly training sessions.

3.10. Healthy vs. chronically diseased participants

When analyzing IsoQ, lean body mass, leg extensor power, CSA and visceral fat content in healthy and chronically diseased participants separately, we observed that both groups revealed same conclusion regarding group*time interactions. However, for IsoQ we did observe a different relative change compared with the overall analysis with no longer difference between HRT and MIT in healthy and no difference between MIT and CON in diseased participants. Further, the relative change in lean body mass between HRT and MIT was only significantly different in the healthy group ($p < .05$). In contrast, there was no differences in the relative change in visceral fat content in healthy but still significantly different between HRT and MIT as well as between HRT and CON in diseased participants. Further, when comparing the training compliance between healthy and chronically diseased, we did not find any significant differences between groups (82% ± 23% (SD) vs. 76% ± 23% (SD), respectively, $p > .05$).

4. Discussion

The pre-determined primary outcome of this study, leg extensor power, did not respond to the 1 yr intervention with heavy resistance training (HRT) or moderate intensity resistance training (MIT). Secondary outcomes such as knee extensor muscle strength and lean body mass all increased in response to HRT and to a lesser extent in response to MIT, when compared with a non-exercising control group. Further, we demonstrated that only HRT significantly increased muscle size and decreased whole-body fat percentage and visceral fat content in response to 1 yr of strength training. The compliance to the 1 yr training in our study was excellent and almost as high as seen in shorter lasting studies of weeks to months (Bechshøft et al., 2017; Fielding et al., 2002; Leenders et al., 2013; Marsh et al., 2009; Oh et al., 2017). Notably, the compliance was markedly higher than observed in a study with two years training duration (Aartolahti et al., 2019). Thus, the results indicate that long-term supervised strength training can be implemented with good compliance both in healthy and chronically diseased elderly individuals.

It was somewhat to our surprise that we did not find any improvement in leg extensor power in response to the implemented training, as another study, using a similar strength training protocol, demonstrated a marked increase in muscle power already after 12 weeks (Bechshøft et al., 2017). However, in that study participants were markedly older than in our study, which supports the view that improvements in muscle power is more likely to be observed in older and more functionally impaired individuals than in the age-range (62–70 years) included in the present study. Another likely explanation for the lack of improved muscle power is that no specific emphasis was put upon performing the exercises in an explosive, high velocity pattern. Explosive strength training may be necessary to improve muscle power as supported by studies showing improvements in leg power as a result of explosive strength training and not after regular strength training with low velocity (Fielding et al., 2002; Marsh et al., 2009).

Whereas muscle power did not increase, the maximal muscle strength improved markedly in response to both strength training

Table 6
Questionnaires; Physical Activity for Elderly (PASE) and Health-related quality of life (SF-36) score before (baseline) and after 1 yr of either heavy resistance training (HRT), moderate intensity resistance training (MIT) or habitual physical activity (CON) (mean ± SE).

	HRT		MIT		CON		Sample
	Baseline	1 yr	Baseline	1 yr	Baseline	1 yr	size
PASE	136.6 ± 5.3	148.3 ± 5.5	135.5 ± 4.1	141.3 ± 5.4	135.3 ± 4.5	139.2 ± 5.3	411
SF-36 Physical Summary	53.1 ± 0.5	53.1 ± 0.6	53.1 ± 0.4	52.5 ± 0.6	52.9 ± 0.5	53.2 ± 0.5	413
SF-36 Mental Summary	56.3 ± 0.6	57.5 ± $0.5^{\$}$	57.6 ± 0.4	56.8 ± 0.5	56.3 ± 0.6	56.2 ± 0.7	413

\$: change from baseline to 1 yr was significantly different compared to change in MIT ($p < .05$).

regimes. The degree of improvement in HRT was comparable to previous 1–2 years training interventions in older adults (Aartolahti et al., 2019; Sundstrup et al., 2016). Interestingly, the strength improvement in our study was not markedly higher than that obtained in short-term studies even though we used periodization (i.a. 12 weeks, 3 times/week) (Bechshøft et al., 2017; Marsh et al., 2009), which suggests that strength gains are dependent upon weekly training intensity and volume, rather than total length of a training intervention. However, more prolonged training could potentially play a role in initiating a positive long-term change in physical activity habits. MIT also improved maximal strength, underlining that lower intensity resistance training for 1 yr appear sufficient to significantly improve muscle strength. However, as expected the increase in muscle strength was less pronounced with MIT than with HRT. This finding fits well with the findings by García-Pinillos and colleagues, who found a higher response after combined high-intensity interval strength and endurance training compared with regular low-moderate intensity continuous training (García-Pinillos et al., 2019). This knowledge could benefit individuals who are unable or unwilling to undertake heavy resistance training. In studies using MIT-like training over a shorter duration (8–24 weeks) there are ambiguous conclusions as to the effect upon muscle strength (Borde et al., 2015; Martins et al., 2015; Oh et al., 2017). Thus, our findings could indicate that in order to obtain a significant improvement in muscle strength and function with MIT, the training period should be of longer duration than a few months. Both for MIT and HRT the emphasis was placed upon lower extremity exercises, and it is thus not surprising that no improvement was obtained in handgrip strength.

In line with increased muscle strength, lean body mass and knee extensor muscle size (CSA) increased with HRT. Our findings fit well with the effects of heavy resistance training found by others in healthy elderly without any chronic diseases (Leenders et al., 2013). With regards to muscle size, our results are comparable to studies on very old individuals performing strength training (Bechshøft et al., 2017).

The present study reports no specific effect of strength training upon functional muscle performance such as the number of chair-stands over 30 s or 400 m walking time. However, in agreement with others (Sundstrup et al., 2016) we did find an improvement in the chair-stand performance in all three groups irrespective of training. First, the improvement in all groups indicates an unspecific improvement in tests from the first to second trial that could be related to a learning effect or an unspecific effect of participating in an exercise study. Additionally, results from the chair-stand test reflects that our training was not targeted specifically towards this mode of physical activity. The latter is supported by findings from Santanasto et al., where a similar training program was supplemented with balance and walking exercises, resulting in an improved walking time as an effect of the training intervention (Santanasto et al., 2017). Further, the Santanasto study included mobility limited participants only, which could explain the difference of training upon muscle function outcome. In contrast, we have included well-functioning moderately old individuals where the potential for conversion of improved muscle strength towards improved function is more limited. Further, in the present study, we used 400 m walking time as a measure of functional ability because of its good reproducibility (Pettee Gabriel et al., 2010) and the fact that it provides a valid estimate of peak VO_2 in older adults (Simonsick et al., 2006). However, it cannot be excluded that the response to the intervention had given other results on functional ability if we instead had chosen 10 m gait speed. This is so, since it has been suggested in a cross sectional study that gait speed was the best to represent physical function, because it correlated well with handgrip strength, 30-s chair-stand test as well as skeletal muscle mass (Garcia-Pinillos et al., 2016). Additionally, the participants in our study were quite active even prior to the study walking approximately 10,000 steps/day, which is markedly more than previously observed in older individuals (Bechshøft et al., 2017). Although we did not study the lifestyle of our participants in detail, it cannot be excluded that even though ≈80% of the participants had a chronic disease, the entire group of participants in the present study maintained a healthy lifestyle in general (e.g. food and activity). Thus, it was more difficult to demonstrate any further improvement in health parameters than would have been the case in a more average part of the background population.

With regard to whole-body fat percentage, we found that prolonged HRT led to a significant decrease in accordance with the results of an earlier study using strength training (Leenders et al., 2013). Further, we found a significant decrease in visceral fat content in HRT only. The majority of other strength training studies in elderly found no evidence of influence on visceral fat (Ismail et al., 2012), whereas there is a more generally accepted effect of aerobic exercise training being beneficial for a loss in visceral fat (Maillard et al., 2018). When comparing our results to most other strength training studies reporting no beneficial effect upon visceral fat mass, the present study is of much longer duration (Bechshøft et al., 2017; Phillips et al., 2017). The reduction of visceral fat in response to HRT in our study is important in relation to a reduction in the risk for development of metabolic diseases like type 2 diabetes (Fox et al., 2007). Interestingly, we did find a drop in blood pressure and VLDL over time in all groups independent of strength training, which indicates an unspecific effect of participating in a controlled study potentially related to changes in life style (e.g. food intake). The only specific positive effects of HRT and MIT upon circulating metabolic factors we found, was an increase of HDL after HRT and a decrease in LDL after MIT both when comparing with CON. This is in accordance with other strength training studies, and emphasizes that strength training may have positive metabolic effects, besides changes in body composition (Ihalainen et al., 2019; Tsuzuku et al., 2007).

An interesting aspect of our finding was that when we compared the influence of strength training upon muscle strength, -mass, -power, or visceral fat, the ≈20% of the studied elderly that were without any disease diagnosis, and the ≈80% that had one or more chronic diseases responded the same way to the intervention. This underlines the ability to strength training to influence skeletal muscle and visceral fat in elderly independent of chronic diseases.

In accordance with findings from a meta-analysis (Fraser et al., 2015), we observed an overall decrease in hippocampus volume over one year for all groups. In contrast to most previous studies supporting a long-term positive association of hippocampus volume in relation to aerobic training (Erickson et al., 2011; Jonasson et al., 2016), we did not detect an effect of 1 yr of strength training on hippocampus volume. Only few studies have investigated the effect of strength training on brain readouts. A one year strength training program suggested to improve functional plasticity of response inhibition processes in the cortex, but any changes in hippocampus volume were not reported (Liu-Ambrose et al., 2012). Further, Kim et al. reported an increase in hippocampus volume following 24 weeks of strength training compared to a control group (Kim et al., 2017). However, in contrast to the present study, their sample size was small ($n = 21$ participants), all participants were women, and they were generally older (67–81 years). Further, the activity level of this study cohort was lower compared to our participants, which could explain the discrepancy compared to our findings. In contrast, the questionnaire SF-36 mental summary score improved more in HRT than MIT. Our results together with findings by others (Hart and Buck, 2019) support the view that regular physical training also in the form of strength training may improve the mental aspects of health-related quality of life in elderly, and furthermore that this effect is related to training intensity.

Clearly, the present study did not compare the effects of other types of training (e.g. endurance training) with that of strength training, but as we do find a significant positive effect of strength training upon muscle mass and strength, we recommend strength training as a valuable intervention in order to improve muscle function.

A limitation of the present study was the difference in supervision between HRT and MIT, as benefits from supervised exercise training may be higher than unsupervised training. MIT was primarily home based due to the overall goal of implementation of training at home, whereby it potentially should be more likely to continue the training also after completion of the intervention compared with those in HRT where a fitness center was necessary. Further, our choice of supervision in MIT with one time a week supervised at the hospital and two times a week non-supervised training at home, had the consequence that training compliance relies predominantly on self-report.

Further, it could be argued that the inclusion of a mix of healthy and chronically diseased individuals could provide a higher variation in the determined data. However, from the background data the two groups did not differ markedly from each other in physiological parameters, and that any small group difference is outweighed by the strength of the study to include both healthy and chronical diseased elderly individuals, and thus produce results that are more applicable to older adults in general.

5. Conclusion

Leg extensor power was not affected by strength training. However, heavy resistance strength training improved muscle strength and size, and reduced whole-body fat percentage as well as visceral fat, and did so more pronounced than for lower intensity strength training (i.e. MIT). Together, the results indicate that long-term supervised strength training in both healthy and chronically diseased elderly individuals can be implemented with good compliance and induces consistent changes in physiological parameters of muscle and fat. This could contribute to recommendations for individuals approaching retirement age in order to counteract long-term decline in overall function, metabolism and health.

CRediT authorship contribution statement

Anne Theil Gylling:Validation, Formal analysis, Investigation, Writing - original draft.**Christian Skou Eriksen**:Investigation, Validation, Writing - review & editing, Project administration.**Ellen Garde**:Conceptualization, Methodology, Validation, Writing - review & editing.**Cathrine Lawaetz Wimmelmann**:Investigation, Validation, Writing - review & editing.**Nina Linde Reislev**: Investigation, Validation, Writing - review & editing.**Theresa Bieler**:Investigation, Validation, Writing - review & editing.**Andreas Kraag Ziegler**:Investigation, Validation, Writing - review & editing, Project administration.**Kasper Winther Andersen**:Investigation, Writing - review & editing.**Christian Bauer**:Investigation, Writing - review & editing.**Kasper Dideriksen**:Investigation, Validation, Writing - review & editing.**Maria Baekgaard**:Validation, Investigation, Visualization, Writing - review & editing.**Kenneth Hudlebusch Mertz**:Investigation, Validation, Writing - review & editing.**Monika Lucia Bayer**:Investigation, Validation, Writing - review & editing.**Mads Bloch-Ibenfeldt**:Validation, Investigation, Visualization, Writing - review & editing.**Carl-Johan Boraxbekk**: Investigation, Validation, Writing - review & editing.**Hartwig Roman Siebner**:Conceptualization, Methodology, Validation, Writing - review & editing.**Erik Lykke Mortensen**: Conceptualization, Methodology, Validation, Writing - review & editing.**Michael Kjaer**:Conceptualization, Methodology, Validation, Writing - review & editing, Supervision.

Declaration of competing interest

There was no conflict of interest.

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PHD-THESIS
DECLARATION OF CO-AUTHORSHIP

The declaration is for PhD students and must be completed for each conjointly authored article. Please note that if a manuscript or published paper has ten or less co-authors, all co-authors must sign the declaration of co-authorship. If it has more than ten co-authors, declarations of co-authorship from the corresponding author(s), the senior author and the principal supervisor (if relevant) are a minimum requirement.

1. Declaration by	
Name of PhD student	Anne Theil Gylling
E-mail	a_gylling@hotmail.com
Name of principal supervisor	Michael Kjær
Title of the PhD thesis	Physical activity as intervention for age-related loss of muscle mass and function, the LISA study: A randomized controlled trial

2. The declaration applies to the following article	
Title of article	The influence of prolonged strength training upon muscle and fat in healthy and chronically diseased older adults
Article status	
Published ☒ Date: 8/4-2020	Accepted for publication ☐ Date:
Manuscript submitted ☐ Date:	Manuscript not submitted ☐
If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information).	

3. The PhD student's contribution to the article ***(please use the scale A-F as benchmark)*** Benchmark scale of the PhD-student's contribution to the article **A**. Has essentially done all the work (> 90 %) **B**. Has done most of the work (60-90 %) **C**. Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant	**A, B, C, D, E, F**
1. Formulation/identification of the scientific problem	C
2. Development of the key methods	C
3. Planning of the experiments and methodology design and development	B
4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	B
5. Conducting the analysis of data	A
6. Interpretation of the results	A
7. Writing of the first draft of the manuscript	A
8. Finalisation of the manuscript and submission	A
Provide a short description of the PhD student´s specific contribution to the article.[i] The PhD student has been a part of most of the planning of and conducting the experimental work and data collection. The PhD student has conducted all statistically analysis of data and interpretation of the results. Further, the PhD student has writing the first draft of the manuscript and finalised it for submission.	

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Does the article contain work which has also formed part of another thesis, e.g. master's thesis, PhD thesis or doctoral dissertation (the PhD student's or another person's)?	Yes: ☐ No: ☒
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5. Signatures of the co-authors[iii]

	Date	Name	Title	Signature
1.	13/5-20	Anne Theil Gylling	MSc	Anne Theil Gylling
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6. Signature of the principal supervisor

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date: 14/5-20
Principal supervisor:

7. Signature of the PhD student

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Date: 13/5-20
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"Any articles included in the thesis may be written in cooperation with others, provided that each of the co-authors submits a written declaration stating the PhD student's or the author's contribution to the work."
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Paper 2:

Maintenance of muscle strength following a one-year resistance training program in older adults.

Anne Theil Gylling, Mads Bloch-Ibenfeldt, Christian Skou Eriksen, Andreas Kraag Ziegler, Cathrine Lawaetz Wimmelmann, Maria Baekgaard, Carl-Johan Boraxbekk, Hartwig Roman Siebner, Erik Lykke Mortensen, Michael Kjaer.

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Maintenance of muscle strength following a one-year resistance training program in older adults

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ABSTRACT

Background: Muscle mass, strength and function declines with advancing age. Strength training (ST) improves these parameters in older adults, but the gains often disappear after completion of a short-term intervention. The purpose of the present study was to investigate muscle mass, -strength and -function one year after the completion of a successful long-term (12 months) supervised ST program in older adults.
Method: Men and women ($n = 419$, age: 62–70 years) completed one year of supervised heavy resistance training (HRT, $n = 143$) or moderate intensity resistance training (MIT, $n = 144$) and were compared to a non-exercising control group (CON, $n = 132$). At 1-year follow-up, 398 participants returned for measurements of muscle power, -strength and -mass, physical function, body composition, hippocampus volume and physical/ mental well-being. The results were compared to pre-training (baseline) and post-training (1-year) values. Further, the participants from the two previous training groups (HRT + MIT, $n = 265$) were divided into 1) those who on their own continued the ST program (> 9 months) the year after completion of the supervised ST program (CONTIN, $n = 65$) and 2) those who stopped during the follow-up year (< 9 months) (STOP, $n = 200$).
Results: Out of all the improvements obtained after the 1-year training intervention, only knee extensor muscle strength in HRT was preserved at 1-year follow-up ($p < 0.0001$), where muscle strength was 7% higher than baseline. Additionally, the decrease in muscle strength over the second year was lower in CONTIN than in STOP with decreases of 1% and 6%, respectively ($p < 0.05$). Only in CONTIN was the muscle strength still higher at 1-year follow-up compared with baseline with a 14% increase ($p < 0.0001$). The heavy strength training induced increase in whole-body lean mass was erased at 1-year follow-up. However, there was a tendency for maintenance of the cross-sectional area of m. vastus lateralis from baseline to 1-year follow-up in HRT compared with CON ($p = 0.06$). Waist circumference decreased further over the second year in CONTIN, whereas it increased in STOP ($p < 0.05$).
Conclusion: Even though long-term strength training effectively improved muscle function and other health parameters in older adults, only knee extensor muscle strength was preserved one year after completion of heavy (but not moderate intensity) resistance training. Continuation of strength training resulted in better maintenance of muscle strength and health, which indicates that it is required to continue with physical activity to benefit from the long-term effects of strength training upon muscle function and health in older men and women.

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1. Introduction

Muscle mass, -strength and physical function are known to decline with advancing age (Suetta et al., 2019; Fielding et al., 2011; Cruz-Jentoft et al., 2019), but can partly be counteracted with strength training (Borde et al., 2015; Fielding et al., 2002; Bechshøft et al., 2017; Leenders et al., 2013; Churchward-Venne et al., 2015). However, previous studies have shown that gains obtained in muscle mass and -strength either fully disappear or are only partly preserved after the termination of a prescribed training period (Trappe et al., 2002; Bickel et al., 2011; Fatouros et al., 2005; Kalapotharakos et al., 2007; Correa et al., 2013, 2016; Lee et al., 2017). To our knowledge, this has predominantly been studied after shorter duration interventions (10–24 weeks) with one type of strength training investigated in healthy adults only. Only few studies have investigated older adults in the follow-up period (without any training instructions) after a long-term period with supervised strength training (Snijders et al., 2019; Karinkanta et al., 2009; Uusi-Rasi et al., 2017; Fernández-Lezaun et al., 2017). It has previously been demonstrated that muscle strength was only partly preserved 6–12-months after 6 or 9 months of strength training in healthy older adults (Snijders et al., 2019; Fernández-Lezaun et al., 2017), perhaps explained by discontinuation of training after the intervention. Similarly, training studies of even longer durations (12–24 months) demonstrated that muscle strength gains disappeared or were only partly preserved one or two years after the exercise intervention (Karinkanta et al., 2009; Uusi-Rasi et al., 2017). However, these two studies included only women with an average age above 70 years. Additionally, the long-term effects of 1-year of strength training upon health-related parameters as circulating blood parameters and visceral fat are unknown.

In a recent long-term (1 yr) intervention study, we found improvements of muscle mass and -strength as well as other health parameters (e.g. visceral fat and whole-body fat percentage) in both healthy and chronically diseased older adults in response to heavy resistance training (HRT) and to some degree moderate intensity resistance training (MIT) (Gylling et al., 2020), underlining that strength training with lower intensity for one year also has beneficial effects on muscle function, which can be useful for individuals who are unable or unwilling to undertake heavy resistance training. In addition, the health-related quality of life improved with HRT, whereas hippocampus volume declined over time unaffected by the strength training programs. In the present study, we wanted to investigate whether the observed improvements in muscle strength and -mass as well as in body composition, visceral fat and health-related quality of life persisted one year after completion of the strength training intervention. Further, it is unknown to what extent one year of organized strength training, with two different intensities, leads to a more permanently active lifestyle with strength type exercises (and other types of exercises) implemented as a part of the daily routine in a mixed group of both healthy and chronically diseased older adults. Therefore, the continuation of strength training was investigated at 1-year follow-up, also in order to investigate the potential difference in training adherence between HRT and MIT. Further, whether the gains obtained during the one year of supervised strength training were maintained differently in HRT and MIT were investigated at 1-year follow-up in all participants who completed the 1-year supervised training. We also determined whether any difference was obtained between those who continued strength training on their own during the follow-up year and those who stopped the regular strength training.

We hypothesized that one year after completion of the strength training intervention, participants in the previous training groups had maintained the improvements in muscle mass, -strength and other health-related parameters, primarily due to continuation of strength training and other physical activities on an individual basis. We also hypothesized that participants in MIT would more likely continue training primarily due to the already implemented training at home.

2. Method

2.1. Study design

The present study is the 1-year follow-up in the LISA study, which investigates the long-term effects of a 1-year strength training intervention upon muscle mass, muscle strength, physical function and mental well-being in 451 independently healthy and chronically diseased men and women aged 62–70 years. The full methodological description is provided previously (Eriksen et al., 2016). In brief, all participants went through a baseline assessment including a medical screening, physical testing, body composition, muscle thigh cross-sectional area (CSA of m. vastus lateralis) and brain imaging before they were randomized to either one year of heavy resistance training (HRT), moderate intensity resistance training (MIT) or a non-exercising control group (CON). The study plan is to follow the participants over a 10-year period (9-years follow-up period after completion of 1-year training intervention) and the present study evaluates the results obtained one year after completion of the 1-year intervention (called 1-year follow-up). All participants in the initial 1-year intervention were invited to assessments at 1-year follow-up, irrespective of whether they had complied to training or not in the first year, whether they had continued any training on their own in year 2 and whether they had obtained any new diseases during our observation period.

Exclusion criteria for the original study were defined as more than 1 h/week of regular strenuous exercise training, severe unstable medical diseases (e.g. active cancer or severe heart disease) and musculoskeletal diseases that inhibited training ability. Furthermore, participants using medication that may influence the effects of training (e.g. androgens or antiandrogens), and drugs that caused safety concerns in relation to training were excluded. All participants signed an informed consent before participating. The study was approved by the regional ethical committee (Capital Region, Copenhagen, Denmark, No. H-3-2014-017), complied with the declaration of Helsinki, and was approved by the Danish Data Protection Agency and registered on clinicaltrials.gov (NCT02123641).

After completion of the 1-year strength training intervention (or non-exercise control), there were no imposed restrictions for exercise training in any of the three groups, so all participants (incl. CON) could perform any kind of exercise training (or no training). One year after the training intervention was completed, all participants were invited to a 1-year follow-up assessment including the same assessments as before and after the 1-year strength training intervention. Of the randomized 451 participants at baseline, and 419 participants at 1-year, 398 participants came to 1-year follow-up and were included in the analysis. Fig. 1 illustrates the flow of participants in a flow-chart. Further, based on self-reports we divided the participants from the two strength training interventions into two groups: those who continued with the exact same strength training program as during the intervention for > 9 months (CONTIN) and those who did not (STOP).

2.2. Randomization and interventions

At baseline the participants were stratified according to sex (man/woman), functional ability (chair-stand test ≤11 or > 11) and body mass index (BMI ≤28 or > 28) and randomized into one of three groups; HRT, MIT or CON. The initial strength training program was performed 3 times per week for one year. A progressive whole-body training program with increasing load was performed in both training groups. The training in HRT was a linear periodized regime over a 9-week period and consisted of three sets of 6–12 repetitions with intensity between ≈70–85% of 1 repetition maximum (RM) performed in TechnoGym fitness machines with increasing loads every second week for 8 weeks and restitution in the last week. MIT consisted of three sets of 10–18 repetitions with intensity between ≈50–60% of 1RM performed with rubber bands and own body weight. The participants in the control group were encouraged to continue their habitual physical activity level (less than 1 h of strenuous physical activity per week) and

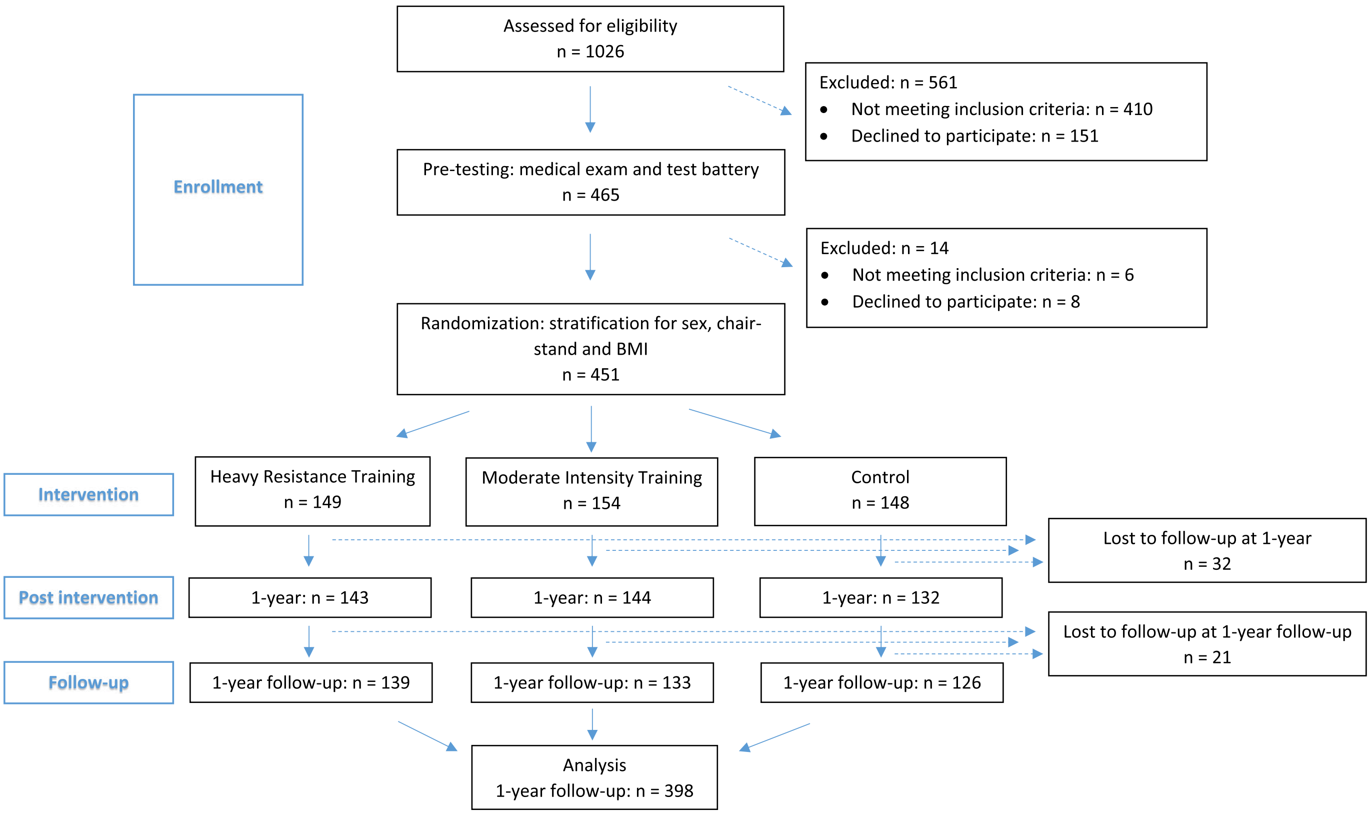

Fig. 1. Study flow chart from the enrollment of the participants to 1-year follow-up.

were offered to participate in social and cultural non-exercise activities approximately two times per month during the 1-year intervention. Details of the intervention are described previously (Eriksen et al., 2016; Gylling et al., 2020).

2.3. Measurements

On the first experimental day, the medical screening was performed in the fasted state and included blood sampling, measurements of blood pressure, height, weight and waist circumference. At the medical screening, an accelerometer (activPAL) was mounted on the thigh to determine the physical activity level. The accelerometer was worn for five consecutive days to measure the total amount of steps performed. The second experimental day included measurements of body composition and examination of physical function. Body composition was assessed using dual-energy X-ray absorptiometry (DXA)-scan, where lean body mass, lean leg mass, fat percentage and visceral fat content was determined. The physical test battery consisted of five different tests including both strength and functional measurements performed in the following order; 400 m walking test, leg extensor power measured in the Leg Extensor Power Rig (Queen's Medical Centre, Nottingham University, UK), 30 s chair-stand test, and maximal muscle strength (handgrip and isometric knee extension) measured with a SAEHAN DHD-1 Digital Hand Dynamometer and in a Good Strength device (V.3.14 Bluetooth; Metitur, Finland), respectively. On the third experimental day, magnetic resonance imaging (MRI) was performed to determine CSA of m. vastus lateralis, and hippocampus and brain volume. The CSA of the vastus lateralis muscle was manually drawn using the JIM software (Xinapse systems). From the mid slice 20 cm above the tibia plateau, the region-of-interest (ROI) was drawn. For ROI delineation, the data was randomized between baseline and 1-year, so the radiographer performing the drawing was blinded to time of scanning. The drawing of 1-year follow-up was performed consecutively and not at the same time as baseline and 1-year, leaving the radiographer blinded to only group but not to time point. To estimate hippocampus volume (mm3) for baseline, 1-year and 1-year follow-up, we used freesurfer version 6.0 longitudinal stream (Reuter et al., 2012). The first quality control of the T1-images was performed by radiographers, and secondly the hippocampus volumes were controlled using the ENIGMA guidelines. As a covariate, intracranial volume was used to take the hippocampus volume change in relation to total brain volume into account. Finally, health-related quality of life (Short-Form Health Survey 36, SF-36), self-reported physical activity (The Physical Activity Scale for the Elderly, PASE) and the participant's physical activity during the year after the intervention were evaluated through questionnaires. The questionnaires were completed at home between the first and the second experimental day. The adherence questionnaire allowed us to separate participants who from year 1 to year 2 had maintained the strength training program on their own (for > 9 months, CONTIN), from those who did not continue strength training for the second year (stopped within the first 9 months after supervised training was terminated, STOP). For a more complete description of the measurements see previous publication (Eriksen et al., 2016).

2.4. Statistics

A two-way mixed model with repeated measures was used to evaluate the overall effects of group and time for all parameters, except sex distribution, including data from all three time points. In case of a significant group × time interaction, Tukey post hoc analysis was used to evaluate within group comparisons as well as a one-way ANOVA (a generalized linear model) to detect any group differences from baseline to 1-year, baseline to 1-year follow-up as well as from 1-year to 1-year follow-up. If no significant group × time interaction was observed, the same model but without interaction was used to evaluate time effects. For sex distribution a frequency analysis was used. In all these statistical models, only participants who came to all three assessments were included in the analysis. In Tables 1, 2 and 3, we have mixed all three groups, as there was no differences between groups, but only an effect of time (a) in some parameters. To evaluate the effects of unsupervised

Table 1
The development of anthropometric measurements, muscle function, physical activity level and total hippocampus volume measured before (baseline), after the 1-year intervention (1 year), and one year after completion of intervention (1-year follow-up) in all participants from HRT, MIT and CON (mean ± SE).

	Baseline	1-year	1-year follow-up	Sample size
Sex (men/women) %	39/61	–	–	398
BMI (kg/m^2)[a]	25.8 ± 0.2	25.6 ± 0.2	25.6 ± 0.2	398
Waist circumference (cm)[a]	92.8 ± 0.6	91.8 ± 0.6	92.3 ± 0.6	395
Weight (kg)[a]	75.5 ± 0.7	75.0 ± 0.7	75.1 ± 0.7	398
Leg extensor power (W)	192.2 ± 3.3	194.4 ± 3.2	191.6 ± 2.6	392
Handgrip strength (kg)[a]	34.9 ± 0.5	34.6 ± 0.5	34.3 ± 0.4	394
30 s chair-stand (reps)[a]	16.9 ± 0.2	19.3 ± 0.3	19.9 ± 0.2	390
400 m walking time (s)	240 ± 2	236 ± 2	238 ± 2	383
Total step count (steps/day)	9607 ± 174	9641 ± 167	9599 ± 171	379[b]
Total hippocampus volume (mm^3)[a]	7701 ± 42	7642 ± 43	7583 ± 43	305[b]

[a] Main effect of time (BMI $p < 0.05$ with differences between baseline vs. 1-year, and baseline vs. 1-year follow-up; Waist circumference $p < 0.01$ with differences between baseline vs. 1-year, and 1-year vs. 1-year follow-up; Weight $p < 0.05$ with differences between baseline vs. 1-year, and baseline vs. 1-year follow-up; Handgrip $p < 0.01$ with difference between baseline vs. 1-year follow-up; Chair-stand $p < 0.0001$ with differences between baseline vs. 1-year, baseline vs. 1-year follow-up, and 1-year vs. 1-year follow-up; Total hippocampus volume $p < 0.0001$ with differences between baseline vs. 1-year, baseline vs. 1-year follow-up, and 1-year vs. 1-year follow-up).
[b] Missing data due to technical error (total step count and hippocampus volume) or claustrophobia (total hippocampus volume).

Table 2
The development of blood parameters and blood pressure measured before (baseline), after the 1-year intervention (1-year), and one year after completion of intervention (1-year follow-up) in all participants from HRT, MIT and CON (mean ± SE).

	Baseline	1-year	1-year follow-up	Sample size
Total cholesterol (mmol/l)[a]	5.77 ± 0.05	5.61 ± 0.05	5.56 ± 0.05	398
HDL (mmol/l)	1.93 ± 0.03	1.94 ± 0.03	1.91 ± 0.03	397
LDL (mmol/l)[a]	3.31 ± 0.05	3.15 ± 0.05	3.14 ± 0.05	391
VLDL (mmol/l)[a]	0.52 ± 0.01	0.51 ± 0.01	0.49 ± 0.01	393
Triglycerides (mmol/l)	1.19 ± 0.04	1.15 ± 0.03	1.13 ± 0.03	398
CRP (mg/l)[a]	1.52 ± 0.13	1.66 ± 0.24	2.52 ± 0.48	206[b]
HbA1c (mmol/mol)[a]	36.63 ± 0.22	37.10 ± 0.24	37.11 ± 0.25	398
Systolic BP (mmHg)[a]	144 ± 0.9	137 ± 0.9	137 ± 0.9	387
Diastolic BP (mmHg)[a]	86 ± 0.5	82 ± 0.5	82 ± 0.5	387

[a] Main effect of time (Total cholesterol, LDL, Systolic BP and Diastolic BP $p < 0.0001$ with differences between baseline vs. 1-year, and baseline vs. 1-year follow-up; VLDL and CRP $p < 0.05$ with difference between baseline vs. 1-year follow-up; HbA1c $p < 0.01$ with differences between baseline vs. 1-year, and baseline vs. 1-year follow-up).
[b] Missing data due to late start up for analyzing CRP.

Table 3
Questionnaires; the development of Physical Activity for Elderly (PASE) and Health-related quality of life (SF-36) scores measured before (baseline), after the 1-year intervention (1-year), and one year after completion of intervention (1-year follow-up) in all participants from HRT, MIT and CON (mean ± SE).

	Baseline	1-year	1-year follow-up	Sample size
PASE (score)	136.0 ± 2.8	142.7 ± 3.2	141.0 ± 3.2	390
SF-36 physical summary (score)[a]	53.1 ± 0.3	53.1 ± 0.31	52.1 ± 0.4	389
SF-36 mental summary (score)[a]	56.8 ± 0.3	56.9 ± 0.3	56.0 ± 0.4	389

[a] Main effect of time (SF-36 physical summary $p < 0.01$ with differences between baseline vs. 1-year follow-up, and 1-year vs. 1-year follow-up; SF-36 mental summary $p < 0.05$ with difference between 1-year vs. 1-year follow-up).

strength training the year after the intervention, a two-way mixed model with repeated measures was used (group and compliance) to assess the effects of strength training group and compliance on changes from 1-year to 1-year follow-up. There was no group × compliance interaction in the changes from 1-year to 1-year follow-up in the two training groups in any of the parameters, why we only considered main effects of continuation of strength training independent of intensity. A one-way ANOVA evaluated whether there were any differences between CONTIN and STOP at baseline and whether the responses to the 1-year intervention were different as well. In these statistical models, only participants in the two strength training groups were included.

All data are presented as mean ± SE unless otherwise stated. All missing data were removed for the same participant at all time points (e.g. if a participant had one missing data from baseline, data from 1-year and 1-year follow-up were removed). We chose a significance level of 0.05 for the mixed model and ANOVA. All statistical analysis was performed using SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Compliance of participants

At baseline, 451 participants were included and randomized, and 419 (93%) completed the 1-year intervention. At 1-year follow-up, 398 participants (88%) completed the assessments (139 HRT, 133 MIT and 126 CON). The 53 participants who dropped out did so primarily due to lack of time, motivation or illness (Fig. 1). Of the 398 participants, 77% had at least one self-reported chronic disease. There were no differences between the three intervention groups in any of the parameters at baseline.

Of the participants in the two strength training groups ($n = 272$), 24% (significantly more participants in HRT (41) than MIT (24) ($p < 0.05$)) reported to continue with the same strength training program in the year following completion of the intervention (CONTIN) with 2.3 sessions/week in average. Participants who stopped during the first 9 months after the intervention was completed (STOP) corresponded to 74% (94 HRT, 106 MIT) and of those, 114 participants (51 HRT, 63 MIT) did not continue at all (0 months). The final 2% was missing data, as 7 participants did not reply to the adherence questionnaire (4 HRT, 3 MIT). Comparisons are shown between CONTIN and STOP. However, we also compared CONTIN with the 114 participants who did not continue at all, and the statistical analysis for that comparison did not differ in significance as compared to the CONTIN to STOP comparison.

3.2. Muscle power and -strength

3.2.1. Leg extensor power

Leg extensor power was unaffected by previous training status at 1-year follow-up, and there was no effect of time either (Table 1).

3.2.2. Isometric knee extensor strength

A significant group × time interaction was displayed for knee extensor muscle strength ($p < 0.0001$). At 1-year follow-up, the knee extensor muscle strength in HRT decreased significantly compared with 1-year ($p < 0.01$), but it was still significantly higher compared with baseline ($p < 0.0001$) (Fig. 2). Further, the relative change between baseline and 1-year follow-up was significantly higher in HRT compared with both MIT and CON (both $p < 0.01$). For MIT, the knee extensor muscle strength had returned to baseline at 1-year follow-up and the observed difference in the relative change compared with CON at 1-year was not different at 1-year follow-up anymore. In CON, we did not observe any change over time (Fig. 2).

3.2.3. Handgrip strength

For handgrip strength, no group × time interaction was detected. However, we did observe a main effect of time with an overall decrease for the entire group from baseline to 1-year follow-up ($p < 0.01$) (Table 1).

3.3. Muscle mass and body composition

3.3.1. Lean body mass and lean leg mass

Lean body mass displayed a significant group × time interaction ($p < 0.0001$). Post hoc analysis revealed that the interaction was caused by the increase in HRT in response to the 1-year strength training intervention compared with MIT ($p < 0.01$) and CON ($p < 0.0001$), and further the difference observed between HRT (which increased slightly)

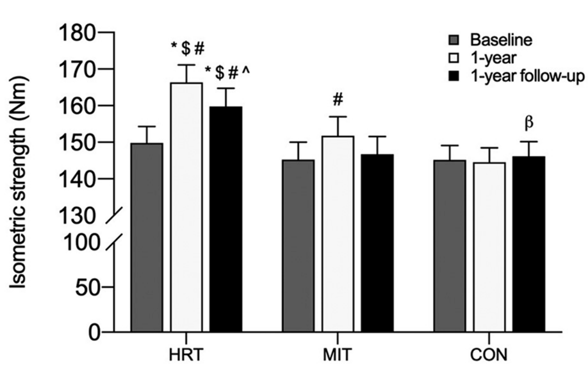

Fig. 2. Isometric knee extensor strength ($n = 389$) before (baseline, grey bars), after one year of either heavy resistance training (HRT), moderate intensity resistance training (MIT) or habitual physical activity (CON) (1-year, white bars), and one year after completion of intervention (1-year follow-up, black bars) (mean ± SE).
*: significantly different from baseline (both $p < 0.0001$).
^: significantly different from 1-year ($p < 0.01$).
#: change from baseline significantly different compared with change in CON (HRT 1-year $p < 0.0001$ and 1-year follow-up $p < 0.01$, MIT $p < 0.01$).
$: change from baseline significantly different compared with change in MIT (HRT 1-year $p < 0.0001$ and 1-year follow-up $p < 0.01$).
β: change from 1-year significantly different compared with change in HRT and MIT (both $p < 0.01$).

and MIT (which decreased slightly) from baseline to 1-year follow-up ($p < 0.01$). The changes from baseline to 1-year follow-up in HRT and MIT were, however, not different from CON, and neither HRT nor MIT was different from baseline at 1-year follow-up.

For lean leg mass, the higher relative rise in HRT compared with CON in response to the 1-year strength training program, which caused a group × time interaction ($p < 0.01$), was no longer different at 1-year follow-up (Fig. 3B). Further, we found a significant decrease in MIT during the follow-up period ($p < 0.01$). Lean leg mass for CON was unchanged at all three time points (Fig. 3B).

3.3.2. Cross-sectional muscle area (CSA)

The previously observed group × time interaction for CSA of the vastus lateralis muscle (Gylling et al., 2020) was no longer significant ($p = 0.1$). However, there was a significant effect of time with a decreased CSA over time ($p < 0.01$) (Fig. 3C). At 1-year follow-up CSA in HRT returned to baseline values and was no longer different from MIT or CON as was observed after the 1-year intervention, but there was a tendency to a difference in the relative change from baseline to 1-year follow-up between HRT and CON ($p = 0.06$). Further, we did observe a significant decrease from baseline to 1-year follow-up in CON ($p < 0.05$) (Fig. 3C).

3.3.3. Visceral fat content

For the visceral fat content, there was a tendency towards an overall group × time interaction ($p = 0.08$), which was caused by a decrease in HRT as a response to the 1-year strength training program ($p < 0.01$) (Fig. 4A). At 1-year follow-up, the visceral fat content in HRT was no longer significantly different from baseline. Further, we observed an overall effect of time with a significant decrease from baseline to 1-year ($p < 0.05$), whereas an increase from 1-year to 1-year follow-up was seen ($p < 0.05$) (Fig. 4A).

3.3.4. Whole-body fat percentage

There was a significant group × time interaction for whole-body fat percentage ($p < 0.05$), which was caused by a decrease in whole-body fat percentage in HRT observed in response to the 1-year intervention. At 1-year follow-up, whole-body fat percentage increased in HRT and was no longer different from baseline values ($p < 0.001$), and thus all three groups were at the same level at 1-year follow-up (Fig. 4B).

3.3.5. BMI, weight and waist circumference

During the two years, we did not observe any group differences in BMI, weight or waist circumference. However, from baseline to 1-year a main effect of time with a decrease in BMI ($p < 0.05$), weight ($p < 0.05$) and waist circumference ($p < 0.01$) was observed (Table 1). At 1-year follow-up, independent of intervention group, weight and BMI were still significantly lower compared with baseline (both $p < 0.05$), whereas waist circumference increased significantly during the follow-up ($p < 0.05$) in all participants (Table 1).

3.4. Functional performance

3.4.1. Chair-stand performance and 400 m walking time

There was no overall group × time interaction for the chair-stand performance over the two years observation period (Table 1). However, a main effect of time with an increased chair-stand performance was observed ($p < 0.0001$) with differences between baseline and 1-year ($p < 0.0001$), baseline and 1-year follow-up ($p < 0.0001$), and 1-year and 1-year follow-up ($p < 0.01$). Interestingly, the post hoc analysis detected that besides the improvements in HRT and MIT ($p < 0.0001$), the control group also had an improved chair-stand performance at 1-year ($p < 0.001$) and at 1-year follow-up compared with both baseline ($p < 0.0001$) and 1-year ($p < 0.05$) (Table 1).

For the 400 m walking time, we did not observe any changes after the 1-year strength training program or at 1-year follow-up in the three intervention groups (Table 1).

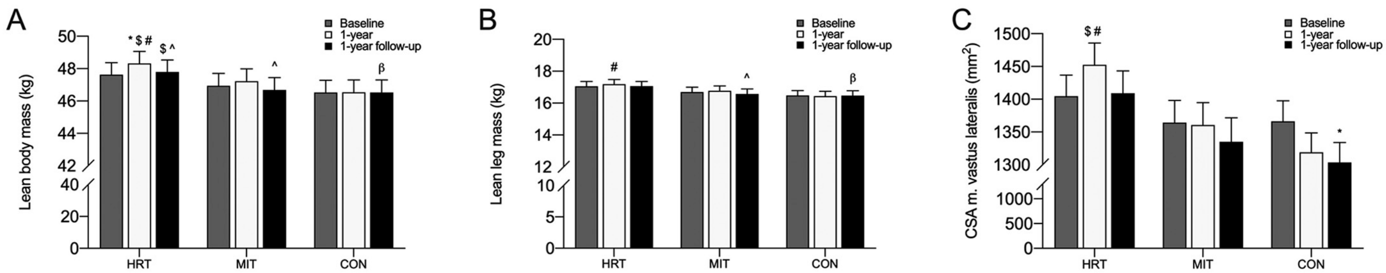

Fig. 3. Lean body mass (A, $n = 398$), Lean leg mass (B, $n = 398$) and CSA of m. vastus lateralis (C, $n = 342$) before (baseline, grey bars), after one year of either heavy resistance training (HRT), moderate intensity resistance training (MIT) or habitual physical activity (CON) (1-year, white bars), and one year after completion of intervention (1-year follow-up, black bars) (mean ± SE).
*: significantly different from baseline (A: $p < 0.0001$, C: $p < 0.05$).
^: significantly different from 1-year (A: $p < 0.0001$; B: $p < 0.001$).
#: change from baseline significantly different compared with change in CON (A: $p < 0.0001$; B: $p < 0.01$; C: $p < 0.0001$).
$: change from baseline significantly different compared with change in MIT (A: $p < 0.01$; C: $p < 0.05$).
β: change from 1-year significantly different compared with change in HRT and MIT (A: $p < 0.001$; B: HRT $p < 0.05$, MIT $p < 0.01$).

3.4.2. Activity monitoring

We did not observe any changes in the total step count in response to the 1-year intervention or after the follow-up year in any of the three intervention groups. Additionally, there was no effect of time (Table 1).

3.5. Blood parameters

3.5.1. Lipids, CRP and HbA1c

The previous significant improvement of HDL and LDL in response to the 1-year intervention compared with CON (Gylling et al., 2020) did no longer reveal a significant group × time interaction at 1-year follow-up. Neither did any of the other measured blood parameters displaying a significant group × time interaction at 1-year follow-up. However, we did observe an overall effect of time for most of the parameters from baseline to 1-year follow-up (Table 2). For total cholesterol and LDL, we observed a decrease from baseline to 1-year ($p < 0.01$), which was maintained to 1-year follow-up resulting in a difference between baseline and 1-year follow-up as well ($p < 0.0001$), whereas the decrease in VLDL only was significantly different between baseline and 1-year follow-up ($p < 0.05$). In addition, we observed an increase in HbA1c from baseline to 1-year ($p < 0.05$), which was still significantly higher at 1-year follow-up compared with baseline ($p < 0.01$), whereas the increase in CRP was significantly different at 1-year follow-up compared with baseline only ($p < 0.05$). Further, there was no effect of time for HDL or triglyceride (Table 2).

3.5.2. Systolic and diastolic blood pressure

We did not observe any significant group × time interaction for blood pressure, but the post hoc analysis did indicate a decline in both systolic and diastolic pressure in all three intervention groups from baseline to 1-year as well as from baseline to 1-year follow-up. This decrease resulted in a main effect of time with a reduction in systolic and diastolic blood pressure at both 1-year and 1-year follow-up compared with baseline (all $p < 0.0001$) (Table 2).

3.6. Hippocampus volume

When analyzing the hippocampus volume, a main effect of time was observed ($p < 0.0001$) (Table 1). The hippocampus volume decreased significantly from baseline to 1-year ($p < 0.01$), from baseline to 1-year follow-up ($p < 0.0001$) as well as from 1-year to 1-year follow-up ($p < 0.0001$). The decrease from baseline to 1-year follow-up corresponded to 1.5%. No difference was observed between the groups.

3.7. Questionnaires

3.7.1. Physical Activity for Elderly (PASE)

The evaluation of the participant's physical activity level obtained from PASE did not demonstrate any response to the intervention. Further, the self-reported physical activity levels were unchanged over the two years, independent of group (Table 3).

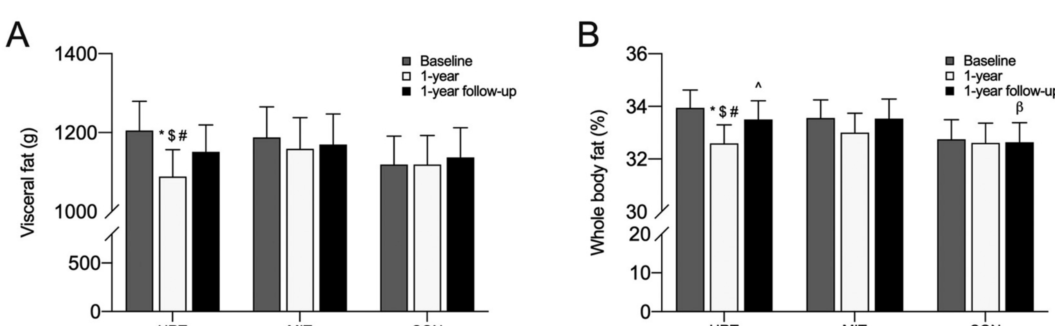

Fig. 4. Visceral fat content (A, $n = 398$) and whole-body fat percentage (B, $n = 398$) before (baseline, grey bars), after one year of either heavy resistance training (HRT), moderate intensity resistance training (MIT) or habitual physical activity (CON) (1-year, white bars), and one year after completion of intervention (1-year follow-up, black bars) (mean ± SE).
*: significantly different from baseline (A: $p < 0.01$); B: $p < 0.0001$).
^: significantly different from 1-year (B: $p < 0.001$).
#: change from baseline significantly different compared with change in CON (A: $p < 0.001$; B: $p < 0.0001$).
$: change from baseline significantly different compared with change in MIT (A: $p < 0.05$; B: $p < 0.05$).
β: change from 1-year significantly different compared with change in HRT (B: $p < 0.01$).

3.7.2. Health-related quality of life (SF-36)

For the SF-36 physical summary, we observed an overall effect of time with a decrease in score ($p < 0.01$), which was caused by a decrease during the follow-up year. The score was significantly lower at 1-year follow-up compared with both baseline ($p < 0.05$) and 1-year ($p < 0.05$) (Table 3). For SF-36 mental summary, the previous observed higher score in HRT compared with CON after the 1-year intervention (Gylling et al., 2020) revealed no longer a significant group × time interaction. In line with the physical summary score, we observed an overall effect of time with a decrease in the mental score caused by a decline during follow-up ($p < 0.05$) (Table 3).

3.8. CONTIN vs. STOP

When comparing CONTIN with STOP, we observed that CONTIN had a significantly smaller decline in the training induced improvement in knee extensor muscle strength compared with the decline seen in STOP with decreases of 1% and 6%, respectively ($p < 0.05$). Further, we observed a significant difference in waist circumference changes, where CONTIN decreased and STOP increased ($p < 0.05$) from year 1 to year 2. From the SF-36 mental summary score, there was a tendency to a difference between CONTIN and STOP, where CONTIN increased and STOP decreased the score ($p = 0.06$) (Table 4). For all other measurements (e.g. lean body mass, whole-body fat percentage or visceral fat content), we did not observe any differences between CONTIN and STOP. For instance, the observed decrease in lean body mass as well as the increase in whole-body fat percentage and visceral fat content from 1-year to 1-year follow-up were similar in the two groups. At baseline, lean body mass, knee extensor muscle strength and the SF-36 mental summary score were significantly higher ($p < 0.05$, $p < 0.01$ and $p < 0.05$, respectively) and whole-body fat percentage lower ($p < 0.001$) in CONTIN compared with STOP (Table 4). Further, the response to the 1-year strength training program was also higher in knee extensor muscle strength ($p < 0.001$), leg extensor power ($p < 0.05$), chair-stand performance ($p < 0.05$) and 400 m walking time ($p < 0.05$) in CONTIN compared with STOP (Table 4). Moreover, knee extensor muscle strength ($p < 0.0001$), leg extensor power ($p < 0.05$), chair-stand performance ($p < 0.0001$), whole-body fat percentage ($p < 0.01$), and waist circumference ($p < 0.05$) in the CONTIN group were still significantly improved at 1-year follow-up compared with baseline, whereas only chair-stand performance was significantly higher at 1-year follow-up compared with baseline in STOP ($p < 0.0001$) (Table 4). The relative change in chair-stand performance from baseline to 1-year follow-up only tended to be higher in CONTIN compared with STOP ($p = 0.07$).

4. Discussion

This study demonstrated that training-induced improvements in knee extensor muscle strength (and to some extent thigh muscle cross-sectional area) in response to one year of strength training were only partly preserved in the elderly individuals over an unsupervised 1-year follow-up period. Moreover, this occurred only in those elderly who were allocated to more intense rather than moderate strength training during the 1-year intervention. Further, the muscle strength improvements reached over the first year of supervised training were only maintained at 1-year follow-up in individuals who continued training. In contrast, the training induced gains in lean body mass, lean leg mass, whole-body fat percentage and visceral fat from one year of heavy resistance training were all lost at 1-year follow-up. In addition to knee extensor muscle strength, waist circumference demonstrated a difference between those who continued training (where it decreased) and those who did not (where it increased) at 1-year follow-up. Finally, other parameters with relevance to body composition, functional performance or health were not influenced by training, and they were mostly stable over time, but some changed in a beneficial direction (e.g. blood pressure and total cholesterol were lowered and chair-stand performance was increased in all groups over time). Thus, the results indicate that improvements obtained during a long-term strength training intervention are lost one year later if training is not continued, whereas continued activity can postpone the age-related loss in muscle mass and -strength.

As demonstrated in previous studies, strength training is an effective method to increase muscle mass, -strength and physical function in a dose-dependent manner (Borde et al., 2015; Fielding et al., 2002; Bechshøft et al., 2017; Leenders et al., 2013; Kalapotharakos et al., 2007; Fatouros et al., 2005; Gylling et al., 2020). However, gains in muscle mass and -strength obtained after short-term interventions have also been demonstrated to disappear or are only partially preserved after a period of detraining or a period without any supervised exercise instructions (Trappe et al., 2002; Bickel et al., 2011; Correa et al., 2013; Snijders et al., 2019). Further, it has been demonstrated that 9 months of organized strength training led to improved exercise-related

Table 4
Muscle function and body composition before (baseline), after one year of strength training (1-year), and one year after completion of intervention (1-year follow-up) in participants who continued with strength training (CONTIN) and participants who stopped (STOP) during the one year follow-up period (mean ± SE.)

	Baseline		1-year		1-year follow-up		Sample size
	CONTIN (n = 65)	STOP (n = 200)	CONTIN (n = 65)	STOP (n = 200)	CONTIN (n = 65)	STOP (n = 200)	
Isometric knee extensor strength (Nm)	164.7 ± 6.9$^{£}$	143.0 ± 3.7	184.5 ± 7.8$^{*\alpha}$	152.5 ± 3.8*	182.8 ± 7.8$^{*\Delta\alpha}$	145.1 ± 3.7$^{\wedge}$	260
Leg extensor power (W)	208.3 ± 9.0	191.4 ± 4.6	219.1 ± 9.4$^{\alpha}$	191.5 ± 4.2	220.1 ± 9.5$^{*\alpha}$	187.0 ± 4.5	263
30 s chair-stand (reps)	17.6 ± 0.5	16.7 ± 0.3	21.0 ± 0.6$^{*\alpha}$	19.2 ± 0.4*	21.4 ± 0.7*	19.6 ± 0.4*	261
400 m walking time (s)	235 ± 3	243 ± 2	227 ± 3$^{\alpha}$	239 ± 3	227 ± 3	243 ± 4	256
Lean body mass (kg)	49.5 ± 1.1$^{£}$	46.7 ± 0.6	50.2 ± 1.2*	47.1 ± 0.6*	49.7 ± 1.2$^{\wedge}$	46.5 ± 0.6$^{\wedge}$	265
Whole-body fat (%)	30.7 ± 1.1$^{£}$	34.6 ± 0.5	29.2 ± 1.0*	33.8 ± 0.6*	29.6 ± 1.1$^{*\alpha}$	34.6 ± 0.6$^{\wedge}$	265
Waist circumference (cm)	91.7 ± 1.5	94.0 ± 0.8	90.3 ± 1.4	93.0 ± 0.8	90.1 ± 1.4$^{*\Delta\alpha}$	93.9 ± 0.8$^{\wedge}$	264
SF-36 mental summary score	58.3 ± 0.6$^{£}$	56.7 ± 0.4	57.0 ± 0.8	57.3 ± 0.4	57.5 ± 0.8	55.5 ± 0.6	259

* Significantly different compared with baseline (isometric strength and chair-stand $p < 0.0001$; leg extensor power $p < 0.05$, lean body mass $p < 0.01$; whole-body fat% $p < 0.01$ (CONTIN + STOP); waist circumference $p < 0.05$.)

^ Significantly different compared with 1-year (Isometric strength $p < 0.0001$; lean body mass (CONTIN) $p < 0.05$; lean body mass (STOP) $p < 0.0001$; whole-body fat% $p < 0.0001$; waist circumference $p < 0.05$).

£ Significantly different compared with STOP at baseline (isometric strength $p < 0.01$; lean body mass $p < 0.05$; whole-body fat% $p < 0.001$; SF-36 mental score $p < 0.05$).

α Change from baseline to 1-year and/or 1-year follow-up significantly different compared with STOP (isometric strength 1-year $p < 0.01$, 1-year follow-up $p < 0.0001$; leg extensor power 1-year $p < 0.05$, 1-year follow-up $p < 0.01$; chair-stand $p < 0.05$; walking time $p < 0.05$; whole-body fat% $p < 0.01$; waist circumference $p < 0.05$).

Δ Change from 1-year to 1-year follow-up significantly different compared with STOP ($p < 0.05$).

motivational and volitional characteristics in older adults. These improvements were additionally related to continuation of unsupervised strength training after the intervention (Kekäläinen et al., 2018). In addition, we have demonstrated that 1-year of heavy resistance training also resulted in an improved mental health (SF-36) (Gylling et al., 2020). Therefore, we hypothesized that one year of strength training would be enough to implement changes in behavior towards more physical activity in everyday life that in turn could be sufficient to preserve the training induced improvements. However, even though 24% reported to continue with strength training during follow-up, we could not demonstrate any change in the self-reported physical activity level (PASE) of the participants in the previous training groups, and neither did they demonstrate any rise in daily step counts over the two years period.

Knee extensor muscle strength was only partly preserved one year after completion of the initial supervised heavy resistance training, whereas lean body mass and CSA was returned to baseline at 1-year follow-up. This is in accordance with previous findings that a decrease in muscle mass occurs faster than muscle strength after a training intervention (Trappe et al., 2002; Bickel et al., 2011; Correa et al., 2013; Snijders et al., 2019). This could be caused by a potential longer lasting neuromuscular adaptation induced by strength training that persists even after reduced training (Häkkinen et al., 1998), whereas muscle mass could be more sensitive to reduced muscle loading. The strength training induced improvement in muscle strength from baseline to 1-year in the moderate intensity training group was not different from the control group anymore at 1-year follow-up. A loss in muscle strength has previously been shown following both moderate (Kalapotharakos et al., 2007) or somewhat more heavy resistance training programs (Karinkanta et al., 2009) in both older men (68 years) and women (72 years). Further, lean body mass decreased from 1-year to 1-year follow-up in MIT causing a difference in lean body mass from baseline to 1-year follow-up between HRT and MIT, but CSA was unaltered during the two years of investigation in MIT. Interestingly, the observed decrease in CSA in the control group in the present study could indicate that strength training with both heavy and moderate intensity somehow counteracts and postpones the age-related decrease in muscle mass. A postponing of the otherwise expected declines in e.g. lean body mass, CSA and muscle strength is beneficial for older adults since their functional ability potentially would be affected later in life leading to longer time of independency and high quality of life (Cruz-Jentoft et al., 2019; dos Santos et al., 2017; Janssen et al., 2002). It seems that only prolonged training programs with high intensity preserve muscle strength in older adults. In order to improve the maintenance of muscle strength and -mass, supervision for a longer period or stricter instructions on the importance of performing strength training may be needed.

Leg extensor power was still unaffected one year after the intervention was completed, and we did not observe any significant decrease over time in the three groups. A likely explanation for the lack of improved muscle power in response to the 1-year strength training intervention could be that the training was not performed with high-velocity, which previously has been suggested to be necessary to improve muscle power (Fielding et al., 2002; Marsh et al., 2009). Similar to the present study, Walker et al. did not find any improvement in peak power after 12 weeks of moderate-load strength training also performed with lower velocity (Walker et al., 2017). However, the group that continued training during the follow-up period had an improved leg extensor power in response to the 1-year training intervention, which was maintained at 1-year follow-up, whereas those who stopped training did not change over time. This indicates that strength training with lower velocity can also improve muscle power at least in a specific group of individuals. It has previously been suggested that leg extensor power decreases markedly only after the age of 60 years, but with variable degree dependent on individual levels of daily physical activity (Skelton et al., 1994; Suetta et al., 2019). The participants in the present study were relatively active at baseline with daily step counts close to 10,000 and therefore may already have had a high leg extensor power level, which may have caused a ceiling effect.

Handgrip strength was unaffected by one year of strength training, but for this parameter we did observe an overall decrease over time, which is in line with a previously shown age-related decline unrelated to exercise training (Suetta et al., 2019). In the present study, the strength training program focused on the lower extremities, limiting the potential for observing an effect on handgrip strength.

Whole-body fat percentage and visceral fat content was improved in response to one year of HRT but this was lost at 1-year follow-up. These results correlate well with the present findings of an overall effect of time upon waist circumference, where the decrease during the first year was replaced with an increase the year after completion of the intervention. An increase in fat mass returning to baseline values was also observed by Snijders et al. one year after completion of the intervention (Snijders et al., 2019). However, the relative change in whole-body fat percentage was still improved in the group that continued training during the follow-up year compared with those who stopped training, which emphasizes that ongoing activity is important for a long-term effect of metabolic changes. Interestingly, we did observe a drop in weight, total cholesterol, LDL, VLDL and blood pressure as well as an increase in chair-stand performance over time in all groups, which could indicate an unspecific effect of participating in an intervention study potentially related to a change in life style, which is maintained after the supervised intervention. However, as would be expected, we did observe an increase in basal inflammation measured as CRP as an effect of time across all groups (Bartlett et al., 2012). Unfortunately, we were not able to demonstrate a long-term positive association of hippocampus volume as a response to the 1-year strength training intervention, which has been detected in relation to endurance training interventions (Erickson et al., 2011; Jonasson et al., 2016). The knowledge of the effect of long-term strength training on hippocampus volume is limited and more investigations are needed. However, we did observe an overall decrease in hippocampus volume of 1.5% over the two years of observation, which is a bit less than what we could have expected (Fraser et al., 2015). Further, the time to walk 400 m or the spare time physical activity level (steps/day) was not affected by intervention nor by time, which could be due to the fact that we included strength training naive, but well-functioning participants already at the beginning of the intervention, and thereby the potential for improving these parameters could have been limited.

Besides the effects of strength training on muscle mass, -strength and physical function, a long-term strength training program could potentially play a role in initiating a positive long-term change in physical activity habits in older adults, including implementation of weekly strength training. It has been demonstrated that strength training for 9 months improved the exercise-related motivational and volitional characteristics in older adults, which were linked to continuing of strength training during the 1-year follow-up period (Kekäläinen et al., 2018). Of all participants in our previous strength training groups, 24% (15% HRT, 9% MIT) reported that they had continued with the same strength training program in the year after the intervention was completed. This was less than Snijders et al. where 45% of the participants continued with some sort of strength training (Snijders et al., 2019). In the present study however, we assessed whether or not the participants continued with the exact same exercise program, and in fact 46% of all participants in our training study continued doing some form of strength training from year 1 to year 2, which is comparable with previous findings investigating adherence after a strength training intervention (Snijders et al., 2019; Kekäläinen et al., 2018; Van Roie et al., 2015).

In the present study, it is clear that the 24% who continued both heavy and moderate intensity training after ending the supervised program were the ones that maintained the muscle strength and -power improvements. We observed that participants who continued with strength training had a minor decline in knee extensor muscle strength compared with those who did not continue. To our knowledge we are the first to show this since Snijders et al. did not find any further differences in muscle strength in those who continued with unsupervised strength training during follow-up (Snijders et al., 2019). In contrast, there were no differences between the two groups in the present study regarding lean body mass and CSA preservation. This was somewhat to our surprise, since Snijders et al. found a better preservation in both lean body mass and CSA in the exercise group compared with the non-exercising group (Snijders et al., 2019). In previous studies investigating maintenance of muscle mass and -strength, it has been demonstrated that continuing training once per week after a short-term strength training intervention (12–16 weeks) is enough to maintain muscle strength (Walker et al., 2018), whereas the conclusion regarding training once per week is more ambiguous regarding the maintenance of muscle mass (Trappe et al., 2002; Bickel et al., 2011; Walker et al., 2018). Again, our results in muscle strength and -mass indicate that these act differently with a faster loss in muscle mass, after a period with supervision of strength training.

Interestingly, lean body mass, knee extensor muscle strength and the SF-36 mental summary score was significantly higher and whole-body fat percentage lower in CONTIN than STOP at baseline. Additionally, knee extensor muscle strength, leg extensor power, chair-stand performance, and 400 m walking time improved more in CONTIN compared with STOP in response to the 1-year strength training intervention. This indicates that the continuation of strength training involved those participants who apparently were more well functioned and had a higher response to the strength training intervention from the beginning of the study. The present findings are in accordance with a previous study demonstrating that the participants who e.g. had a higher satisfaction with body function upon entrance into the intervention and also those who experienced the most pronounced changes during the intervention were most likely the ones that continued with physical activity after termination of an intervention (Baruth and Wilcox, 2014).

It was a limitation to the present study that training activity in the follow-up period was self-reported with regards to whether the participants had continued with the strength training program or not and the exact volume and intensity of the strength training was in addition unknown. However, as individuals are likely to over-report their physical training frequency and content (Prince et al., 2008), we are risking to include STOP persons into CONTIN. However, as we did in fact observe a difference between the two groups, we are convinced that the differences are robust.

In conclusion, one year after completion of supervised heavy resistance training (not moderate intensity), only knee extensor muscle strength (and to some degree thigh muscle area) could be partly maintained, whereas most other muscle, functional and health parameters with a previous positive response to the strength training intervention returned to baseline values in a mix of healthy and chronically diseased older adults. Importantly, only if the strength training was continued on individual basis after termination of supervision, the training-induced adaptations in muscle strength was maintained. In addition, continuation of strength training also resulted in improved muscle power, fat percentage and waist circumference. This emphasizes the importance of ongoing physical activity for ensuring long-term effects of strength training upon muscle function and health in elderly. The present findings indicate that one year of organized strength training is not sufficient to ensure long-term effects for most health-related parameters, perhaps due to the relatively few individuals who continued with strength training. Further investigations are needed in order to find solutions for changing daily routines that are sufficient to maintain the improvements achieved by an intervention.

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Anne Theil Gylling: Validation, Formal analysis, Investigation, Visualization, Project administration, Writing – Original Draft.
Michael Kjaer: Conceptualization, Methodology, Validation, Supervision, Writing – Review & Editing.
Hartwig Roman Siebner and Erik Lykke Mortensen: Conceptualization, Methodology, Validation, Writing – Review & Editing.
Carl-Johan Boraxbekk: Methodology, Investigation, Validation, Writing – Review & Editing.
Mads Bloch-Ibenfeldt and Maria Baekgaard: Validation, Investigation, Visualization, Writing – Review & Editing.
Christian Skou Eriksen and Andreas Kraag Ziegler: Investigation, Validation, Project administration, Writing – Review & Editing.
Cathrine Lawaetz Wimmelmann: Investigation, Validation, Writing – Review & Editing.
All authors have given final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of competing interest

There was no conflict of interest.

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PHD-THESIS
DECLARATION OF CO-AUTHORSHIP

The declaration is for PhD students and must be completed for each conjointly authored article. Please note that if a manuscript or published paper has ten or less co-authors, all co-authors must sign the declaration of co-authorship. If it has more than ten co-authors, declarations of co-authorship from the corresponding author(s), the senior author and the principal supervisor (if relevant) are a minimum requirement.

1. Declaration by	
Name of PhD student	Anne Theil Gylling
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Name of principal supervisor	Michael Kjær
Title of the PhD thesis	Physical activity as intervention for age-related loss of muscle mass and function, the LISA study: A randomized controlled trial

2. The declaration applies to the following article	
Title of article	Maintenance of muscle mass and strength following a one-year resistance training program in older adults
Article status	
Published ☐ Date:	Accepted for publication ☐ Date:
Manuscript submitted ☒ Date: 29/4-2020	Manuscript not submitted ☐
If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information).	

3. The PhD student's contribution to the article ***(please use the scale A-F as benchmark)*** Benchmark scale of the PhD-student's contribution to the article **A**. Has essentially done all the work (> 90 %) **B**. Has done most of the work (60-90 %) **C**. Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant	**A, B, C, D, E, F**
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2. Development of the key methods	C
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4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	B
5. Conducting the analysis of data	A
6. Interpretation of the results	A
7. Writing of the first draft of the manuscript	A
8. Finalisation of the manuscript and submission	A

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The PhD student has been a part of most of the planning of and conducting the experimental work and data collection. The PhD student has conducted all statistically analysis of data and interpretation of the results. Further, the PhD student has writing the first draft of the manuscript and finalised it for submission.

4. Material from another thesis / dissertation[ii]	
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5. Signatures of the co-authors[iii]

	Date	Name	Title	Signature
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6. Signature of the principal supervisor

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date: 14/5-20
Principal supervisor: [illegible]

7. Signature of the PhD student
I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge. Date: 13/5-20 PhD student: Anne Theil Gylling

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[i] This can be supplemented with an additional letter if needed.

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