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Abstract

Background: Gait speed, both preferred and fast, are decreasing with age. Reduced gait speed is associated with disability, mortality and falls. Interventions has shown to improve gait speed, but current research does not agree which interventions that is most effective. Many earlier studies have compared the effect of resistance training and aerobic training on gait speed, but no known study compare different aerobic interventions at different intensity. The main aim of this study was to assess the effect of moderate and high-intensity aerobic training on gait speed; preferred, fast and dual task gait speed. Our second aim was to investigate if gender end baseline leg strength influenced gait speed response to exercise.

Materials and methods: This is a randomized controlled trial investigating the effect of training on gait speed in 1567 community-dwelling older individuals, aged 70-76 years. Participants were randomized into either control group (CON), moderate-intensity training (MIT) or high-intensity training (HIT) group. Data were collected at baseline and 3 years. Gait speed data was collected with ProtoKinetics Zeno walkway. We performed both per protocol analysis (ANCOVA) and intention-to-treat analysis (Mixed Model with Repeated Measures), comparing groups pairwise; HIT vs CON, MIT vs CON and HIT vs MIT.

Results: In the per protocol analysis, we found significant improvements in preferred (3.1 cm/sec, p=0.002) and fast (3.6 cm/sec, p=0.001) gait speed of HIT when comparing HIT and CON. When comparing MIT and CON, we found no significant differences in any gait condition. Significant difference between MIT and HIT on gait speed response was found, in favor HIT – significant change in preferred gait speed (p=0.003) and near-significant change in fast gait speed (p=0.0058). We found that females had significantly larger improvement in dual task gait speed of both HIT and MIT, as well as female had largest improvement in fast gait speed of HIT when comparing HIT and CON. We found that baseline leg strength significantly influenced improvements in all gait conditions, where larger leg strength was associated with larger improvement in gait speed following both HIT and MIT. Exercise compliance had no effect on gait speed response. When performing intention-to-treat analysis, we found no significant effect of exercise on any gait condition.

Conclusion: Our results indicate that HIT was most effective in term of improving preferred and fast gait speed. We found no significant difference in gait speed between CON and MIT, suggesting that MIT alone have no impact on gait speed. No change in dual task gait speed

was observed between groups. Both gender and leg strength significantly influenced gait speed response to MIT and HIT.

Sammendrag

Bakgrunn: Ganghastighet, både selvvalgt og rask, reduseres med alderen. Redusert ganghastighet er assosiert med nedsatt funksjonsevne, tidlig død og økt antall fall. Trening har vist å kunne øke ganghastighet, men man har ikke funnet den mest effektive treningen for å øke ganghastighet. Flere tidligere studier har sammenlignet effekten av styrketrening og kondisjonstrening på ganghasithget, men ingen kjente studier har sammenlignet ulik kondisjonstrening med ulik intensitet. Hovedmålet til denne studien var å se på effekten av moderat- og høy-intensiv kondisjonstrening på ganghastighet; selvvalgt og maksimal ganghastighet, samt dual-task ganghastighet. Sekundærmålet til studien er å se på om kjønn og benstyrke påvirker treningens effekter på ganghastighet.

Metode: Dette var en randomisert kontrollert studie med 1567 deltagere. Hjemmeboende eldre i alderen 70-76 år ble inkludert og randomisert i tre ulike grupper; kontrollgruppe (CON), moderat-intensitetstrening (MIT) eller høy-intensitetstrening (HIT). Data ble samlet ved baseline og ved 3 års testing. Målinger av ganghastighet ble gjort med elektronisk gangmatte, ProtoKinetics Zeno. Det ble utført to analyser: per protokoll-analyser (ANCOVA) og intention-to-treat-analyser (Mixed Model med repeterte målinger), med parvise sammenligniner mellom gruppene; HIT mot CON, MIT mot CON og HIT mot MIT.

Resultater: I per protokoll-analysene fant vi signifikant forbedring i selvvalgt (3.1 cm/sek, p=0.002) og maks (3.6 cm/sek, p=0.001) ganghastighet av HIT når vi sammenlignet HIT og CON. Når vi sammenlignet MIT og CON, fant vi ingen signifikant forskjell forskjell i noen av ganghastighetene. Vi fant signifikante forskjeller mellom HIT og MIT på ganghastighet, i favør HIT - signifikant forskjell i selvvalgt (p=0.003) og nær-signifikante forskjeller i maks ganghastighet (p=0.0058). Vi fant at kvinner har signifikant større forbedring i dual-task ganghastighet etter både HIT og MIT, i tillegg hadde kvinner størst forbedring i maks ganghastighet etter HIT når vi sammenlignet HIT og CON. Vi fant benstyrke hadde en signifikant innvirkning på forbedring hos alle ganghastigheter, hvor økt benstyrke ved baseline var assosiert med med større fremgang i ganghastighet etter HIT og MIT. Etterlevelse av trening hadde ingen effekt på fremgang i ganghastighet. Når vi utførte intention-to-treat-analysene, ble ingen signifikante forskjeller i effekt på ganghastighet mellom gruppene funnet.

Konklusjon: Resultatene i denne studien indikerer at den mest effektive treningen for å øke ganghastighet var HIT. Ingen signifikant forskjell ble funnet mellom MIT og CON, som typer

på at MIT alene har ingen effekt på ganghastighet. Ingen endring i dual-task ganghastighet ble observert i gruppene. Både kjønn og benstyrke påvirker MIT og HIT sin effekt på ganghastighet.

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Simen Westnes Brennvik

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1.0 INTRODUCTION

Today, 12% of the population in Norway are 80 years or older. That number is believed to raise up to 1.5 million in year 2060. This group will then account for over 20 % of the population (Kristiansen, 2015). As we humans age, most of us gradually evolve problems in handling daily tasks at some point in our life - one of those tasks are walking. Walking is a big part of activities of daily living, and therefore impairment of walking ability is something that will affect our life. The speed at which one walks, decreases with age and is a predictor of disability and mortality (J. L. Purser et al., 2005; Toots et al., 2013). Research shows that after the seventh decade of life, preferred gait speed decreases with 12% to 16% per decade, and about 20% per decade for fast gait (Judge, Ounpuu, & Davis, 1996). The rate of decline in preferred and fast gait speed increases through the 9th decade of life (Forrest, Zmuda, & Cauley, 2007). Changes in gait in older adults are also associated with falls, dementia and disability (Montero-Odasso, Verghese, Beauchet, & Hausdorff, 2012). The same study found that gait instability and slower gait speed during single and dual task testing also indicate early disturbances in cognitive processes such as attention, executive function and working memory. On the other side, a study by Hardy, Perera, Roumani, Chandler, and Studenski (2007) observed that even transitory improvements in gait speed decrease mortality risk. In the future, it may therefore be important to find effective interventions to improve gait speed because of an aging population with increased load on our healthcare system.

Gait speed as a vital sign

Gait changes over time, and can lead to decline in gait speed and mobility of elderly individuals. Vermeulen, Neyens, van Rossum, Spreeuwenberg, and de Witte (2011) conducted a systematic review and found that gait speed is a solid and reliable predictor of incident disability. Another study (Viccaro, Perera, & Studenski, 2011) supported this and found that gait speed could assist the prediction of decline in ADL ability, overall health decline and falls. It is suggested that reduced gait function not only is caused by aging process alone, but rather induced by common disease in older age along with lifestyle and sedentary activity. A systematic review found a strong association of gait speed with adverse outcomes (i.e. disability, cognitive impairment, falls and mortality) in elderly individuals (Abellan van Kan et al., 2009; Fritz & Lusardi, 2009). Gait speed, like blood pressure, may be a general indicator that can predict future events and reflects underlying physiological processes (Studenski et al., 2003). Just as blood pressure isn't the only sign of heart disease, gait speed can be used as a ”vital sign” to help to determine functional status and the need for rehabilitation.

Gait speed and aging

When we talk about gait speed, it is common to further divide it into ”fast gait” or ”preferred gait”. Research have found some interesting differences between those two gait conditions. When talking about the predictive ability of gait speed, research has suggested that there is difference between “fast gait speed” and “preferred gait speed”. A study found that preferred gait speed was the most sensitive measure in predicting future dependence in people aged 75 and older, while maximal gait speed was most sensitive in predicting dependency in those between 65-74 years old (Shinkai et al., 2000). A study (Hollman, McDade, & Petersen, 2011) showed that common age related changes in gait are reduced gait speed and shorter step length. They interestingly also found significant gender differences. Men walked at a lower cadence and with longer steps, compared to women who walked with higher cadence and shorter steps. Gait speed was also significantly different between genders, where men walked faster than women (Hollman et al., 2011). This suggests that men and women may respond differently to gait interventions, but this is highly unsure.

Dual task during gait

Slowing of gait during dual-task interference is recognized as a functional mobility concern among older adults, and is an important public health problem because of the association with risk of falls (Beauchet et al., 2009). Walking while performing a cognitive task has shown to provoke significant changes in gait; reduction in cadence and step length, and increase in medio-lateral instability in the dual-task conditions (Beauchet et al., 2002). A meta-analysis looked at the effect of dual-task on gait speed in community dwelling older adults. It showed that the addition of a cognitive task significantly reduced preferred gait speed (Smith, Cusack, & Blake, 2016). A possible advantage of dual-task measurement is that it may reflect the reality of daily living, which often requires walking while simultaneously performing other tasks. In the last years, research has begun to use dual-task methodology to assess interplay between gait and cognition, and found that older adults who are at risk of falling show increased gait variability and reduced gait speed compared to non-fallers during dual-task gait (Beauchet et al., 2003; Kressig, Herrmann, Grandjean, Michel, & Beauchet, 2008; Olsson, 2010). Walking is a complex and voluntary motor behavior that needs attention, and decrease in gait performance during dual-tasks may be important clinical screening tool to prevent falls and other adverse outcomes.

Studies observing exercises and influence on gait speed

A randomized controlled trial by Sarkisian et al. (2000) showed improvement in gait speed early after strength and/or endurance training in community-dwelling older individuals (mean age 73 years), indicating that gait speed at old age is modifiable. A meta-analysis (Lopopolo, Greco, Sullivan, Craik, & Mangione, 2006) investigated the effect of therapeutic exercise on gait speed in community-dwelling older people (mean age was 65-83 years). They found that therapeutic exercises, both strength and combination of strength and aerobic exercise, had a significant effect on preferred gait speed, although the effect size was rather small and not clinically meaningful. They found no effect of therapeutic exercises on fast gait speed. There was difference in exercise dosage and intensity between studies, making the studies difficult to compare directly. The researchers discuss if the lack of specificity was an explanation for the small effect, as the exercise was not walking-exercises. The lack of effect of therapeutic exercises on fast gait could also be explained by different instructions during gait testing, where some studies instructed fast gait as ”walk as fast as you can”, while other got verbal instructions like ”faster than normal speed”. Another study (Buchner, Larson, Wagner, Koepsell, & de Lateur, 1996) found no effect of therapeutic exercises on gait speed. The aerobic exercise component here was cycling, and again it is debatable if the lack of specificity may be an important factor for the missing effect. On the other hand, Sipila, Multanen, Kallinen, Era, and Suominen (1996) found and reported increasing fast gait speed following both resistance and aerobic training. Henderson et al. (2016) newly investigated gait speed response to aerobic and resistance training in overweight and obese older adults. Both interventions showed significant improvements in preferred gait speed, but only aerobic training group improved fast gait speed. They also found in the resistance training group that lower baseline knee strength was associated with less improvements in preferred gait speed. In the aerobic training group, lower baseline VO2peak was associated with less improvements in fast gait speed. These associations between gait speed and baseline knee strength and aerobic fitness are supported by two other studies (Faber, Bosscher, Chin, & van Wieringen, 2006; Marsh, Chmelo, Katula, Mihalko, & Rejeski, 2009), but the results are conflicting, as other studies have found that larger improvements in preferred gait speed was seen in individuals with lower function at baseline (Chandler, Duncan, Kochersberger, & Studenski, 1998; Meuleman, Brechue, Kubilis, & Lowenthal, 2000). This suggests that both maximal oxygen uptake and knee strength influence how gait speed responds to exercise interventions. It is an interesting question if baseline status influences the functional response to training, as this can help us tell who has the most potential and benefit of an exercise intervention. The meta-analysis by Lopopolo et al. (2006), mentioned earlier in this paragraph, is pointing out one problem with the analyzed studies. Many exercise programs don't specify or lack information about exercise intensity and dosage, and Lopopolo et al. suggests that these factors may be important in producing a change in the habitual walking speed of community-dwelling elderly people.

Dual task gait speed and effect of intervention is a smaller research field compared with studies on preferred and fast gait speed. But, a relatively new meta-analysis showed that physical exercise interventions can improve dual-task walking in older adults primarily by increasing the speed at which individuals walk in dual-task conditions (Plummer, Zukowski, Giuliani, Hall, & Zurakowski, 2015). The nature of the physical exercise interventions varied across the studies, but every intervention was including a dual-task component; cognitive activities, dual-task balance challenges, i.e. Not one of the included studies did only have aerobic exercise as an intervention.

Measurements of gait speed

Measurements of gait speed is performed in several different ways, and there is little consensus regarding which protocol is optimal. The way gait speed has been measured in former studies varies broadly, from using a 3 meter walkway to 100 meter. Gait tests vary in pace and length, and often tests are chosen based on available space and convenience. One of the most commonly used test are the 10-meter walk test (Ota, Yasuda, Horikawa, Fujimura, & Ohara, 2007; Perera, Mody, Woodman, & Studenski, 2006). This test is space requiring as it needs a total of 20-meter walkway, 5 m for acceleration and deceleration. Shorter test are also commonly used, including 3-, 4- and 6–m gait speed tests (Jorgensen et al., 2010). A study investigated the validity of the 4-Meter Walk Test compared with the 10-Meter Walk test and found that there was not enough agreement that these two test could be used interchangeably in healthy elderly adults (Peters, Fritz, & Krotish, 2013). They recommended the 10-Meter Walk Test for obtaining the most valid assessment, but that the 4-m test can be used if space is limited. Interestingly, they found that handheld stopwatches were as reliable as automatic timers in measurements of gait speed.

Increased gait speed and health outcomes

Further questions that need to be addressed is if increased gait speed following exercise can cause positive health outcomes in elderly individuals. Hardy et al. (2007) showed that 0.1 m/sec is a meaningful change in gait speed in older community-dwelling adults, and that increase in gait speed due to interventions can reduce the absolute risk of death up to 17.7 %. In addition to mortality, it is interesting to see if exercise-induced changes in gait speed also reduces ADL disability in elderly individuals. As mention earlier, gait speed can predict decline in function ability, but we currently don’t know if increasing gait speed leads to slower decline or even increased functional ability. If this is the case, then it is important to reveal the interventions that causes biggest increase in gait speed or slows down the reduction in gait speed the most.

To round up, gait speed is an important aspect of gait and is widely used as a performance measure of functional ability. Not only is it important for its implications for initiating preventive strategies in an elderly individual, but also its relation to different health outcomes such as predicting functional decline (Montero-Odasso et al., 2005) and determining rehabilitation needs (J. L. Purser et al., 2005). Gait speed decreases with age and decline in gait speed has been associated with factors such as disability, loss of independence and hospitalization. To my knowledge, there are no randomized controlled trials comparing different intensities of aerobic training on gait speed. Improvements in gait speed has shown beneficial effects, and more knowledge about interventions that improve gait speed is therefore needed.

1.1 The present study

The main aim of this study is to assess the effect of moderate and high-intensity aerobic training on fast, preferred and dual task gait speed compared to controls. We also want to investigate which of the two exercise-arms improves gait speed most. Secondary aims are to investigate if effect of different exercise-intensities on gait speed are influenced by gender and leg strength.

It is expected that both exercising group will increase gait speed compared to the control group, for all gait speed conditions; preferred, fast and dual task. When comparing high- and moderate-intensity training, our hypothesis is that high-intensity training leads to largest increase in fast gait speed. Fast walking is a big part of the high-intensity exercises in our trial, and due to the higher specificity and possible greater transfer value, we expect these results. Lopopolo et al. (2006) also suggests in their meta-analysis that exercise intensity may be important for gait speed response. A study (Hollman et al., 2011) did find significant difference in gait between men and women, and we may therefore expect to find that gender has an effect on response in gait speed to different the intervention-arms. Baseline leg strength has been found to influence gait speed response to exercise program and we therefore expect to find an effect of leg strength on gait speed change to the different intervention-arms (Henderson et al., 2016).

2.0 Methods and materials

2.1 **Design**

This is a parallel, multiple-arm randomized controlled trial, conducted in Trondheim. Data collection was done as a part of the Generation 100-project, a randomized clinical controlled trial investigating the effect of exercise on morbidity and mortality in older community-dwelling adults (Stensvold et al., 2015). All men and women born between 1936-1942 and currently living in Trondheim were invited to be a part of the study. Participants were randomized to either a control group or to an exercising group. The exercising group was further randomized and divided into moderate or high intensity exercise. All personnel were blinded for group belonging. Data collection took place at St.Olavs Hospital in Trondheim and started in Aug 2012, and will be continue to June 2018, making the intervention 5 years long. Assessments have been performed at baseline, at one year, at three years follow-up, and will be further assessed at five years follow-up. The present study will only use data from baseline test and the three year follow-up.

2.2 **Participants**

Nearly 7000 individuals were invited (6966 people). Inclusion criteria were: Born during 1936-1942, be able to walk a minimum of 1 km consecutive, and be able to complete the exercise program. Exclusion criteria were; illness or disabilities that preclude exercise or hinder completion of study, uncontrolled hypertension, symptomatic valvular, hypertrophic cardiomyopathy, unstable angina, primary pulmonary hypertension, and heart failure or severe arrhythmia. Also, those with diagnosed dementia, cancer that makes exercise contraindicated, chronic communicable infectious diseases, test results indicating that study participation is unsafe, participation in other studies conflicting with participation in Generation 100, were excluded.

Of the total invited individuals, 3212 responded. Of those, 1790 filled the inclusion criteria for participation in the study. Some withdrew, did not show up for testing or were excluded. Finally, 1567 individuals (790 women) were included and randomized. The participants gave informed, written consent to the main study. The study is approved by Regional Committee for Medical Research Ethics, Norway (REK 2012/281 B).

2.3 **Equipment**

Gait Speed

In collection of gait speed data, the ProtoKinetics Zeno walkway was used (figure 1). This is a gait mat very similar to the GAITRite walkway. It is a three-layered walkway with all the sensor technology in the mid-layer. This is a portable walkway that detects footfalls with its embedded pressure sensors. The active part of the walkway was 6.10 meters. We also arranged an acceleration- and deceleration zone of 1.16 meters at each end of the gait mat in order to fit with the available walking length area. All the output data from the gait mat was recorded with the PKMAS software installed on a computer. A study by Egerton, Thingstad, and Helbostad (2014) investigated the difference between PKMAS and GAITRite software used for processing instrumented walkway data. They concluded that both programs can be used interchangeably for evaluation of gait among older people.

Figure 1: This is the Zeno walkway that participants walked on, with the red marking where the active sensors are (to the right of the red line).

Maximal oxygen uptake

MetaMax II (Cortex, Leipzig, Germany) was used to measure oxygen capacity. This is a gas analyzer used to collect respiratory data. Values of absolute terms (L/min) and relative to body weight (ml/kg/min) were obtained. Testing of VO2max was performed with participants walking on a treadmill. Participants with heart diseases were tested under ECG monitoring. After a 10-minute warm-up, an individualized protocol was performed to measure VO2peak. When oxygen uptake stabilized, speed and inclination were increased by 2%. A leveling of oxygen uptake despite increased workload and a RER >1.05 were used as a criterion for maximal oxygen uptake. Ventilatory threshold was also used as an indication of reached anaerobic threshold.

Leg strength

Leg strength was tested isometrically in a seated leg-press machine with 110 degrees of flexion in knees (FCM 5540 Leg Press Rehab Standard, Helsinki University of Research, HUR, Finland). The subjects were instructed to push both legs simultaneously as hard as possible against a rigid force plate and were told to stop when the examiner observed a decrease in peak force, shown on a computer screen. Subjects performed 4 trials, where one leg was measured at each trial, giving two tests for each leg.

2.4 **Procedures**

All testing took place at St. Olavs Hospital, were the participants underwent two days of examination. Data was collected through questionnaires, clinical examinations and physical tests at baseline, 1 year and 3 years. Blood sample and blood pressure was obtained in addition to measurements of gait, objectively measured physical activity level, VO2 max, grip strength, leg strength and cognitive tests. For complete description of all variables and procedures, read main study (Stensvold et al., 2015). In this study, we only used data collected on baseline and three years testing on gait speed, leg strength and exercise compliance.

Gait speed

Every subject walked a total of 8 times over the gait mat at 4 different speed conditions – 1) preferred, 2) slow, 3) fast and 4) dual task walk. They were instructed to first walk at a "usual" pace two times. Next, they were instructed to walk back and forth over the gait mat calmly "like they were waiting for the bus", two times. Then they were instructed to walk as fast as possible without running, two times. For the last condition, the subjects were instructed to walk at their preferred pace while simultaneously performing a math test. On the first attempt, they were told to subtract 3 from 80 and counting downward throughout the walkway. In the second walk, they were supposed to do the same but this time start at 100 to avoid learning effect. The gait tests were performed before the maximal oxygen uptake to ensure that the subjects were well rested.

Demographic & covariates

Questionnaires were used to retrieve information on education, age, medication and function in activity of daily living (ADL). Education was divided into 7 different categories; from the lowest alternative "elementary school" up to the highest alternative "college or university with more than three years". Regarding falls, the subjects were asked how many falls they've had during the last year. Number of falls were again converted into a dichotomous variable, dividing fallers from non-fallers. The use of medications includes only number of prescribed medicine. BMI was measured by height and weight. Blood testing was performed by collecting blood sample from an arm vein using standard procedures for blood testing, St.Olavs Hospital, Trondheim. To measure grip strength a JAMAR Hydraulic Hand Dynamometer (Lafayette Instrument Company, USA) was used. Levels of physical activity were measured with SenseWear Armband activity monitor (BodyMedia 7, Pittsburgh, Pennsylvania, USA) or by Actigraph (GT3X, Manufacturing Technology Inc, Florida, USA). Participants wore it for 7 days continuously.

Intervention

The exercising group was randomized into either high intensity training or moderate intensity training. Also, the exercise groups were asked to report after every exercise session in a paper diary that was monthly submitted, or in a web-based diary (Stensvold et al., 2015). Data on total number of workouts conducted (compliance) the first year have been analyzed so far, and are reported here as a measure of compliance. Self-reported physical activity in the control group was reported once a year through questionnaires.

High intensity training

The participants are instructed to use Borg scale (6-20) as guidance for correct exercise intensity during active breaks and intervals (Borg, 1982). The high intensity training was defined as 4 intervals at 85-90% of peak heart rate (corresponding approximately 16 on Borg scale) with a duration of 4 minutes, two times per week. Between intervals, subjects were supposed to perform active breaks with heart rate at 65-70% of peak heart rate, corresponding to 12 on Borg scale. The participants had the opportunity to join a supervised training session with an instructor and heart rate monitors every sixth week and to join organized training sessions twice a week. Participants could also train on their own but were encouraged to take part in the supervised training sessions every sixth week.

Moderate intensity training

Moderate-intensity was training performed at 70% of peak heart rate with duration of 50 minutes, continuous work, two times per week. Participants was instructed to use the Borg scale as a guidance for exercise intensity, and the correct intensity was 13 on the Borg scale. Organized training sessions were offered twice a week, where participants could choose to participate or perform exercise by themselves as recommended. Every sixth week participants were encouraged to join a supervised training session with an instructor and heart rate monitoring.

Control group

The control group was instructed to follow present recommendations for physical activity in Norway at the time the study was initiated. At the time being these recommendations consisted of 30 minutes of daily physical activity at moderate activity.

2.5 Data Processing and statistical analyses

Gait speed data were gathered using the Zeno walkway directly connected to the PKMAS software. Data for each single footstep were inspected before calculation of gait variables for each single walk. From this the software produced text files with values for the selected gait variables that were transferred to Excel and reorganized to make a data matrix for all subjects, gait conditions and gait variables. A custom made Matlab script was used for the reorganization of the text files to a matrix suitable for further data analysis. The files were further converted to SPSS-format for statistical analysis. Every subject had two walks at each condition, and from this also mean gait speed for each gait condition was calculated.

For the statistical analyses, the software IBM SPSS Statistics version 24 was used (SPSS, Inc, Chicago, IL). Sample descriptives are presented as means and standard deviation (SD). To assess normality of the variables we used visual inspections of QQ-plots and Kolmogorov-Smirnov test. For variables that were not normally distributed, median with quartile 25% and 75% were used instead of means. Chi square test were used for between-group comparisons of categorical variables at baseline between intervention-arms. Independent t-test were used to compare means at baseline and three year. For all statistical analyses, significance was accepted at $p<0.05$. To measure effect of interventions between groups, we analyzed the data by both per protocol and intention-to-treat (ITT) analyses. It is recommended to run both analyzes in a clinical trial to ensure correct interpretations of data (Shah, 2011). In our study, we had considerable loss to follow up which strengthens the importance of performing both analysis. Based on the hypotheses of the study, we did pairwise comparisons of change in gait speed between two and two groups instead of analysis of differences in change between all three groups. According to the hypotheses we compared the exercise and control group in term of effect on gait speed, and also assessed which one of the two exercise-arms that improved gait speed the most. Because of the a priori hypotheses of changes between two and two groups, we did not control for multiple comparisons by using e.g. Bonferroni correction. We did this to reduce the likelihood of type II error (i.e rejecting a true significant result where one exists). In addition, when using Bonferroni-corrections, the larger number of comparisons the more conservative the correction tend to become (Proschan & Waclawiw, 2000). To claim statistical significance with three comparisons, Bonferroni adjustment method requires that the p-value be less or equal to $0.05/3 = 0.017$. This is an argument justifying pairwise-comparisons (Proschan & Waclawiw, 2000).

We first used linear regression (analysis of covariance, ANCOVA) for the per protocol analysis to check for differences in change in gait speed between two and two groups according to the hypotheses, and to assess the effect of baseline leg strength, gender and exercise compliance on the results. This was checked in three different models controlling for one variable in each model. We compared groups pairwise; 1) control group (CON) against high-intensity training (HIT), 2) control group (CON) against moderate-intensity training (MIT) and 3) moderate-intensity training (MIT) against high-intensity training (HIT). In the ITT analysis, we used a Mixed Model with Repeated Measures, because this analysis takes into consideration data for all subjects, even when data are missing, thus being able to include data from all randomized participants. We did pairwise comparisons including all randomized subjects regardless of any departures from randomized treatment with no adjustments of gender, leg strength or exercise compliance. When having a high percentage of missing values, it is suggested that the mixed model approach without any ad hoc imputation is more powerful than other options (Chakraborty & Hong, 2009).

3.0 Results

The results are presented in sections *3.1 sample characteristics*, *3.2 per protocol analysis* and *3.3 intention-to-treat analysis*.

3.1.1 Sample characteristics

The sample size in the present study consisted of 1567 randomized subjects (n=387 in the MIT group, n=400 HIT group and n=780 controls), and this sample was included in the intention-to-treat analysis. After checking for missing data and excluding those loss to follow up, a total of 1003 participants (n=239 in the MIT group, n=247 HIT group and n=517 controls) were included in the per protocol analysis. Background data and characteristics at baseline are presented in Table 1, and Figure 1 presents the flow chart of participants throughout the study. A Chi-square test and independent sample t-tests indicated that there was no statistically difference between groups on any demographical variables at baseline (all p’s>0.47). No difference in maximal oxygen uptake or leg strength was found between groups (all p’s> 0.05).

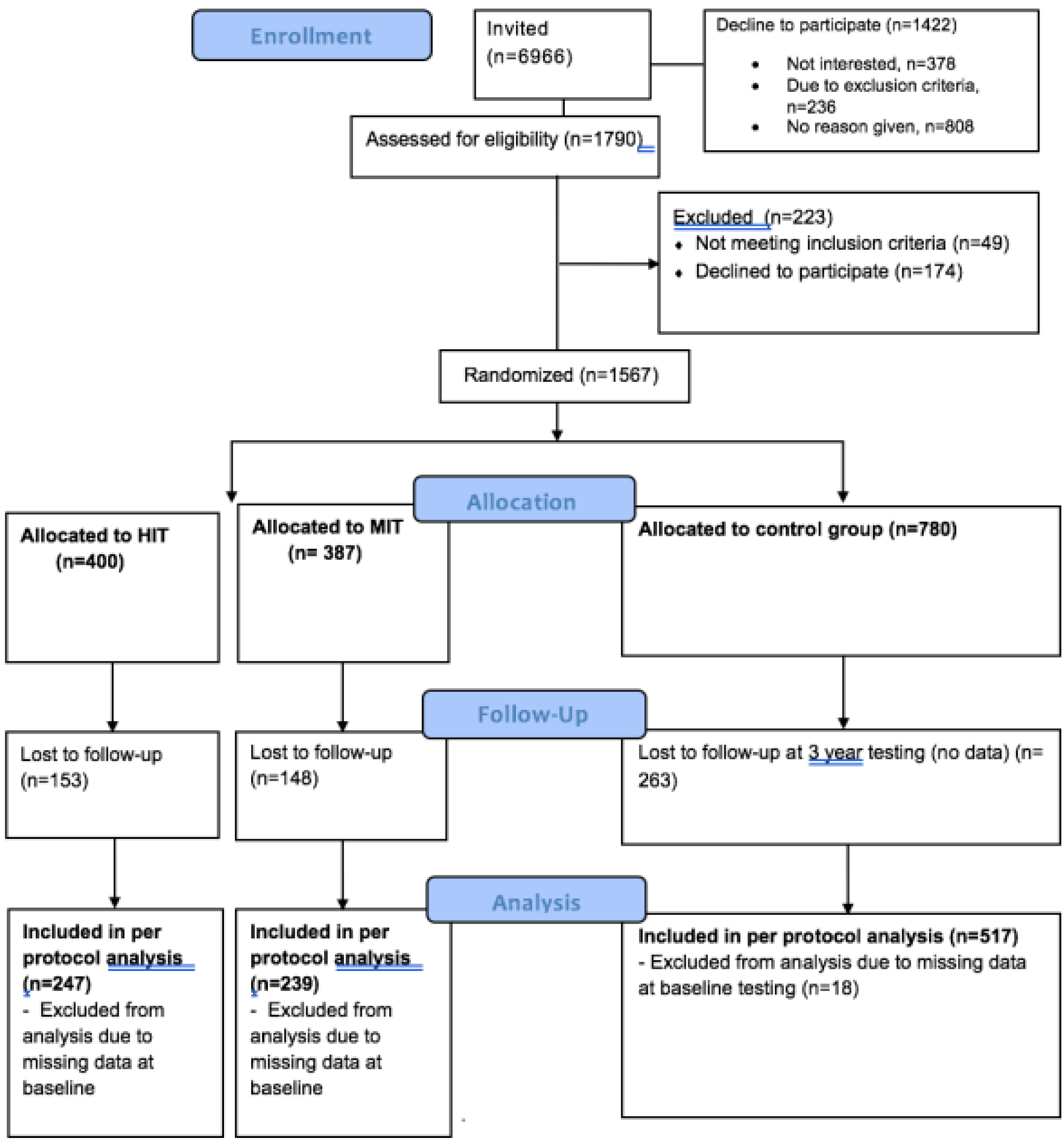

Figure 1. Flow chart of participants

Table 1. Sample characteristics at baseline for the per protocol analysis.

	CON (N=517)	**MIT (N=239)**	**HIT (N=247)**
Characteristics	Mean (SD)	Mean (SD)	Mean (SD)
Mean age (years)	72.8 (2.1)	72.8 (2.0)	72.9 (2.1)
BMI (kg/m2)	25.9 (3.4)	25.9 (3.7)	26.1 (3.7)
Systolic blood pressure (mmHg)	136.8 (19.2)	135.5 (18.7)	136 (18.7)
Diastolic blood pressure (mmHg)	81.4 (11.0)	81.4 (10.5)	81.4 (10.3)
VO2peak (ml/kg/min)	28.6 (6.4)	28.6 (6.7)	28.9 (6.4)
Higher education (years)****	4.9 (2.0)	4.9 (2.1)	4.9 (2.0)
Number of prescribed medications	2.0 (1.9)	2.3 (1.9)	2.1 (2.0)
Grip strength (kg)**	34.0 (36.4)	34.0 (10.6)	35.8 (34.3)
Isometric leg strength in newton meters (median)***	263.6 (161, 393)	256.0 (152. 399)	280.9 (159, 431)
Characteristics	n (%)	n (%)	n (%)
Number of fallers last 12 months (%)	30	30	30
Physical activity in moderate to vigorous intensity*	3.3	3.3	3.2
Female	51	51	51

Abbreviations: CON= control group, MIT= moderate intensity training group, HIT= high intensity training group, n= number of participants. ***=**Objectively measured with SenseWear or Actigraph activity monitor (accelerometer). Shows percentage of total daily activity spent in moderate to vigorous activity intensity. ****=**Measured with preferred hand and calculated mean score of 3 attempts. *****=**Mean score of between legs for maximal rate of force development. ****=Years of education above high school.

3.2.0 EFFECT OF EXERCISE ON GAIT SPEED: PER PROTOCOL ANALYSIS

3.2.1 Mean gait speed at baseline and three year testing

Table 2 shows gait speed at baseline and three years testing presented as means and 95% confidence intervals. As can be seen in the Table 2 preferred gait speed, both CON and MIT seems to be lower at three years compared to baseline, while the tendency for HIT is that gait speed is at the same level at three years testing compared to baseline. In fast gait speed HIT has higher gait at three years compared to baseline, while MIT has slightly higher gait speed at 3 years than CON. In the dual task gait speed condition, all groups have higher gait speed at three years.

Table 2. Gait speed at baseline and three years testing in means and with confidence intervals (95%).

	CON (N=517)		**MIT (N=239)**		**HIT (N=247)**	
	MEAN (cm/s)	95% Cl	MEAN (cm/s)	95% Cl	MEAN (cm/s)	95% Cl
Pref 0 yrs	134	132 - 136	134	132 - 137	134	131 - 136
Pref 3 yrs	130	129 - 132	130	127 - 133	134	131 - 136
Fast 0 yrs	192	189 - 194	193	189 - 196	193	190 - 197
Fast 3 yrs	189	186 - 191	192	188 - 196	196	192 - 200
DT 0 yrs	103	100 - 106	96	92 - 110	100	96 - 105
DT 3 yrs	107	104 - 110	100	95 - 104	105	101 - 109

Abbreviations: CON= control group, MIT= moderate intensity training group, HIT= high intensity training group, N= number of participants, Pref= preferred speed, Fast= fast speed, DT= dual task speed.

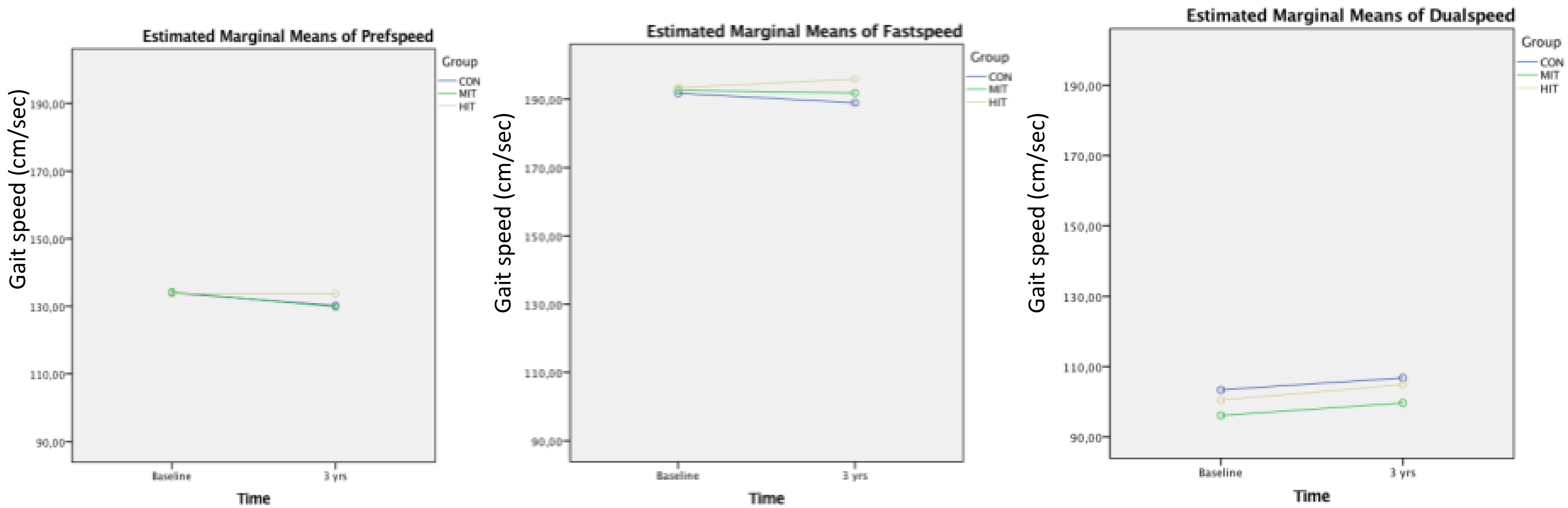

Figure 2 – Changes in preferred, fast and dual task gait speed from baseline testing to 3 years testing.

3.2.2 Linear regression analysis - ANCOVA

Pairwise-comparisons

ANCOVA was conducted to determine a statistically significant difference between two intervention groups on gait speed by pairwise comparing HIT, MIT and CON, following the hypotheses of the study (Table 3). There was significant difference between CON and HIT regarding preferred and fast gait speed, while dual task gait speed was not significant in term of improvement following intervention. When comparing CON and MIT, we found no significant difference, meaning no significant effect of MIT on gait speed compared to CON. When comparing both exercise intervention-arms, HIT and MIT, we found significant difference in preferred gait speed of HIT, while difference in fast speed was near-significant (p=0.058). There was no significant difference in dual task gait speed between exercise interventions.

Effect of gender, leg strength and exercise compliance

When assessing the effect of gender, leg strength and exercise compliance, we found following results (Table 2). Gender significantly influenced dual gait speed inn all groups, where female had the largest improvements in dual task gait speed following intervention. We also found significant effect of gender on change in fast gait speed of HIT when comparing HIT and CON, whereas female had the largest improvements. When comparing MIT and CON regarding improvements in fast gait speed and gender differences, results was insignificant of MIT (p=0.104). Exercise compliance did not significantly influence gait speed response – but a minor tendency towards effect of compliance was observed in preferred gait speed change of HIT when comparing HIT and CON (p=0.9). The higher exercise compliance, the larger improvements in preferred gait speed after HIT intervention. When assessing the influence of leg strength, we found significant effect of baseline leg strength in all gait conditions of both HIT and MIT. Subjects with highest leg strength at baseline had largest improvement in preferred, fast and dual task gait speed following HIT and MIT.

Table 3. Between-group change in gait speed from baseline to three year Positive values mean change in favor first mentioned condition.

	MEAN CHANGE FROM BASELINE TO THREE YEAR (cm/s)	95% CONFIDENCE INTERVAL (cm/s)
HIT vs CON		
Pref	3.7	1.3 to 6.2
Fast	5.3	2.2 to 8.5
Dual task	0.3	-3.8 to 5.8
MIT vs CON		
Pref	0.7	-3.3 to 1.8
Fast	2.0	-1.2 to 5.1
Dual task	0.2	-4.6 to 4.9
HIT vs MIT		
Pref	4.4	1.4 to 7.4
Fast	3.3	-0.4 to 7.1
Dual task	0.8	-4.8 to 6.5

Abbreviations: CON= control group, MIT= moderate-intensity training group, HIT= high-intensity training group, Pref= preferred speed, Fast= fast speed, Dual task= dual task speed.

Table 4. Differences in change in gait speeds between intervention groups with per protocol ANCOVA-analysis. Positive-values indicate an increase in gait speed, negative values indicate a decrease in gait speed from baseline to three years.

	GROUP		**EXERCISE COMPLIANCE**		**LEG STRENGTH**		**GENDER**	
	(t)	p-value	(t)	p-value	(t)	p-value	(t)	p-value
HIT vs CON								
Pref	3.1	0.002	1.7	0.090	2.4	0.017	-1.0	0.316
Fast	3.6	0.001	0.9	0.379	3.6	0.001	-2.0	0.044
Dual task	0.2	0.862	0.6	0.579	2.5	0.013	-2.7	0.008
MIT vs CON								
Pref	0.5	0.600	-0.7	0.440	3.4	0.001	-1.0	0.327
Fast	1.4	0.175	1.5	0.142	3.6	0.001	-1.6	0.104
Dual task	1.5	0.143	0.6	0.550	3.3	0.001	-2.2	0.027
HIT vs MIT								
Pref	3.0	0.003	0.5	0.592	3.2	0.001	0.2	0.847
Fast	1.9	0.058	0.8	0.423	2.2	0.027	0.0	0.980
Dual task	1.0	0.297	1.3	0.180	3.4	0.001	-2.0	0.036

Abbreviations: CON= control group, MIT= moderate intensity training group, HIT= high intensity training group, Pref= preferred speed, Fast= fast speed, Dual task= dual task speed.

3.3 EFFECT OF EXERCISE ON GAIT SPEED: INTENTION-TO-TREAT ANALYSIS

3.3.1 Linear Mixed Model analysis with repeated measures

When performing a linear mixed model analysis with repeated measures, the only significant difference in gait speed was found between CON and MIT in dual task speed (Table 4). Further analysis showed no statistically significant difference between HIT and CON, nor between MIT and HIT for any gait speed condition. We found a tendency of larger difference in change in gait speed of HIT compared to CON for fast gait speed.

Table 4. Between-group comparison in change at different gait speeds with Mixed Model with Repeated Measures-analysis. Positive values indicate an increase in gait speed, negative values indicate a decrease in gait speed from baseline to three years.

Variable	(t)	p-value
HIT vs CON*		
Pref	1.3	0.187
Fast	1.7	0.062
Dual task	-1.1	0.267
MIT vs CON*		
Pref	0.4	0.241
Fast	0.9	0.376
Dual task	-2.9	0.004
HIT vs MIT*		
Pref	0.7	0.440
Fast	0.8	0.410
Dual task	1.5	0.126

Abbrevations: * = set to zero. CON= control group, MIT= moderate intensity training group, HIT= high intensity training group, Pref= preferred speed, Fast= fast speed, Dual task= dual task speed.

4.1 Discussion

4.1.1 Main findings

The main objective of this randomized controlled trial was to investigate the effect of exercise-intensity on gait speed in preferred, fast and dual task gait. A secondary aim was to investigate if gender and leg strength influenced the results. In the per protocol analysis, we found significant improvements in preferred and fast gait speed of HIT when comparing HIT and CON, but no difference in dual task gait speed was observed. When comparing MIT and CON, we found no significant differences in any gait condition, meaning that MIT had no improvements in gait speed compared to CON. Comparing the two exercise intervention-arms, HIT and MIT, we found significant difference in gait speed response. Significant improvement in preferred gait speed and near-significant (p=0.058) improvement in fast gait speed of HIT was observed, meaning that HIT improved preferred and fast gait speed more than MIT. In the intention-to-treat analysis none of these findings was significant, except change dual task gait speed following MIT when comparing MIT and CON. For our second research question, we found that females had significantly larger improvement in dual task gait speed of both HIT and MIT, as well as female had largest improvement in fast gait speed of HIT when comparing HIT and CON. We found that baseline leg strength significantly influenced improvements in all gait conditions, where larger leg strength was associated with larger improvement in gait speed following both HIT and MIT. When assessing influence of exercise compliance on gait speed improvement following the exercise intervention, no significant difference was found.

4.1.2 Effect of intervention on gait speed

When looking at fast gait speed, the largest improvement from baseline to three years was observed after HIT when comparing HIT and CON, mean change in fast gait speed was 5.3 cm/sec (p=0.001). In the same group-comparison, preferred gait speed improved 3.7 cm/sec (p=0.002). When comparing HIT and MIT against each other, the gait condition that had the largest improvement from baseline to three year was preferred speed with 4.4 cm/sec (p=0.003) – for fast gait speed the improvement was 3.3 cm/sec (p=0.058). In terms of a meaningful clinical change (at least 10 cm/sec) defined by (Hardy et al., 2007), these effect size are smaller than a meaningful change. A study by Henderson et al. (2016) looked at gait speed response to aerobic training versus resistance training in older adults and found clinically significant change in gait speed, both aerobic training and resistance training. Only aerobic training clinically improved fast gait speed. Compared to our study, the participants in their study had slower gait speed at baseline, mean preferred speed was 100 cm/s and fast speed was 123 cm/s. The aerobic training was walking continuously 20 min in 65-70% of peak heartrate. It is important to mention that they also measured gait speed over 400 meter, explaining why fast gait speed was considerable lower than our study. Walking 400 meter may demand more aerobic capacity than walking 4 meter. Sipila et al. (1996) used a 10-meter test and suggested a ceiling effect since final fast gait speed in all groups was >180 cm/s. There is reasonable to think that there is a natural limitation in gait speed, and it may be expected that the subject with their already "exceptional" preferred gait speed had small room for improvements. Buchner et al. (1997) suggests the same, that if strength and endurance is adequate prior to exercise, a further increase in strength and endurance is not expected to alter walking speed or other basic tasks. There are no results in our analysis suggesting a dosage-response relationship between exercise and preferred gait speed.

Our analysis showed that there was a significantly difference in change for fast gait speed between CON and HIT, suggesting that there is an effect of high intensity exercise on fast gait speed. On the other hand, the results in this meta-analysis by Lopopolo et al. (2006) could not support a relationship between therapeutic exercise and changes in fast gait speed in community-dwelling older adults. A major limitation with this meta-analysis is that it's only based on cohort studies. They also suggest that future studies should address the issue with variety of fast gait speed instructions that they thought may be a reason for the lack of relationship. Although, our findings agrees with the meta-analysis by Lopopolo et al. (2006) on preferred speed – they concluded that "…therapeutic exercise appears to improve gait speed in community-dwelling elderly people, although the effect is rather small". An interesting approach in future research would be to investigate if the response on gait speed of high-intensity training is dependent on baseline gait speed and further if those with low gait speed have better potential of progress.

Regarding the ITT-analysis, the only significant results we found was on dual task of MIT. It showed a significant decrease in dual task gait speed of MIT when compared with CON. We currently don't have a good explanation of this results. A small possibility is that it comes from random error.

4.1.3 Exercise dosage and specificity

A study (Daley & Spinks, 2000) found no effect of therapeutic exercises on fast gait speed, while we found effect on both fast and preferred speed. The lack of specificity may explain why no effect of exercise was found – exercise in that study consisted of only cycling as the aerobic component and not walking. The high intensity exercise in our study consisted of fast gait walking in 85-90% of peak heartrate giving.

In this meta-analysis (Lopopolo et al., 2006) they found that only high intensity and high-dosage exercise training (strength training or combination training consisting of aerobic exercises) produced a significant effect on preferred gait speed, and our findings support this. Province et al. (1995) suggest that high intensity exercise program is needed to produce improvements in strength, power and functional abilities – including gait, for older community-dwelling adults. With our results and knowledge of current research, there may not be enough evidence to recommend high intensity training as an effective gait speed intervention. High intensity training may nevertheless still be an important training program for the elderly population. High intensity training was first used among athletes for improving performance, and has later shown to have positive effect in medical management plans of older adults as well (Ross, Porter, & Durstine, 2016). Midgley, McNaughton, and Carroll (2007) compared moderate and high intensity training and reported greater training improvements in maximal aerobic capacity in high intensity group. They concluded that there is considerable evidence of the use of high intensity training strategies for patients with chronic disease.

Our results regarding effect of intervention on dual task gait speed is conflicting with findings in this meta-analysis (Smith et al., 2016). We found no significant effect of any exercise on this condition, but this may be explained by difference in exercise intervention and population between studies. The studies that investigated effect of exercise on dual task gait speed had specific dual-task exercises while walking, standing balance and cognitive exercise – while our exercise only had focus on exercise intensity and dosage, and no emphasis on gait, dual-task or cognitive training at all. The authors of this meta-analysis emphasized the limitation with the cross-sectional design of the included studies and made quality assessment difficult.

They also wrote that it remained high heterogeneity, possibly due to participant characteristics and testing protocols. This may explain the lack of effect of exercise on dual task gait speed.

4.1.4 Gait speed and effect of gender, leg strength and compliance

Henderson et al. (2016) found that lower leg strength at baseline was associated with less improvements in preferred gait speed, but not fast gait speed. Our results suggested the same, where those with higher leg strength at baseline had most improvement for preferred speed. In contrary, we also found that leg strength influences response in fast gait speed. Other studies have shown association between higher leg strength and gait speed response (David M. Buchner et al., 1996; Jama L. Purser, Pieper, Poole, & Morey, 2003), supporting our findings. Higher leg strength may potentially increase propulsion-power, making it possible to walk faster.

We found that females had significantly larger improvement in dual task gait speed of both HIT and MIT, as well as female had largest improvement in fast gait speed of HIT when comparing HIT and CON. We observed the same tendency in fast gait speed of MIT when comparing HIT and CON, but the results were not significant (p=0.104). No other known studies have investigated if there are gender differences on gait speed response following exercise-interventions. We do not know why aerobic exercise would better improve dual task gait speed in females compared to males, but studies have suggested that some intrinsic characteristics such as muscle strength, skeletal alignment and anthropometric parameters may contribute to difference in gait performance between male and female, and thereby respond different to exercise (Ferber, Davis, & Williams, 2003). The underlying factors are out of the scope of this trial and may be further investigated in future research.

When assessing for effect of exercise compliance on change in gait speed between groups, we found no significant effect. This means that the number of conducted workout does not influence change gait speed. The compliance data has some major limitations that may contribute to the lack of effect. A limitation with this data is that it only contains number of workout, and not intensity and length. We also only have compliance data from baseline to one year, and thereby missing last two years. It is reasonable to think that the participants degree of completion drops during the follow-up, making the total number of workouts underestimated. Some of the subjects actually reported to us that they have trained as prescribed but not written it down.

4.1.5 Data analysis

When analyzing data with intention-to-treat (ITT) which includes all randomized participants regardless of loss to follow up and missing data, the statistically difference in gait speed between groups disappeared. ITT analysis has become a widely-accepted method for the analysis of controlled clinical trials. ITT analysis, as suggested by Schwartz and Lellouch (1967), is a pragmatic approach to avoid bias in estimating the effect of treatment assignment in randomized clinical trials. In this way therapists in clinical settings may more easily evaluate and predict effect in their own patients, as 100% compliance to intervention or treatment is unrealistic for the most of us. ITT best reflects the effects of treatment in everyday practice, while per protocol analysis best reflects the effects of treatment when taken in an optimal manner ("Intention to treat analysis and per protocol analysis: complementary information," 2012). When excluding patients that deviates from the protocol, one can introduce bias in which the groups of patients being compared no longer have similar characteristics. The use of ITT ensures maintenance of comparability between groups as obtained through randomization, eliminates bias and maintains sample size (Ranganathan, Pramesh, & Aggarwal, 2016).

4.1.6 Participants

Descriptive data were made for both participants, those who did not want to participate and those who dropped out during the study (Stensvold et al., 2015). When comparing included participants with those who did not want to participate, we found that the included participants are more active, have higher education and better health. In the non-participating group, 32 % reported to have higher education, and in the participating group the number is 50%. In the participating group, 87% reported to have good health compared to 66% in the non-participating group. The portion of sedentary behavior is lower in the participating group.

Studenski et al. (2011) found that preferred gait speed over 100 cm/sec had better life expectancy than average, and gait speed over 120 cm/sec suggested exceptional life expectancy. They investigated 9 cohort studies with baseline gait speed data. A total of 34 485 community-dwelling older adults was included in the analysis, and mean age was 73.5 (5.9) years. Mean gait speed was 92 (27) cm/sec. Mean preferred gait speed in our study was approximately 135 cm/sec at baseline and 129 m/sec at three years testing, suggesting that our participants had considerable higher gait speed than average.

4.1.7 Strength and limitations

This trial has both strength and possible limitations. This is a randomized controlled trial with blinding of the test personnel, and this design is often referred to as "gold standard" compared to other clinical research designs. A big strength with this study is the long training period combined with the large sample size. This makes the results more reliable and we get to see long-term effects of exercise on gait speed.

Testing of the subjects are following strict protocols and it is objectively measured with electronic gait mat and isometric leg strength against force plate. The electronic gait mat used in this study has shown to exhibit excellent reliability for most temporo-spatial gait parameters in both young and older subjects (Menz, Latt, Tiedemann, Mun San Kwan, & Lord, 2004). Regarding measurement of gait speed in this study, we used a reliable assessment of walking speed (Peters et al., 2013).

On the other hand, the study also have some potential limitations that need to be mentioned. With a long follow up, other unknown factors can influence exercise and gait speed and thereby create bias. Another challenge with this long follow up is of course participants' compliance and adherence to the exercise-intervention. Two weekly workouts during three years is a lot to demand of participants, but this is handled with offering group workouts weekly and having participants writing a training diary. In this way could keep participants motivated, and we could also use that data to control for possible confounding. Participants are also invited to join a supervised exercise with heart rate monitor every sixth week, making sure that participants exercise at the right intensity.

Measurement of compliance may not be reliable, as many participants may not report all the exercise that has been performed. Future studies should find other ways to report workouts in a more reliable and objective manner, i.e. exercise watches or activity monitors.

In this study, the loss to follow up was 36%. It is expected to have a high loss to follow up over three years when subjects are instructed to exercise this often. Regarding characteristics of those who dropped out, we know that they are a less fit population, fewer reports good health and they tended to walk slightly slower at baseline (Stensvold et al., 2015). All this is important to take in to considerations when the results are interpreted and results may not generalize to the entire population. We did not see any difference in loss to follow up between exercising groups, meaning that there is probably no form of training that is more difficult to follow than the other. During this trial, participants have instructors and weekly sessions to motivate and ensure highest compliance possible. We would probably expect lower compliance if subjects had no follow up on exercise, as we usually don't have in our workouts in daily life.

Another limitation with this study is some of the covariates are obtained with questionnaires, which may lead to underestimation of falls (forget falls, ashamed, etc.), medicine and comorbidity – and other possible biases. Since subjects get invited to participate in this trial, we also have selection bias – meaning that there may be a specific part of the population that has a higher possibility to join this study. It is reasonable to think that the more active part of the elderly population has greater motivation in joining and stick to this training-trial.

5.0 Conclusion

These results indicate that high intensity training was the most effective intervention in term of improving preferred and fast gait speed compared to moderate intensity training. However, improvement in gait speed is not enough to count as a clinically meaningful change. We found no significant difference in gait speed between CON and MIT, suggesting that MIT alone have no impact on gait speed. No change in dual task gait speed was observed between groups. We found that leg strength had a significant effect on change in preferred, fast and dual task gait speed in both high intensity training and moderate intensity training, where increased leg strength was associated with larger improvement in gait speed. Gender significantly influenced gait speed response to exercise, were it seems that females have the largest improvements.

With this findings, we conclude that high-intensity aerobic training alone is not enough to effectively improve preferred or fast gait speed in healthy community-dwelling older adults. Future research may compare high-intensity training versus combination-training (both strength, balance and aerobic) in gait speed improvements, as well as looking at the effect of baseline gait speed to investigate if "slow"-walkers have bigger improvements compared to "fast"-walkers. In addition, the intervention-arms in this trial was not designed to improve gait speed but investigate the effect of exercise on morbidity and mortality. Therefore, interventions specifically designed to improve gait speed may be more effective.

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