Master's thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Neuromedicine and Movement Science

Sadegh Alizadeh

The Association Between Muscle Strength and Risk of Developing Alzheimer's Disease Among Older Adults in Norway

A prospective cohort sub-study of the Generation 100 Study

Master's thesis in Physical Activity and Health
Supervisor: Atefe R. Tari
Co-supervisor: Ulrik Wisløff, Aleksi Matias Huuha
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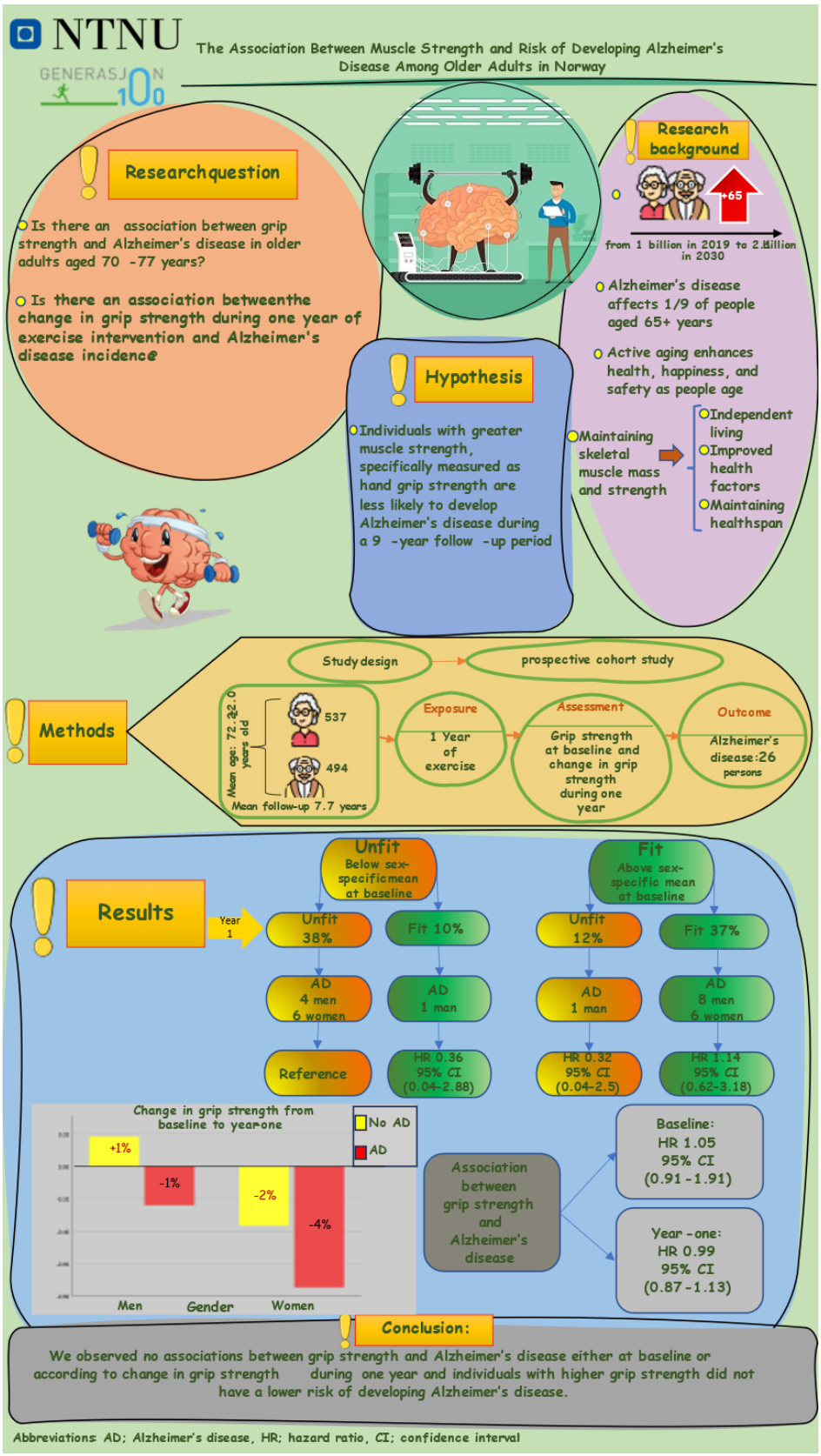
Infographic



Acknowledgments

First, I would like to acknowledge and give my warmest thanks to my supervisors Ulrik Wisløff, Atefe R. Tari, and Aleksi Matias Huuha who made this work possible with their patience, motivation, and immense knowledge. Their consistent support and invaluable advice like guiding lights carried me through all the stages of my thesis. Studying at NTNU was my dream one day and being a small member of this amazing people's group was beyond my dreams, now, it has come true.

Second, I like to give special thanks to Ph.D. student Mariana Cecilia Magdalena Meza Vázquez in particular for her critical reading, and constructive input, as well as for generously sharing her insights and experiences with me. A huge thanks to Emma Ingestrøm, for her statistical assistance and insightful remarks, which improved overall the quality of this work. My sincere thanks also go to Helene Haugen Berg, the project's neurologist for her help in the method part. I also like to thank my fellow student Daniel Esti Brissach for his support and insightful observations have been truly valuable.

Third, My heartful appreciation goes to Dorthe Stensvold for letting me to be part of this great Generation 100 Study. I also would like to thank Thomas Fremo, Lars Valderhaug, Ingrid Haagenrud Langmo, and the NeXt Move core facility fellow students who helped me in mastering the Short Physical Performance Battery (SPPB) and cardiopulmonary exercise test. The nice and kind participants of the Generation 100 Study, through their participation, made this project done.

Fourth, I would like to express my gratitude to my mother for her prayers and spiritual support throughout my life, especially during these years spent away from family.

Fifth, I would like to thank my family, girlfriend, friends, and everyone who has played a role in facilitating my education at NTNU and experiencing this amazing life in Norway. Your unbreakable belief in me has been an important motivator.

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Abbreviations

AD	Alzheimer's disease
BMI	Body mass index
CI	Confidence intervals
CVD	Cardiovascular disease
GS	Grip strength
HR	Hazard ratio
USA	United States of America

Definitions

Alzheimer's disease (AD) is a type of degenerative brain disease that is characterized clinically by a progressive deterioration in memory and other cognitive abilities (3). The greatest hallmark of AD is an accumulation of extracellular beta-amyloid plaques and intracellular tau tangles. The disease begins years before symptoms emerge and becomes worse with time and interferes with the individual's everyday activities (3).

Dementia is not a single disease, but a general term that refers to a broad range of cognitive impairments such as memory loss, language problems, difficulty in problem-solving, and other thinking skills that disrupt individuals' daily functioning. AD is the most common cause of dementia accounting for 60 to 70 percent of cases (4).

Frailty is defined as possessing a poor state of health and lack of physical strength capacity, which is linked to an increased risk of developing disability, dementia, falls, hospitalizations, and premature mortality (5).

Generation 100 Study is a randomized controlled trial study, started in Trondheim, Norway, in 2012, that included residents aged 70 to 77 years. Its primary aim was to study the effects of exercise training on morbidity and all-cause mortality. Clinical examinations were performed at baseline, 1st, 3rd, 5th, and 10th-year of study (6).

Muscle strength refers to a health-related component of physical fitness that relates to the ability of the muscle to exert force (7). Among all muscles such as respiratory, pelvic floor, and trunk muscles, limb muscle strength commonly becomes of interest. Of the many limb muscles, the muscles that provide grip strength (GS) are the most regularly measured (8). GS is the simplest and least complicated of many examined muscle strength tests, which tends to reflect overall muscle strength and has clinical and prognostic value.

Physical activity can be defined as any bodily movement that is performed by skeletal muscles, causing an increase in energy expenditure above resting values. It can include different activities such as walking, dancing, cycling, running, sports and any active form of recreation. Physical activity can improve health, and enhance well-being and mental health, quality of life, and self-esteem (9).

Physical fitness is defined as the ability to perform everyday activities vigorously and show features and capacities associated with a low risk of developing disorders associated with physical inactivity. Cardiorespiratory fitness, muscular strength, muscular endurance, body composition, and flexibility are the most important components of physical fitness (10).

Sarcopenia can be defined as a gradual decline of skeletal muscle mass and strength along with physical performance after reaching a peak in early adulthood. It is influenced and accelerated by age, gender, nutrition, physical inactivity, and comorbidity, and causes people to stop engaging in physical activity (11, 12).

Abstract

Purpose: To assess the association between muscle strength and risk of developing Alzheimer's disease (AD) among older adults aged 70-77 years in Norway.

Methods: Grip strength (GS) and muscle mass of 1031 apparently healthy older adults (48% men, age of 72.2±1.9 years old) who participated in the randomized controlled trial, Generation 100 Study was measured at baseline and after one year of exercise intervention. GS was measured using a hydraulic hand dynamometer and the lean muscle mass of the dominant arm was obtained using bioelectrical impedance. To identify AD cases over the next 9 years follow-up, hospital records were reviewed by a neurologist. To assess the hazard ratio (HR) at both baseline and year-one we used continuous variables adjusting for sex and level of education. To assess the hazard ratio according to the change in GS we categorized them into, unfit to unfit (below mean at both baseline and year-one and we used that as the reference group), unfit to fit (below mean at baseline and above mean at year-one), fit to unfit (above mean at baseline and below mean at year-one), and fit to fit (above mean at both baseline and year-one).

Result: The mean GS was 21.6% ($p<0.001$) higher in men (18.5±3.1 $kg^{-0.67}$) than in women (15.2±2.6 $kg^{-0.67}$). Over a mean follow-up period of 7.7±0.8 years, 26 participants (2.5%, 14 men) developed AD. Those who developed AD had a mean follow-up of 3.2±1.7 years and had decreased GS by -0.4±1.3 $kg^{-0.67}$ ($p=0.08$) over one year of intervention, not different from those who remained healthy till the end of follow-up (-0.1±2.0 $kg^{-0.67}$, $p=0.11$). The GS from baseline to year-one for women who later developed AD decreased by 4% (-0.7±0.8 $kg^{-0.67}$, $p<0.01$) compared to a 2% decrease (-0.3±1.8 $kg^{-0.67}$, $p<0.001$) among women who did not develop AD during follow-up. Changes in GS for men who later developed AD and those who did not develop AD were -0.2±1.6 $kg^{-0.67}$, $p<0.59$ and +0.1±2.2 $kg^{-0.67}$, $p<0.07$. There was no significant association between GS at baseline or at year-one and risk of developing AD (HR 1.05, 95% confidence interval (CI) of 0.91–1.19, and HR 0.99, 95% CI 0.87–1.13, respectively). There was no significant association between change in GS from baseline to year-one and the incidence of AD. Compared with those who remained unfit at both timepoints, changing from unfit to fit (HR 0.36, 95% CI 0.04-2.88) or remaining fit at both timepoints showed no reduction in risk of AD (HR 1.14, 95% CI 0.62-3.18).

Conclusion: We observed no associations between GS and AD either at baseline or according to change in GS during one year of intervention and individuals with higher GS did not have a lower risk of developing AD.

1 Introduction

The number of the world's population aged above 65 years is increasing rapidly, and at a rate never seen before (13). In 2019, there were 1 billion people aged above 60 years, and this number is estimated to rise to 1.4 and 2.1 billion in the years 2030 and 2050 (13). Diseases such as cardiovascular disease (CVD), cancer, hypertension, type 2 diabetes, and cognitive disorders like dementia, Alzheimer's disease (AD), and depression are all linked to the aging process and it is accompanying functional and physiological changes, such as a decrease in maximum oxygen uptake, muscle mass, mobility and activity (14). Human health research has recently changed from extending lifespan to expanding healthspan, which is defined as the time spent in a state of functional independence with no signs of serious disease (12). Maintaining skeletal muscle mass and strength during life is crucial to independent living, improved health factors, and maintaining healthspan (12). Prevention of aging-associated conditions can be greatly aided by engaging in regular physical and social activities (15). The term "active aging," proposed by the World Health Organization, refers to a set of behaviours that enhance health, happiness, and safety as people age (13). Furthermore, as the aging process intensifies, individual differences in cognitive and physical function become more notable (16).

1.1 Alzheimer's disease and dementia

Dementia is not a single disease, but a general term that refers to a broad range of cognitive impairments such as memory loss, language problems, difficulty in problem-solving, and other thinking skills that disrupt individuals' daily functioning (4). Dementia is currently the seventh leading cause of death among older adults worldwide and one of the top causes of dependency and disability (4). The global dementia population, currently at 55 million, is projected to almost triple to 132 million by 2050 due to increased lifespan (4). In Norway, number of dementia patients is estimated to increase from today's 101,118 to 236,789 in the year 2050 and 380,134 in the year of 2100 (19). AD is the most common cause of dementia accounting for 60 to 70 percent of cases (4).

AD is a degenerative brain disease that is characterized clinically by a progressive deterioration in memory and other cognitive abilities (3). The greatest hallmark of AD is an accumulation of extracellular beta-amyloid plaques and intracellular tau tangles (3). It is also associated with noncognitive symptoms such as impaired motor function (e.g., gait impairment) (3, 17). AD

pathogenesis begins decades before clinical symptoms manifest (3). Symptoms of AD occur because neurons in parts of the brain involved in thinking, learning, and memory (cognitive function) have been damaged or destroyed. In line with these increasing pathological changes over time, an individual's capacity to do daily activities would be affected (3). Figure 1 illustrates Alzheimer's brain shrinks in size due to neuronal death, compared to the healthy brain.

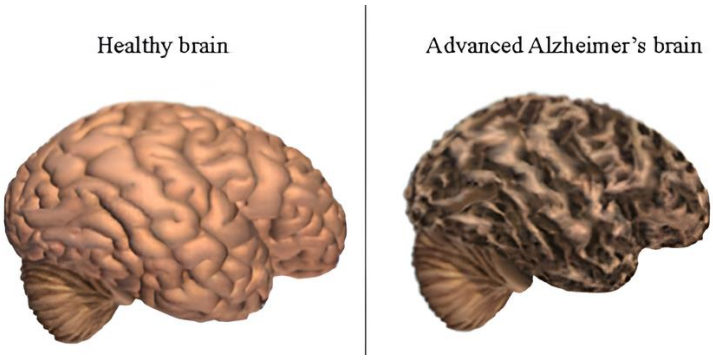

Figure 1. Healthy brain compared with advanced Alzheimer's brain. Figure modified from Alzheimer's Association (1).

AD affects one out of every 9 people aged 65 years and older and about one-third of those aged 85 years and older. It is anticipated that the annual overall cost of medical care, long-term care, and hospice care for people with AD worldwide continue to rise, from US $1313 billion in the year 2019 to US $2 trillion by the year 2030 (3). These numbers highlight the need for more studies on AD risk factors and preventive and therapeutic strategies against the disease.

1.2 Alzheimer's disease continuum

The progression of AD from unnoticeable brain changes to the person affected to the brain changes causing problems with memory and eventually physical disability is called the AD continuum. On this continuum, there are three broad phases; the first phase is preclinical AD in which the individual has some measurable changes in the brain, cerebrospinal fluid, and blood biomarkers that indicate the earliest signs of AD, but no clinical symptoms can be observed (3, 18). The second stage involves mild cognitive impairment due to AD where some biomarkers can confirm pathological changes in the brain (memory and thinking), yet these changes still do not significantly impact an individual's everyday activities. The number and

duration of which individuals with mild cognitive impairment develop dementia or dementia due to AD varies (18). The third stage is clinically diagnosable dementia, dementia due to AD, where cognitive and functional symptoms interfere with activities of daily living. The pace at which symptoms advance from mild to moderate to severe differs from individual to individual. In the severe phase, individuals experience noticeable symptoms such as memory loss, thinking, and behavioral changes. Their physical health is significantly affected due to the damage to the area of the brain involved in movement, leading to a decline in individual's ability to perform activities of daily life, ultimately resulting in individuals becoming bed-bound (3), as illustrated in Figure 2.

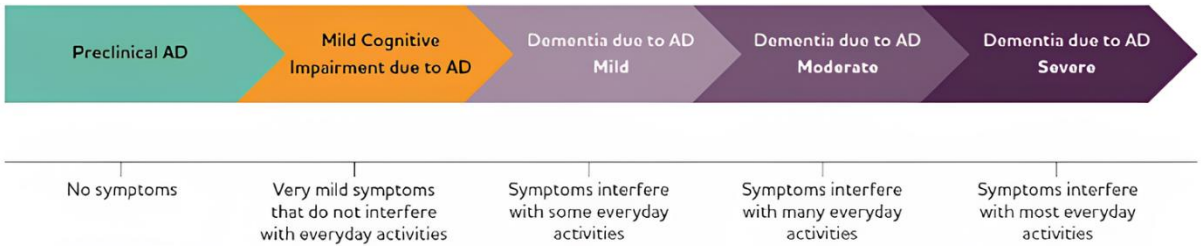

Figure 2. Alzheimer's disease (AD) continuum. Although these arrows are of equal size, the components of the AD continuum are not equal in duration. The figure is taken from AD Facts and Figures, 2021 (3).

1.3 Risk factors for Alzheimer's disease

Risk factors of AD can be broken down into two categories: unmodifiable and modifiable risk factors. Unmodifiable factors include age, which stands as the foremost risk factor for AD, sex (with women exhibiting a greater susceptibility), family history, and the APOE gene (20). In 2020, the Lancet commission defined the specific, potentially modifiable, life-course-ordered risk factors for dementia, including low educational level (early life), hearing impairment, traumatic brain injury, hypertension, excessive alcohol consumption, and obesity (midlife), smoking, diabetes, lack of physical activity, depression, low social contact, and air pollution (later life). Modifying these risk factors might prevent or delay up to 40% of dementias (21), as illustrated in Figure 3.

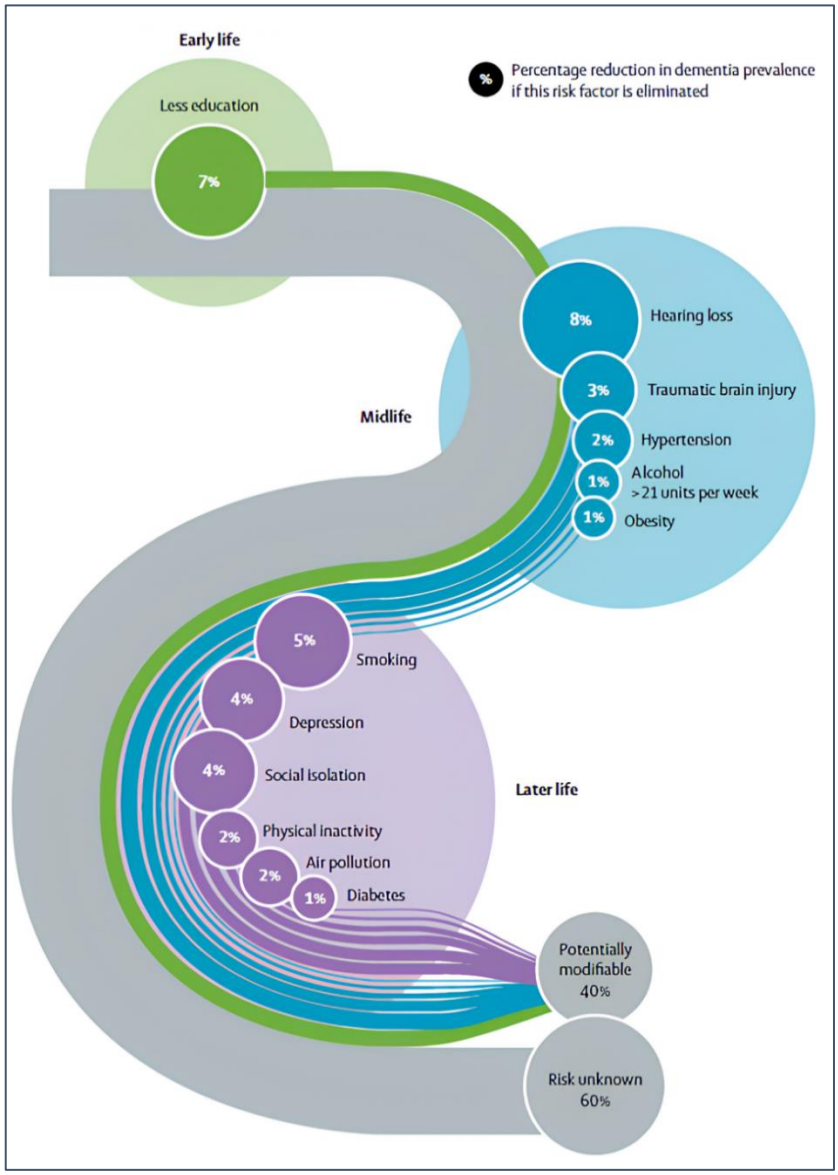

Figure 3. Population attributable fraction of potentially modifiable risk factors for dementia (21). The Figure is taken from the Lancet.

1.4 Physical activity as a treatment for Alzheimer's disease

None of the pharmacologic treatments available for AD today can stop the damage and death of neurons that cause AD (22). A growing body of evidence suggests that exercise and cognitive stimulation are the best nonpharmacological preventive measures for AD (22). As reviewed by Huuha et al. in 2022, regular physical activity is associated with a reduced risk of developing AD or dementia of any form by 35-40% compared to being inactive (23). A meta-analysis (22) concluded that aerobic exercise and a combination of aerobic and other types of exercise had positive effects on cognitive function.

1.5 Motor function and Alzheimer's disease

Age-related motor decline is common and associated with a wide range of negative health outcomes including all-cause mortality, incident disability, and other outcomes, including the development of AD (24). Reduced walking speed, loss of muscular strength and muscle mass, and decreased balance are all symptoms of motor impairment (2). Damage to motor-related brain regions and their location within central nervous system structures may result in a variety of clinical motor impairments. The fact that certain noncognitive symptoms such as motor deficits that can predict the development of AD suggests that noncognitive behaviours may serve as a phenotypic marker of preclinical AD (2), as illustrated in Figure 4.

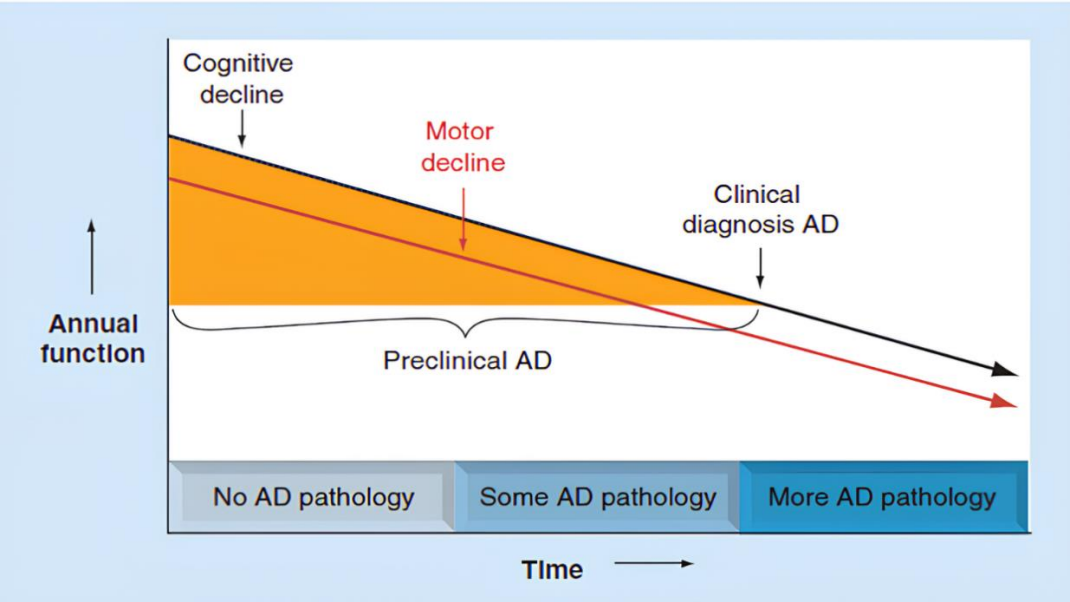

Figure 4. Loss of cognitive and motor function during preclinical Alzheimer's disease. The figure shows the hypothesized relationship between accumulating AD pathology and declining cognitive and motor function before and after the clinical diagnosis of AD. Accumulation of AD pathology during preclinical AD may account for a substantial proportion of cognitive and motor dysfunction currently considered 'normal aging' in older persons without dementia. The figure is taken from Buchman et al., (2).

Cognitive and motor function decline in old age may have the same underlying pathophysiology, and the accumulation of AD pathology contributes to age-related functional decline, including cognitive and motor decline (2). Both the level and rate of motor decline are associated with adverse health outcomes, including AD and mild cognitive impairment, as well as the rate of cognitive decline. All these indicate that the risk factor for cognitive decline may also be a risk factor for motor decline, or they share similar risk factors, such as AD pathology, which may contribute to the loss of cognitive and motor function in older individuals. There

could be other processes such as physical activity, in which motor function can be a proxy for the level of physical activity and a low level of physical activity may contribute to the loss of cognitive and motor function (2).

1.6 Physical fitness and muscle strength

Overall physical fitness can be defined as the ability to perform everyday activities vigorously and showing features and capacities associated with a low risk of developing disorders that are associated with physical inactivity (10). Further, physical fitness is one of the best predictors of an individual's future health condition and is connected with a lower chance of developing chronic diseases and dying prematurely (25). The most essential factors of physical fitness are muscular strength, muscular endurance, cardiorespiratory fitness, body composition, and flexibility. Muscle strength, along with cardiorespiratory fitness, are increasingly being recognized as factors in the development and prevention of chronic illnesses, inversely related to all-cause mortality and metabolic syndrome in both low and moderate cardiorespiratory fitness groups (10, 26). Establishing a clear link between muscle strength and cardiovascular health in older adults who experience frailty and sarcopenia, poses a significant challenge (26). Frailty is defined as possessing a poor state of health and lacking physical strength and is linked to the increased likelihood of developing disability, dementia, falls, hospitalizations, and mortality (5).

Muscle strength is affected by a wide variety of variables, including but not limited to chronological age, gender, genetics, diet, and the presence of any underlying medical conditions (27). Accelerated loss of muscle mass and muscle strength after the age of 65 years can cause sarcopenia, which should be considered when discussing muscle strength (11). Sarcopenia is defined as a gradual decline of skeletal muscle mass and strength along with physical performance after reaching a peak in early adulthood and its prevalence influenced and accelerated by age, gender, poor nutrition, physical inactivity, and comorbidities (11, 12). Sarcopenia can cause people to stop engaging in physical activity, and this decline in physical activity may lead to a decline in general health that has been associated with an increased risk of developing dementia (28). According to a 6-year study, older adults whose walking speeds were consistently slow or decreased over time were shown to have a much higher risk of cognitive decline and dementia, suggesting that slowed gait and decreased GS may play a role in the link between sarcopenia and cognitive decline (29). Mild cognitive impairment was also

found less common in people with higher muscle strength, compared to people with low muscle strength, and interestingly those with high muscle strength were 61% less likely to get AD (16). Cognitive decline with age may be a result of a general slowing of processing throughout the neural system, and reduced muscle strength may be an early indicator of this (30).

1.7 Aging and muscle profile

A decline in muscular mass and strength is observed with increased age (31). Decline in muscle mass and strength capacity during normal aging are characterized by atrophy of type II muscle fibers (32). The decline of muscle mass initiates at an annual rate of 1-2% after age 50 years. Muscle strength declines by 1.5% per year between the age of 50 and 60 years. This decline in muscle strength accelerates to 3% per year after the age of 60 years (31).

1.8 Grip strength as a biomarker of current status and future status

Muscle strength refers to a health-related component of physical fitness that relates to the ability of the muscle to exert force (7). Among all muscles such as respiratory, pelvic floor, and trunk muscles, limb muscle strength commonly becomes of interest. Of the many limb muscles, the muscles that provide GS are the most regularly measured (8). It is commonly measured because it is a simple and straightforward way to assess muscle strength and it is valuable in clinical settings because it can easily indicate an individual's current strength capacity (8). Due to the practicality, measuring GS using hand-grip dynamometry has become a widely adopted measure of overall strength (33). GS was proposed as a biomarker of aging and associated with important clinical measures such as current health status, predicting future outcomes, upper limb function, bone mineral density, fractures, falls, cognitive impairment, depression, quality of life, and all-cause and disease-specific mortality (8, 33). Bohannon's review in 2019 (33) identified GS as a crucial predictor of future outcomes such as complications, resource utilization, and discharge disposition. All these indicate that GS should be considered a vital sign in health screenings of middle-aged and older adults (33).

GS and cognitive function both diminish with age, and there is minimal evidence for a link between longitudinal rates of change in these variables (34). Furthermore, weak GS has been associated with an increased risk of mild cognitive impairment in middle-aged and older adults (35). In a review by Kobayashi et al. in 2018, 6 out of 7 studies documented a significant relationship between GS and cognitive function (36). GS may reflect alterations in nervous

system activity or white matter integrity, making it a potential early indirect noncognitive sign of cognitive decline or dementia (29, 37). Symptoms such as decreased mobility and balance, as well as impairments in executive function and memory, are common in the elderly with poor GS (38).

1.9 Aims and hypothesis

Few studies have examined the association of GS and AD cross-sectionally and longitudinally. To the best of my knowledge, no study has examined the association between GS and AD among apparently healthy older adults in a longitudinal study with a long-term exercise intervention. For this reason, we aimed to investigate the relationship between muscular strength and the risk of AD incidence in apparently healthy older adults. The primary aim of this study was to assess the association between GS and risk of developing AD in older adults aged 70-77 years at baseline. The secondary aim was to assess the association of AD incidence according to the change in GS from baseline to after one year of exercise intervention. We hypothesized that individuals with greater GS would have a reduced risk of developing AD during a 9-year follow-up period.

2 Material and methods

2.1 Study population

This was a prospective cohort sub-study of the Generation 100 Study. The Generation 100 Study is a randomized controlled trial study initiated in 2012. It was undertaken in Trondheim, Norway, specifically targeting residents aged 70 to 77 years (born between 1. January 1936 and 31. December 1942). Its primary aim of the Generation 100 Study was to study the effects of exercise training on morbidity and all-cause mortality (6). Clinical examinations of this study were at baseline, 1st, 3rd, 5th, and 10th year of the study. We used baseline and year-one (1st year) data for this research. The inclusion and exclusion criteria for the Generation 100 Study are presented in Table 1.

Table 1. Inclusion and exclusion criteria for the study population.

Inclusion criteria	Exclusion criteria
• Born between 1936 and 1942. • Capable of finishing the training schedule determined by the researchers. • Not taking part in any other research that could potentially interfere with this one.	• Illnesses or disabilities that make it impossible to exercise or make it hard to finish the study. • Uncontrolled high blood pressure. • Symptomatic valvular, hypertrophic cardiomyopathy, unstable angina, primary pulmonary hypertension, heart failure, or severe arrhythmia. • Diagnosed with dementia. • Cancer, or another illness that makes it impossible to participate or makes exercises dangerous. Taken one at a time and talked about it with the doctor. • Chronic infectious diseases that can be spread, and test results show that taking part in the study is dangerous. • Taking part in other studies that make it hard to take part in Generation 100.

In the Generation 100 Study a total of 6,966 older adults were invited to participate. The study included 1567 participants, with 790 of them being women. In this study, 122 participants did not have GS and lean muscle mass data at baseline. Also, there were 314 participants (21.7%) who dropped out after baseline testing and did not participate in year-one testing. In addition, 6 participants had onset of symptoms before 2014, 64 participants had a stroke, 28 participants had angina pectoris, and 2 participants had heart failure based on hospital reports from the start until the end of end of the follow-up period. All these were excluded from this study. Thus, 1031 participants (537 women) took part in this study, illustrated in the Flowchart in Figure 5.

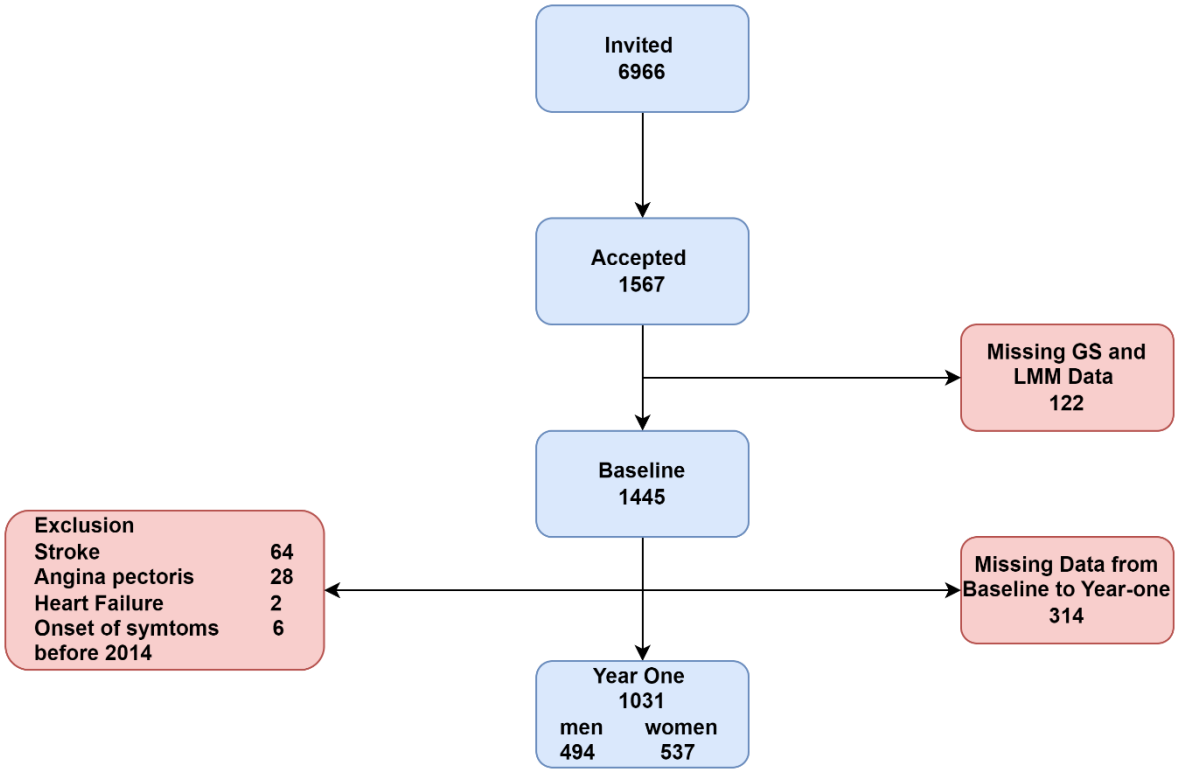

Figure 5. Flowchart of study population: Abbreviations: GS; grip strength, LMM; lean muscle mass.

Originally in the Generation 100 Study, the participants were divided into a control group (following Norwegian recommendation for physical activity, 30 minutes of moderate physical activity every day), moderate-intensity continuous training group (twice a week 50 minutes of exercise corresponding to 70% of peak heart rate) and high-intensity interval training group (twice a week 4x4 minutes high-intensity interval training with the intensity of 85-95% of peak heart rate). For more details about the intervention of the study, see Stensvold et al. (6). In our study, we did not divide participants based on exercise intervention intensity categories.

Instead, to assess the association between GS and AD incidence, we divided all participants into unfit and fit groups for both timepoints. The unfit group refers to the GS value which was below the sex-specific mean of baseline (15.2 $kg^{-0.67}$ for women and 18.5 $kg^{-0.67}$ for men) at both baseline and year-one and the fit group refers to the GS value which was above the sex-specific mean of baseline at both baseline and year-one. To assess the association between change in GS from baseline to year-one and AD incidence, we divided the participants into 4 categories of change: 1) unfit to unfit, for those who were below the sex-specific mean at both timepoints and we used that as the reference group, 2) unfit to fit, for those who were below the sex-specific mean at baseline and above the sex-specific mean at year-one, 3) fit to unfit, for those who were above the sex-specific mean at baseline and below the sex-specific mean at year-one, 4) fit to fit, for those who were above the sex-specific mean at both baseline and year-one.

2.2 Data collection

GS was measured using a JAMAR hydraulic hand dynamometer (Lafayette Instrument Company, United States of America (USA)). It includes a dual-scale readout that displays the isometric grip force from 0 to 90 kilograms and from 0 to 200 pounds. It was administered on a one-to-one basis, with the participant sitting in a chair with the upper arm close to the body, and elbow bent 90 degrees. The test was undertaken by squeezing the hand grip dynamometer as hard as they could. Participants were given 2 trials to reach maximal GS at baseline and 3 trials at year-one using the dominant hand. There was a short break from 30 seconds to one minute between each trial. GS was measured in kilograms and for our analysis we used the average of all trials performed at each time point. Lean muscle mass was measured using bioelectrical impedance (Inbody 720, BIOSPACE, Seoul, Korea). We obtained and used the lean muscle mass of the dominant arm, and to correctly adjust for differences in muscle mass (39, 40), we divided the GS (kg) on lean muscle mass (of the dominant arm) to the power of 0.67.

Blood samples were obtained from an arm vein and total cholesterol was measured using standard procedures at St. Olavs Hospital, Trondheim, Norway. Blood pressure was measured in a fasting state at rest. Hypertension was defined as systolic blood pressure ≥140 mmHg, and/or diastolic blood pressure ≥90 mmHg. Years of education were divided into 3 categories, less than 10 years, 10 to 12 years, and more than 12 years. Body mass index (BMI) was calculated as weight in kilograms divided by height in m^2.

Hospital records were reviewed by a process defined by neurologists at St. Olavs University Hospital in Trondheim, Norway, to identify individuals who later developed AD during the follow-up period. A neurologist reviewed the hospital medical records of participants who had the indicated diagnosis codes (F00-F03, G20, G30-G31, F10.7, R41.8, G12.2 from International Classification of Disease, 10th edition) or search words (dementia, demented, alzheimer, Alzheimer's, cognitive, memory, delirious, confusion, normal pressure hydrocephalus, "mess up", forgetful, disoriented, oriented, cholinesterase) and if cognitive impairment, neurodegenerative illness, or dementia was identified, relevant medical history information was noted. Then, the criteria for AD of Albert and McKhann (41, 42) were used to assess whether the patient met the criteria for having AD. Those who fulfilled these criteria and had onset of symptoms on after January 1, 2014, were included in the study. Participants who experienced cognitive impairment before 2014 were excluded. The date of participation in the 1-year testing was defined as the baseline for AD incidence follow-up and the follow-up period was set to end on December 31, 2021, because it was the last day with updated patient records on AD incidence and health status. Individuals were tracked until the onset of AD symptoms, death, or end of follow-up in December 2021 (31.12.2021). Time to AD incident was determined from the year-one testing date to the onset of symptoms. The initial day of symptoms reported by the patient or their next of kin (supplementary material) was used to determine the onset of symptoms.

2.3 Statistical analysis

Descriptive statistics were calculated using IBM SPSS Statistics 28.0 (IBM Corporation, Chicago, IL). To assess the data distribution, we checked for the normality of residuals through QQ plots and histograms. Visual inspections of AD cases and GS at both timepoints were conducted using scatter plots. For descriptive data, we reported numbers, percentages, arithmetic mean, and standard deviation and performed a one-sample T-test for continuous variables, while using χ^2 test for frequency distribution and percentage for categorical variables. The first descriptive table was created for three groups: first group, containing all participants and the second and third groups for participants who were categorized as 'unfit' and 'fit' based on the sex-specific mean of baseline GS. The second descriptive table was created for four groups based on the change in GS from baseline to year-one. To compare the GS and BMI at both timepoints we employed a paired sample T-test. To assess the risk ratio at both baseline and year-one we used continuous variables and performed the Cox proportional hazard model.

To assess the hazard ratio (HR) according to the change in GS from baseline to year-one (categorized into 4 groups) Cox proportional hazard regression analysis was used. Due to the limited number of AD cases (2.5%) relative to the study population, we adjusted for sex and educational level, which are known risk factors for AD separately each one at a time as covariates. To assess the correlation coefficient (R) and coefficient of determination (R-squared) linear regression analysis was conducted to find out the proportions of variances in the GS that were explained by independent variables such as BMI and height. Effect estimates were presented as HR. All tests were two-tailed, applied 95% confidence intervals (CI), and considered statistically significant p-value <0.05. For infographic visualization, PowerPoint was utilized and the flowchart was created using Draw.io.

2.4 Ethical consideration

The Generation 100 Study has approval from the Regional Ethics Committee (REK, 2012/381). All the participants voluntarily took part in the Generation 100 Study and provided written consent before participating. This master's thesis was a part of the 'Fitness and blood factors in Generation 100 and risk of dementia' study which also received approval from REK (183708).

3 Results

3.1 Baseline and year-one grip strength and risk of Alzheimer's disease

We included 1031 older adults (48% were men, 53% had higher education) that at baseline had a mean age of 72.2±1.9 years, BMI of 25.7±3.4 kg/m^2, fat percentage of 29.9±7.9, total cholesterol of 5.7±1.1 mmol/L, whom 33% had hypertension, and 11% had a CVD history, and no-one had known cognitive impairment. GS for the entire study population at baseline and year-one ranged from 7.4 kg$^{-0.67}$ to 39.1 kg$^{-0.67}$ and 6.0 kg$^{-0.67}$ to 29.0 kg$^{-0.67}$, respectively. The mean GS was 21.6% ($p<0.001$) higher in men (18.5±3.1 kg$^{-0.67}$) than in women (15.2±2.6 kg$^{-0.67}$). Table 2 presents the baseline characteristics of the participants according to the GS level.

Table 2. Baseline physiological characteristics of participants according to grip strength level.

	Total	Unfit	Fit	p-value
Participants, n (%)	1031	517 (50.1)	514 (49.9)	
Sex (%)				
Men	494 (47.9)	243 (47.7)	251 (48.1)	…
Women	537 (52.1)	266 (52.3)	271 (51.9)	<0.001
Age (SD) years	72.5 (2.0)	72.5 (2.1)	72.1 (1.9)	<0.001
GS (SD) $kg^{-0.67}$	16.8 (3.3)	14.6 (2.3)	19.0 (2.6)	<0.001
BMI (SD) kg/m^2	25.8 (3.4)	26.3 (3.6)	25.3 (3.1)	<0.001
Fat% (SD)	29.9 (7.9)	30.8 (8.3)	29.0 (7.4)	<0.001
TC (SD) mmol/L	5.7 (1.1)	5.7 (1.1)	5.8 (1.1)	<0.001
Years of Education (%)				
<10	136 (13.7)	66 (13.5)	70 (13.9)	…
10-12	333 (33.5)	170 (34.7)	163 (32.3)	…
>12	526 (52.9)	254 (51.8)	272 (53.9)	0.721
Hypertension (%)				
No	686 (66.8)	344 (67.6)	342 (65.8)	…
Yes	341 (33.2)	163 (32.1)	178 (34.2)	0.479
CVD (%)				
No	918 (89.0)	445 (87.4)	473 (90.6)	…
Yes	113 (11.0)	64 (12.6)	49 (9.4)	0.102
Smoking (%)				
Never or stopped	912 (93.1)	447 (92.4)	472 (93.8)	…
Occasionally	27 (2.7)	13 (2.7)	14 (2.8)	...
Regular	41 (4.2)	24 (5.0)	17 (3.4)	0.461
BHC (%)				
No	984 (98.0)	479 (97.4)	505 (98.6)	…
Yes	20 (1.9)	13 (2.6)	7 (1.4)	0.148

Data are presented in Table 2 as number, frequency, arithmetic mean, standard deviation, and P value. Group differences were examined by using a T-test for continuous variables, and $\chi 2$ tests were used for proportions of categorical variables. BMI is calculated as weight in kilograms divided by height in m^2. Hypertension was defined as systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg. Years of education were divided into 3 categories, less than 10 years, 10 to 12 years, and more than 12 years. The unfit group refers to the values of GS that were below the sex-specific mean of baseline, the fit group refers to the values of GS that were above the sex-specific mean of baseline. Abbreviations: N; number, GS; grip strength, BMI; body mass index, Fat%; body fat percentage, TC; total cholesterol, CVD; cardiovascular disease, BHC; bad health condition.

Those who were in the fit (above sex-specific mean GS level) category had a lower BMI (3.8%, p<0.001), lower cholesterol levels (1.7%, p<0.001), and lower body fat percentage (5.8%, p<0.001) at the start of the study compared with those below the sex-specific average (unfit). Over a mean follow-up period of 7.7±0.8 years, 26 participants (2.5%; 14 men) developed AD. Those who developed AD had a mean follow-up of 3.2±1.7 years, age of 72.4±2.2 years, and

BMI of 25.7±3.2 kg/m^2. We did not find a significant association between higher GS at baseline or at year-one with a reduced risk of developing AD. HR was 1.05 with 95% CI of 0.91–1.19, and HR; 0.99, 95% CI 0.87–1.13, respectively (Appendix 4, Table 5).

3.2 Rate of change in grip strength from baseline to year-one

Table 3 presents the physiological characteristics of participants according to the change in GS. This cohort exhibited significant diversity, with the rate of change in GS ranging from -23.7 $kg^{-0.67}$ to 9.7 $kg^{-0.67}$. Those who developed AD during follow-up had decreased GS by -0.4±1.3 $kg^{-0.67}$ (p=0.08) over one year of intervention, not different from those who remained healthy till the end of follow-up (-0.1±2.0 $kg^{-0.67}$, p=0.11). The mean GS at baseline was 16.8±3.3 $kg^{-0.67}$ for all participants, 18.5±3.1 $kg^{-0.67}$ for men, and 15.2±2.6 $kg^{-0.67}$ for women. The GS from baseline to year-one for women who later developed AD (12 participants) decreased by 4% (-0.7±0.8 $kg^{-0.67}$, p<0.01) compared to a 2% decrease (-0.3±1.8 $kg^{-0.67}$, p<0.001) among women who did not develop AD during follow-up period. Changes in GS in the men's group for those who later developed AD (14 participants) and those who did not develop AD during follow-up were -0.2±1.6 $kg^{-0.67}$, p<0.59 and 0.1±2.2 $kg^{-0.67}$, p<0.07, respectively (Appendix 6, Table 7).

Table 3. Physiological characteristics of participants according to the change in grip strength.

	Baseline unfit		Baseline fit		p-value
	Y1 unfit	Y1 fit	Y1 unfit	Y1 fit	
Participants, n (%)	401 (39.9)	108 (10.5)	124 (12)	398 (38.6)	
Sex (%)					
Men	187 (46.6)	56 (51.9)	46 (37.1)	205 (51.5)	<.001
Women	214 (53.4)	52 (48.1)	78 (62.9)	193 (48.5)	<.001
Age (SD) year	72.4 (2.0)	72.4 (2.1)	72.3 (1.9)	72 (1.9)	<.001
GS (SD) $kg^{-0.67}$	14.1 (2.3)	15.8 (1.8)	17.6 (2.6)	19.4 (2.4)	<.001
BMI (SD) kg/m^2	26.4 (3.7)	25.6 (3.3)	25.6 (3.4)	24.9 (2.9)	<.001
Fat% (SD)	31.3 (8.2)	28.7 (8.2)	32.1 (6.7)	28 (7.2)	000
TC (SD) mmol/L	5.7 (1.1)	5.6 (1.0)	5.7 (1.0)	5.7(1.1)	<.001
Years of Education (%)					
<10	53 (13.7)	13 (12.6)	19 (16.1)	51 (13.2)	…
10-12	134 (34.6)	36 (35.0)	41 (34.7)	122 (31.5)	…
>12	200 (51.7)	54 (52.4)	58 (49.2)	214 (55.5)	0.898
Hypertension (%)					
No	399 (66.7)	78 (72.2)	80 (65.0)	262 (66.0)	…
Yes	133 (33.3)	30 (27.8)	43 (35.0)	135 (34.0)	0.632
CVD (%)					
No	346 (86.3)	99 (91.7)	118 (95.2)	355 (89.2)	…
Yes	55 (13.7)	9 (8.3)	6 (4.8)	43 (10.8)	0.034
Smoking (%)					
Never or stopped	352 (92.1)	95 (93.1)	110 (95.7)	362 (91.3)	…
Occasionally	12 (3.0)	1 (1.0)	2 (1.7)	12 (3.1)	….
Regular	18 (4.5)	6 (5.9)	3 (2.4)	14 (3.6)	0.669
BHC (%)					
No	377 (97.2)	102 (98.1)	118 (95.2)	387 (97.2)	…
Yes	11 (2.7)	2 (1.9)	2 (1.7)	5 (1.3)	0.473

Data are presented in Table 3 as number, frequency, arithmetic mean, standard deviation, and P value. Group differences were examined by using the T-test for continuous variables and the $\chi 2$ tests were used for proportions of categorical variables. BMI is calculated as weight in kg divided by height in m^2. Hypertension was defined as a systolic blood pressure ≥140 mmHg and a diastolic blood pressure ≥90 mmHg. Years of education were divided into 3 categories, less than 10 years, 10 to 12 years, and more than 12 years. Unfit to unfit, for those who were below the sex-specific mean at both baseline and year-one. Unfit to fit, for those who were below the sex-specific mean at baseline and above the sex-specific mean at year-one. Fit to unfit, for those who were above the sex-specific mean at baseline and below the sex-specific mean at year-one. Fit to fit, for those who were above the sex-specific mean at both baseline and year-one. Abbreviations: Y1; year-one, N; number, GS; grip strength, BMI; body mass index, Fat%; body fat percentage, TC; total cholesterol, CVD; cardiovascular disease, BHC; bad health condition.

3.3 The risk of Alzheimer's disease according to the change in grip strength

In the main analysis, there was no significant association between change in GS from baseline to year-one and the incidence of AD. As presented in Table 4, the HR was 0.32 (95% CI 0.04-

2.50) for those who changed from fit to unfit, HR; 0.36 (95% CI 0.04-2.88) for those who changed from unfit to fit, and HR; 1.14 (95% CI 0.62-3.18) for those who remained fit at both timepoints, compared with those who remained unfit at both timepoints. When controlling for the effect of sex as a confounder for the relationship between change in GS and AD, the result remained insignificant (HR; 0.82, 95% CI 0.38–1.78) for men compared to women. Further, controlling for the educational level did not alter the results for men (HR; 1.10, 95% CI 0.58–2.09) or women (HR; 2.34, 95% CI 0.91–6.00) with a high education level when compared to their peers with a lower level of education.

Table 4. Hazard ratio of Alzheimer's disease according to change in grip strength for the categorized variables.

	Year-one unfit	**Year-one fit**
Baseline unfit, n (%)	391 (38%)	107 (10%)
Events	10 (4 men, 6 women)	1 (man)
HR (95% CI)	ref	0.36 (0.04-2.88)
Baseline fit, n (%)	123 (12%)	384 (37%)
Events	1 (man)	14 (8 men, 6 women)
HR (95% CI)	0.32 (0.04-2.50)	1.14 (0.62-3.18)

Data is presented in Table 4 as numbers, percentages, exponent hazard ratio (Beta Exp (B)) and 95% confidence interval. Unfit to unfit, for those who were below the sex-specific mean at both timepoints we used that as the reference group. Unfit to fit, for those who were below the sex-specific mean at baseline and above the sex-specific mean at year-one. Fit to unfit, for those who were above the sex-specific mean at baseline and below the sex-specific mean at year-one. Fit to fit, for those who were above the sex-specific mean at both baseline and year-one. Abbreviations: N; number, HR; hazard ratio, CI; confidence interval, N; number, ref; reference.

Considering the change from baseline to year-one (Table 4), 391 participants (38%) remained unfit, 123 participants (12%) decreased their GS from fit to unfit, 107 participants (10%) increased their GS from unfit to fit, and 384 participants (37%) remained fit at both timepoints. Among those participants who developed AD during follow-up, 10 participants (4 men, 6 women) remained unfit at both timepoints, 1 man participant decreased from fit to unfit group; 1 man participant improved from unfit to fit group; and 14 participants (8 men, 6 women) remained fit at both timepoints.

3.4 Grip strength, other covariates, and risk of Alzheimer's disease

Since decreased GS might have been affected by muscle degenerative diseases, we repeated the core model after excluding 40 participants (of whom 3 later developed AD) who had muscle degenerative diseases, 9 participants with Parkinsonian signs, and 2 participants with cerebral palsy. The association between GS and AD at both timepoints and the change from baseline to year-one remained unchanged (for baseline HR; 1.08, 95% CI 0.96–1.21). In subsequent analysis, we examined whether the association between GS and AD was affected by BMI, as both extremely low and extremely high BMI have been linked to a negative impact on health. First, we performed a simple linear regression model to assess the proportion of variances in GS, which is explained by BMI. We observed a modest correlation between GS and BMI only at baseline, where approximately 5% of the variance in GS could be explained by BMI (R^2 = 0.05). Remarkably, when we adjusted for the effect of BMI, higher BMI (≥30) compared to lower BMI (<30), we found that the association between baseline GS and the risk of AD remained unaffected (HR; 0.83, 95% CI 0.38–1.82). Moving forward, we also explored the influence of height on GS and its link to AD risk. Approximately 7% of the variance in GS could be attributed to height (R^2 =0.07). However, when we controlled for the effect of height, we found no significant association between GS and the risk of AD (HR; 1.00, 95% CI 0.96–1.05).

To address the possibility that our findings were influenced by the inclusion of participants with undiagnosed or late-stage and severe AD, we excluded 8 participants who developed AD within the first and/or second year of follow-up. This exclusion did not alter the association between baseline GS and risk of AD (HR; 1.05, 95% CI 0.92–1.20). Additionally, we examined the influence of age on GS level among our participants and observed an inverse association; for every year increase in age, GS decreased by -0.1 $kg^{-0.67}$(p=0.003). Furthermore, when we controlled for the effect of age on the association between GS and AD, we found no significant change (HR; 1.05, 95% CI 0.86–1.27).

Finally, we compared the characteristics of 314 participants (21.7%) who dropped out from baseline to year-one with those of the participants who participated in year-one tests. Among them, 53% were women, GS was lower (p<0.001), age (p<0.001) and BMI (p<0.001) were higher, and more had a history of CVD (p<0.001) (data not shown).

4 Discussion

The present study investigated the association between GS and the risk of developing AD over the next 9 years (mean follow-up time 7.7±0.8 years) in a population of 1031 older adults (72.2±2.0 years at baseline) who did not exhibit any cognitive impairment at baseline. The main findings of the present study were that we did not observe any association between GS and risk of developing AD, either at the baseline, year-one or at the change from baseline to one year follow-up. The results persisted even after adjusting for confounding variables such as sex, BMI, height, CVD, and educational level in a pooled population and for sex-specific groups. Thus, the observed results did not support the hypothesis that greater GS was associated with a lower risk of developing AD. The results remained statistically insignificant after conducting sensitivity analyses where we excluded participants with CVD and muscle degenerative disease, indicating no association between higher GS and reduced risk of AD incidents.

The findings in our study are not in line with the main existing knowledge in the literature (16, 43-46). Buchman et al. conducted a longitudinal study over 9 years with 877 older adults (79.3±6.4 years, 269 men) in the USA without dementia at baseline. In that study, 15.1% developed AD during follow-up. They reported a significant association between GS and AD, each one-pound lower GS at baseline was associated with a 1.4% increased risk of AD, and each one-pound decline in annual rate in GS was associated with a 9% increase in risk of AD compared to a person with no change in GS. As in our study, they used a JAMAR hydraulic hand dynamometer to objectively measure GS. We used a kilogram scale, but they used a pound scale. They measured cognitive function using clinical evaluation, medical history, neurologic examination, and cognitive performance testing (46). The discrepancy in results between our study and the mentioned study (46) may be explained by several factors. Firstly, Buchman et al. had 9 years of test follow-up with repeated measures of GS and cognitive function tests every year, whereas we had only one year of test follow-up for GS, which may be too short to see clinically meaningful change in GS and AD development. Secondly, they measured cognitive function in addition to AD diagnosis along with GS to see the rate of change in both GS and cognitive function during the time, whereas we only obtained reports for AD cases from neurologists who reviewed hospital records as we did not have data on the rate of change in cognitive performance during the time of this study. Thirdly, although similar sample size as theirs (46), we had a relatively small sample size considering that we only

followed changes in GS over a year. In line with this notion, most studies that reported a significant association between GS and AD (44) mainly had more participants included than what we had in our study. It is also important to note that we had very few cases of AD (2.5% in our study) compared to other studies (16, 46) which demonstrated that almost 15% of participants developed AD. This lower rate of AD cases indicates that our study population was very healthy compared to other studies' populations.

The mean follow-up period for our study was 7.7±0.8 years, whereas the mean onset of symptoms was after 3.2±1.7 years, which is relatively close to the end of the one-year intervention. Notably, there were very few AD cases during the follow-up period. We conducted a sensitivity analysis, excluding 8 participants (around one-third of cases) who received an AD diagnosis within the first and/or second year of follow-up and found that this exclusion did not alter the association between GS and the risk of AD in this population. Possible explanations for this first could be selection bias, excluding participants who have had a higher risk of developing AD in the main Generation 100 Study, or on the other hand, our participants did not represent the general population of the Trondheim region in Norway, where the study was undertaken. In that region there is an 8.3% prevalence of AD for the population aged 70 years and over (14.6% prevalence of dementia, the most prevalent dementia subtype is AD with 57%) from diverse physical and cognitive conditions (19). Given that AD pathogenesis occurs decades before clinical symptoms manifest (3), for the participants diagnosed within the first two years of the follow-up, the disease may have already progressed to the point where they could not experience the same beneficial modifying effect of exercise intervention on AD or dementia. Furthermore, better health conditions and high physical activity that were reported at the start of the Generation 100 Study, could skew the incidence rate of AD cases.

There exist studies that suggest that using GS as a standalone predictor of total strength may not reflect the overall strength capacity of a person. Thus, it may be crucial to evaluate lower limb strength in addition to GS to provide a more accurate picture of overall strength (33). Patricia Boyle and her colleagues (16) conducted a longitudinal study using a composite measure of muscle strength from 10 different muscle groups in addition to the GS to study the association between muscle strength and the risk of AD. They had a 3.5-year follow-up on around 1000 American residents with a mean age of 80.3±7.5 years. In that study, 138 people (14%) developed AD throughout the study's follow-up period. They discovered that each unit

increase in muscle strength from all muscle groups (based on 11 muscle groups) was associated with a 43% lower incidence of AD. According to their suggestion and based on our results by using only GS values, a comprehensive strength assessment may be more effective in identifying those at risk of cognitive impairment and AD.

4.1 Link between biological and cognitive aging

In our study population, the mean GS of men and women participants before adjusting for differences in muscle mass (39, 40) were 43.8±7.5 kg and 26.4±5.0 kg, respectively. These values are nearly 17% higher compared to the reference values calculated for these participants (36.3±3.2 kg for men and 22.7±1.9 kg for women) using the formula defined by Wang in 2018 (47). It is noteworthy that the observed GS values were even higher than the reference values for individuals aged 60-69 years (48). The higher observed GS confirms the high fitness level of our participants when entering the Generation 100 Study. Furthermore, our study's participants were active and healthy members of society; only 2% reported having bad health conditions at the start of the study. Additionally, when looking at the prevalence of AD among age groups (3% < 65 years old) (49) the participants in our study had an even lower prevalence rate of AD (2.5%) for the reference value for age below 65 years. These observations highlight the limitations of measuring age only chronologically.

To deal with the limitations of chronological age, there is another measure called biological age (63,65), which may be more useful in aging studies. Biological age explores the way vital physiological systems and processes function. It provides a better understanding of a person's physical health in relation to their lifespan (50). For example, as mentioned by MacDonald et al. (45), two people may both be 60 years old, but if one has CVD and the other is healthy, the one with CVD is biologically older. Researchers are interested in studying the biological part of cognitive aging because it can tell us how our minds change as we age. In a study linking biological and cognitive aging, MacDonald et al. (45), measured GS, peak expiratory flow, blood pressure, visual and auditory acuity, and BMI together with the measurement of 5 cognitive domains: verbal processing speed, working memory, reasoning, episodic memory, and semantic memory, in 125 adults aged between 67-95. The results of this study showed that biological age, which is based on a person's physical and cognitive capabilities, maybe a better predictor of cognitive decline and dementia than chronological age. They showed that biological age predicts actual cognitive change independent of chronological age. Also,

chronological age is a proxy for environmental and biological influence (50). Based on the data obtained from our participants with 17% higher GS and a lower rate of AD incidence compared to their chronological age reference values, with a better health condition and higher activity level, on one hand, they may suggest that participants in our study were biologically younger than their chronological age and on the other hand may support MacDonald's findings that biological age may be a better predictor of cognitive decline and dementia than chronological age.

4.2 Effect of exercise intervention on muscle strength

As mentioned before, a decline in muscle mass and strength is observed with increasing age (34). This decline begins at 1.5% per year after age 50 and accelerates to 3% per year after age 60 years (34). Our study participants showed surprisingly low decreases in GS; those who later developed AD exhibited a 2.5% decrease in GS from baseline to one year, whereas those who remained healthy showed only a 0.5% decrease in GS. When examining the impact of gender differences on the change in GS following one year of intervention, distinct patterns emerged among both AD and non-AD groups. Among participants with AD, women exhibited a more pronounced decrease in GS (4%) compared to men (1%). Within the non-AD groups, women displayed a 2% decrease in GS, while men demonstrated a 1% increase in GS. These findings suggest that aerobic exercise played a crucial role in not only preventing age-related muscle strength decline but even leading to potential improvements in muscle strength within this population, as well as suggest that in this study's population gender significantly influences the impact of aerobic exercise intervention on muscle strength.

Another plausible explanation for the low number of AD cases could be associated with the participants who dropped out of the study from baseline to year-one testing. As indicated in our analysis, a significant proportion of participants (21.7%) discontinued their participation and did not undergo year-one GS testing. Notably, this subgroup exhibited distinct characteristics at baseline, indicating lower GS, BMI, and higher reports of CVD. Firstly, it is worth considering the possibility that this group may have had a higher chance of AD, compared to those who have participated in both baseline and year-one testing and showed higher GS, which might have influenced the overall AD case numbers. Secondly, the potential reasons for this dropout from baseline to one year are still not clear, and this dropout may have had an impact on statistical power for reliable results.

It's possible that the diagnostic criteria used in our study were one of the reasons why we didn't find as many cases as other researchers did. AD can be hard to diagnose reliably. To ensure that the cases that had been diagnosed were AD or not, for example, vascular dementia, we used strict criteria that were set up by the neurologist of the project. It's possible that other studies didn't employ as clearly defined criteria. Repeating this study with the same cohort, but extending the follow-up period to 5-10 years from now and using the same strict diagnostic criteria for AD diagnoses, might provide a more accurate understanding of the association between GS and AD.

4.3 Strengths and weaknesses

Strengths of this study include that we used data from the Generation 100 Study, the largest randomized controlled trial in older adults worldwide, objective measure of GS, obtaining AD diagnosis with defined criteria from a neurologist systematically going through all hospital reports rather than relying on the questionnaire for data collection, and assessing only association between GS and AD with apparently healthy older adults at baseline. However, the study had some limitations, such as a short follow-up time for the muscle strength test, a small study population, and a small number of AD cases leading to poor statistical power. Potential selection bias that may have resulted in the study population not representing the general population, lack of whole-body muscle strength assessment, and dropout rate and its potential impact on statistical power are other limitations in the study.

4.4 Conclusion

In conclusion, our study demonstrated no statistically significant association between baseline GS and the risk of developing AD. Change in GS from baseline to one year of intervention was not associated with the development of AD. As a result, there was no evidence to imply that individuals with higher GS have a lower risk of AD. In the future, using data from baseline to the end of the Generation 100 Study encompassing not only GS but also other muscle structures and function (e.g., leg strength, walking test, and balance), as well as brain structure and function with a longer follow-up period we can assess the change in muscle strength and cognitive function longitudinally as well as assessing which variables play the role on and drives others in the association between muscle strength and cognitive function and AD. This comprehensive approach will enable us to better understand the association between these factors during aging and will contribute to more reliable knowledge.

5 References

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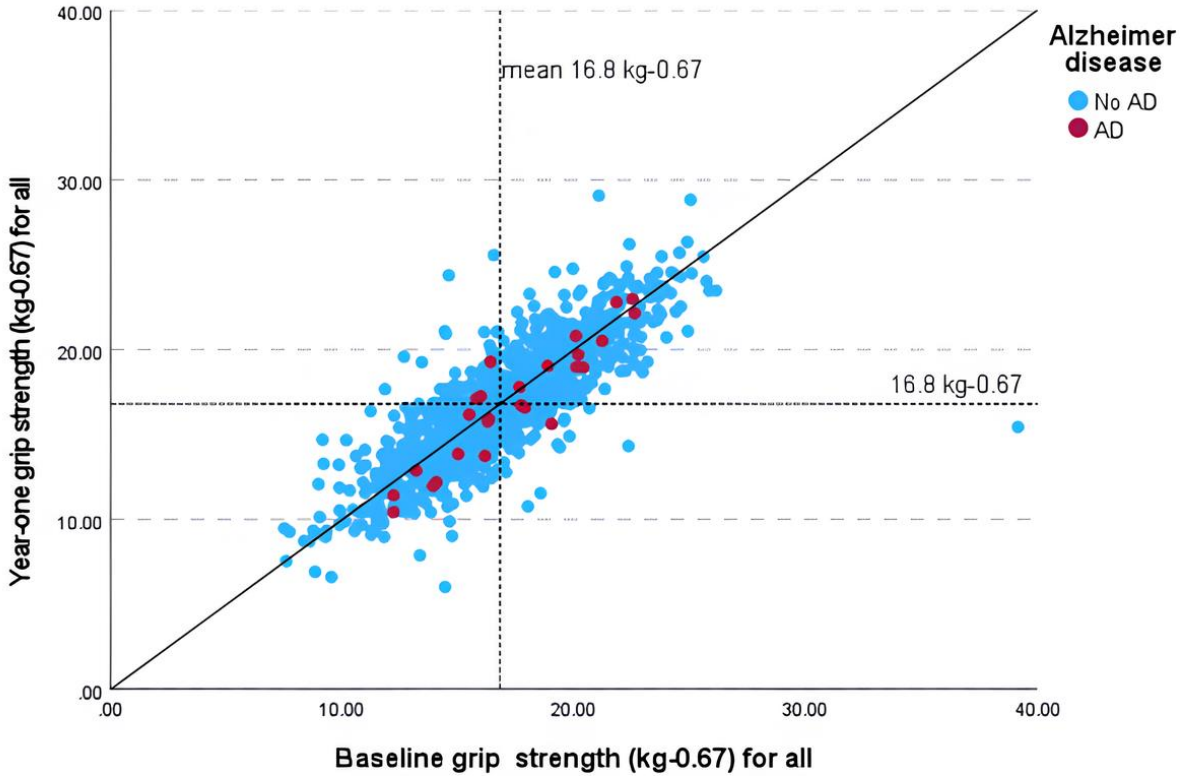
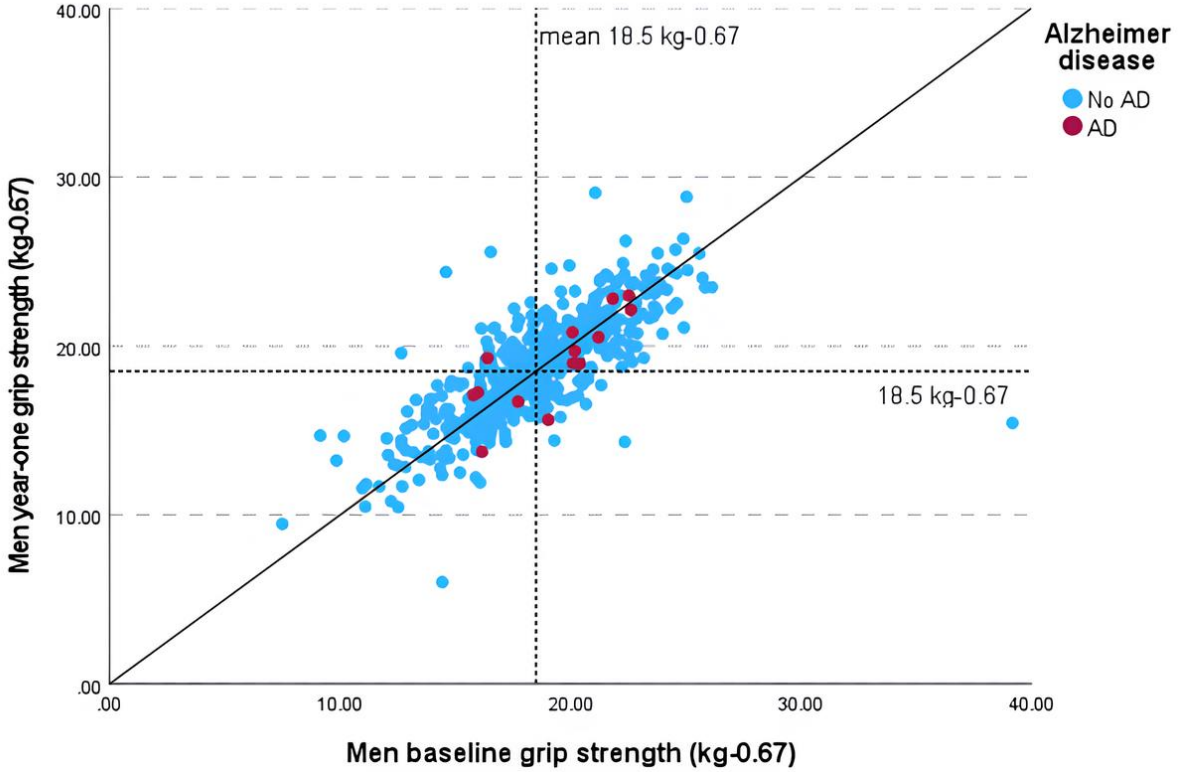
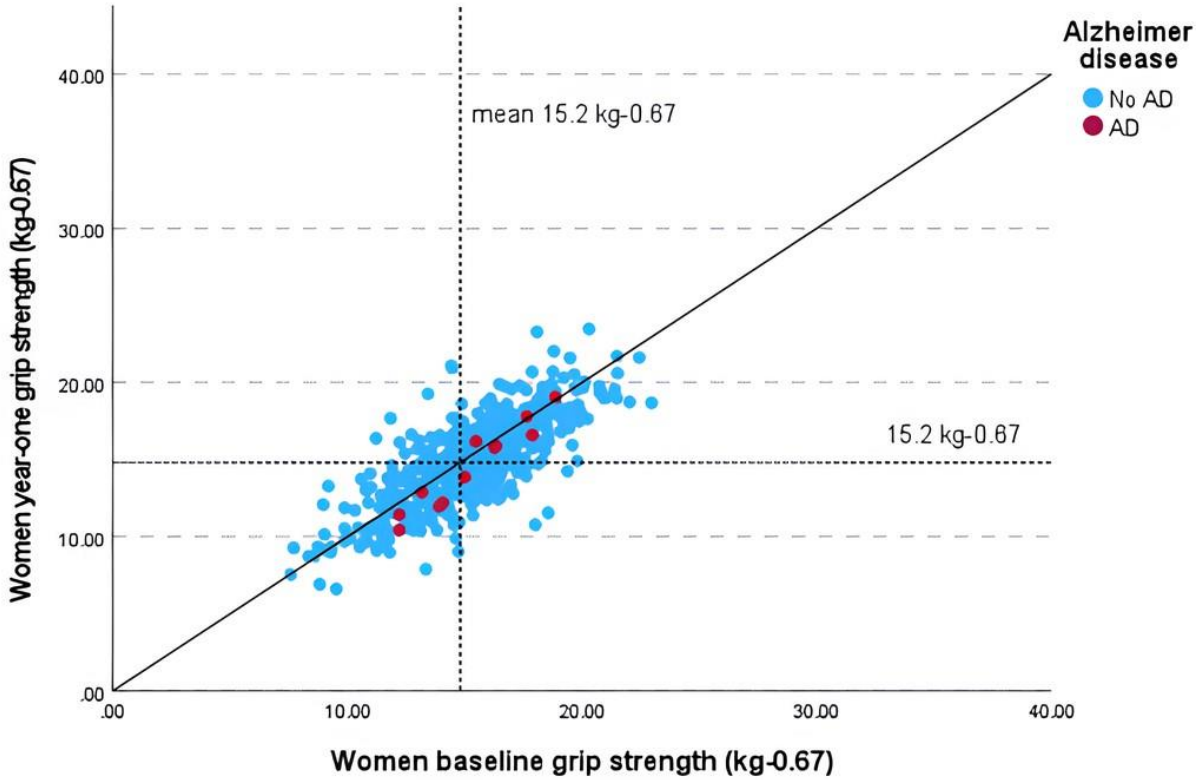
6 Appendix



Appendix 1, Figure 6. Scatter plot of grip strength at baseline and year-one in all participants with and without subsequent AD.



Appendix 2, Figure 7. Scatter plot of grip strength at baseline and year-one for men participants with and without subsequent AD.



Appendix 3, Figure 8. Scatter plot of grip strength at baseline and year-one for women participants with and without subsequent AD.

Appendix 4, Table 5. Association between grip strength and risk of Alzheimer's disease at baseline and year-one for continuous variables.

characteristics	HR	95% CI
All Baseline GS $kg^{-0.67}$	1.05	.91-1.19
All Year-one GS $kg^{-0.67}$	0.99	.87.-1.13
Men's Baseline GS $kg^{-0.67}$	1.06	.91-1.25
Men Year-One GS $kg^{-0.67}$	1.02	.86-1.21
Women's Baseline GS $kg^{-0.67}$	1	.80-1.24
Women Year-one GS $kg^{-0.67}$	0.95	.78-1.17

Data presented in Table 5, shows the result of Cox proportional hazard model for the association between change in grip strength and risk of AD at two timepoints for continuous variables adjusted for sex and educational level covariates. Data presented as hazard ratio (HR) and 95% confidence interval. Abbreviation, GS; grip strength.

The result of multiple regression analysis in Appendix 5 Table 6 shows that 2-5% of variances in GS is explained by BMI compared to 6-7% of the variance in GS which is explained by height.

Appendix 5, Table 6. Multiple regression analysis. The proportion of variances in grip strength is explained by body mass index and height at two timepoints.

Pearson's correlation coefficient	R	R squared	The standard error of the estimate
BL BMI/ GS $kg^{-0.67}$			
Men	0.15	0.02	3.12
Women	0.17	0.03	2.27
Y1 BMI/ GS $kg^{-0.67}$			
Men	0.19	0.03	3.06
Women	0.22	0.05	2.71
BL H / GS $kg^{-0.67}$			
Men	0.26	0.07	7.29
Women	0.28	0.07	4.80
Y1 H / GS $kg^{-0.67}$			
Men	0.26	0.06	7.45
Women	0.25	0.06	4.92

Data is presented in Table 6, as correlation coefficient (R) and coefficient of determination (R squared) to assess the contribution of each predictor variable, BMI and height, in explaining variance in grip strength as the dependent variable. Abbreviations: BL; baseline, Y1; year-one BMI; body mass index, GS: grip strength, H; height.

Appendix 6, Table 7. Paired sample T-test comparing the grip strength of participants from baseline to year-one.

Groups	Grip Strength at baseline $kg^{-0.67}$	Grip Strength at Year-one $kg^{-0.67}$	Mean change of Grip Strength from Baseline to Year-one $kg^{-0.67}$	Change in Grip Strength (%)	P value
All non-AD (SD)	16.7 (3.3)	16.6 (3.5)	-0.1 (2.0)	0.5 % decrease	0.11
All AD (SD)	17.4 (3.0)	16.9 (3.5)	-0.4 (1.3)	2.7 % decrease	0.08
Men non-AD (SD)	18.5 (3.1)	18.6 (3.1)	0.1 (2.2)	1% increase	0.07
Men AD (SD)	19.2 (2.4)	19.0 (2.7)	-0.2 (1.6)	1% decrease	0.59
Women non-AD (SD)	15.2 (2.6)	14.8 (2.7)	-0.3 (1.8)	2% decrease	<.001
Women AD (SD)	15.2 (2.2)	14.4 (2.7)	-0.7 (0.8)	4% decrease	0.01

Data presented in Table 7, as arithmetic mean, standard deviation, and percentage of change in grip strength from baseline to year-one. Abbreviation: M; mean, SD; standard deviation, AD; Alzheimer's disease, Sig; significance level.

Comparing change in grip strength from baseline to year-one, female participants who developed AD during follow-up had the highest decrease among the groups with a 4% decrease

in grip strength. Men participants who did not developed AD had increased GS by 1% from baseline to end of one year.

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