Effect of various exercises on frailty among older adults with subjective cognitive concerns: a randomized controlled trial

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Conflicts of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Abstract

BACKGROUND:

Physical exercise has been linked to reduced frailty but there is insufficient evidence of beneficial effects in community-dwelling older adults with subjective cognitive concerns.

OBJECTIVE:

This study aimed to clarify the effects of physical exercise in this population.

DESIGN: Single-blind randomized controlled trial

SETTING: Toyota, Japan

PARTICIPANTS:

Residents aged 65–85 years were screened using the Kihon checklist; those with subjective cognitive concerns were invited for eligibility assessment. In total, 415 community-dwelling older adults were enrolled and randomized.

Methods:

This trial investigated the effects of aerobic training(AT), resistance training(RT), and combined training(AT+RT) programs on reducing frailty. All participants were randomized into one of the three intervention groups or the control group. Participants in the intervention groups underwent a group training program and self-paced home training for 26 weeks. The control group received lectures about health promotion. A 95-item frailty index(FI) was utilized to determine the effects of training. Participants were followed up at weeks 26 and 52.

RESULTS:

At baseline, mean age of all participants(47% women) was 72.3±4.6 years, with mean FI score of 0.3±0.1. Compared with control group, AT improved total FI by 0.020(CI −0.039 to −0.001,effect size −0.275) and the depression and anxiety component of FI by 0.051(CI −0.084 to −0.018,effect size −0.469) at week 26, but the effects waned at week 52. No significant differences in FI were found in RT and AT+RT groups at week 26 and 52.

CONCLUSIONS:

A 26-week aerobic training reduced frailty modestly, especially in the depression and anxiety component, in older adults with subjective cognitive concerns.

Key words: frailty, cognition, anxiety, depression, physical training

Key points:

1. Aerobic training potentially reverses frailty, especially in the depression and anxiety component, in older adults with subjective cognitive concerns.

2. Using a comprehensive tool such as Frailty Index to assess intervention effects is warranted.
3. Home-based exercise program with minimal equipment and space is worth incorporating into management of frailty.

Introduction

Frailty has been widely shown to be associated with poor health outcomes, including falls, disability, hospitalization, institutionalization, and mortality[1]. A growing body of evidence suggests that multifactorial interdisciplinary intervention, including exercise intervention and nutrition support, may prevent disability[2]. Physical activity consisting of resistance training (RT) and aerobic training (AT) has demonstrated additional benefits for reducing frailty[3, 4]. However, most such trials have been conducted exclusively in cognitively intact older adults[4, 5].

Cognition may affect the beneficial effects of exercise intervention on frailty[6]. Besides mild cognitive impairment (MCI)[7], subjective memory concerns are reported to be an indicator of frailty in cognitively intact older adults[8]. Some interventional studies have shown positive effects of physical activity programs on physical and cognitive function in MCI and dementia patients[6, 9], but stronger evidence is required to support such findings. Additionally, the benefits of physical activity are unclear in individuals at risk for cognitive impairment (e.g., those with self- or caregiver-reported subjective memory concerns). Furthermore, most studies focusing on cognitively impaired patients utilized only individual biomarkers (e.g., gait speed, muscle strength, balance tests) to evaluate frailty[9, 10]. Many trials have investigated primarily cognitive outcomes[6, 11], while other aspects of frailty have received less attention. So far, the use of holistic assessment for frailty such as frailty index (FI) was relatively under-reported[12]. Thus, exploring the effectiveness of exercise intervention in individuals with memory concerns using a comprehensive approach is warranted.

Although there is strong evidence of the effects of exercise on frailty, the potential benefits of exercise (e.g., increased muscle mass) may decrease when training stops, regardless of the initial training load[13]. Therefore, an easy-to-follow, home-based exercise program with minimal equipment and space is recommended to maintain the effects over the long term following a group-based program[14]. Nevertheless, current evidence of the long-term effects of home-exercise program is lacking and insufficient.

Therefore, we designed a randomized controlled trial to investigate the effects of self-directed AT, RT, and combined training (AT+RT) on reducing FI in older adults with subjective memory concerns.

Methods

Study design

We conducted a single-blind randomized controlled trial called TOPICS (TOyota Prevention Intervention for Cognitive decline and Sarcopenia) to compare the effects of AT, RT, and AT+RT with that of standard care (control group). This study included a 26-week intervention followed by another 26-week follow-up period. Eligible participants were randomly assigned in a 1:1:1:1 ratio to the aforementioned four groups by a computer-based system. Investigators were blinded to group membership until the end of the study period. The study protocol was approved by the local ethics committee (Graduate School of Medicine, Nagoya University, approval no. 2014-0155-2) and registered with the University Hospital Medical Information Network (UMIN) clinical trials registry (No. UMIN000014437). Written informed consent was obtained from all participants prior to their inclusion in the study.

Randomization

Randomization was performed using a minimization algorithm[15] in which the allocation list was generated by an independent statistician who was blinded to intervention type, participant assessments, and data collection. The stratification factors included age (≥75 years), sex, education level (≥10 years), presence or absence of amnesia (defined according to Alzheimer's Disease Neuroimaging Initiative [ADNI] criteria) [16], and Mini-Mental State Examination (MMSE) scores (≥24).

Participants

Community-dwelling older adults aged 65–85 years living in Toyota, Japan (22,790 residents) were screened by mail using 3 items out of a 25-item self-reported screening questionnaire (Kihon checklist[17]): Q18. Do your family or your friends point out your memory loss? Q19. Do you make a call by looking up phone numbers? Q20. Do you find yourself not knowing today's date? Respondents who have answered YES to Q18 or

Q20, or answered NO to Q19 were invited to participate in this study. Respondents with a clinical diagnosis of dementia, neurodegenerative disease, or a low MMSE score (≤19) were excluded[16]. Participants were diagnosed with MCI based on Petersen's criteria if they had (a) abnormal memory function corroborated by scores lower than 1.5 standard deviations (SDs) below age- and education-adjusted norms on the Logical Memory II subscale from the Wechsler Memory Scale-Revised and (b) MMSE score ≥24[18, 19]. Details of the recruitment protocol, exclusion criteria, and number of participants are shown in Figure 1.

Intervention

Each exercise intervention comprised 60-min sessions, held 2 days per week, for a total of 52 sessions over 26 weeks in 2 sports centers. Each session attended by 25 participants who got there using public or private transport at their will was supervised by 2 gym trainers who had been certified as fitness instructors for older adults and had practical experiences in group exercise. Each session began with a 10-min warm-up, continued with a 40-min core training program, and ended with a 10-min cooldown. Exercise intensity recorded was modified by ratings of perceived exertion (RPE)[20], in which the targets were "Easy" (rating of 11) for weeks 1–2, "Somewhat hard" (rating of 13) for weeks 3–12, and "Hard" (rating of 15) for weeks 13–26. Participants in the intervention group were also instructed to practice home-based self-training 2 times a week which was modified from the original group exercise program conducted in the sports center, following the exercise instructions and safety advice in a take-home booklet. Participants in the control group were required to attend two health promotion education classes, which provided information regarding healthy aging, healthy diet, cerebrovascular disease prevention, and health management, during the 26-week intervention period; no specific instructions regarding exercise, physical activity, or cognitive health were provided.

Aerobic training (AT)

The 40-min core AT program consisted of a 10- to 15-min step-in-place exercise, a 10- to 15-min walking workout, and rest intervals between training sets. Heart rates were measured with heart rate monitors during workouts. The exercise intensity was titrated gradually according to heart rate reserve (HRR), estimated by the Karvonen method[21]. Disregarding prior levels of physical activity and exercise, the target heart rate zone was set up individually to reach 40% HRR in weeks 1 and 2, 50% HRR in weeks 3–8, 60% HRR in weeks 9–12, and 70% HRR in weeks 13–26. Regarding home-based training, participants were recommended to take walks outdoors and keep records of walking time, heart rates before and after walking, and pedometer-assessed total daily steps.

Resistance training (RT)

The core RT program included two components: resistance-band workouts and bodyweight exercises. Resistance-band workouts using two elastic bands of different tensions comprised bicep curls, chest presses, side raises, seated rowing, leg presses, hip abduction, and side bends. Bodyweight exercises included shrugs, knee-ups, trunk curls, squats, kneeling kickbacks, toe raises, and calf raises. Each motion was performed for two sets of ten repetitions. Participants were recommended to do home-based resistance training using elastic bands and bodyweight exercises and to record training time, repetitions, sets, and RPEs.

Combined training (AT+RT)

Combined AT+RT training consisted of RT followed by AT, with the same intensity but half the training time (20 min for each). For AT, step-in-place exercises and walking workouts were performed in turns; for RT, only one set of ten repetitions was completed in each class. Outdoor walking, home-based resistance training, and bodyweight exercises were recommended.

Measures

A battery of comprehensive neuropsychological tests, physical assessments, and blood tests were conducted with each participant in the sports centers by a group of nurses, clinical psychologists, speech therapists, and occupational therapists who were blinded to group allocation. All assessors were required to complete a half-day training course including workshop practice. Details of the data obtained and cross-sectional findings are publicly available[18, 22-26]. In the present study, we created a FI consisting of 95 items in 6 domains, according to a standardized protocol published by Rockwood group[27, 28]. Total FI scores were constructed by dividing total deficit values (determined by the severity of each deficit) by the total number of included items. The depression and anxiety component was measured with the Geriatric Depression Scale-15 (GDS-15)[29] and the Generalized Anxiety Disorder-7 scale (GAD-7)[30]. The functional component was measured with the fall efficacy scale[31]. The physical component was measured with skeletal muscle mass index, unintentional weight loss (2 kg in the last 6 months), weakness, slow walking speed (<1 m/s), and low physical activity according to the Japanese version of the Cardiovascular Health Study criteria[32]. The disease component included 11 age-related chronic diseases. The cognition component was measured with the Everyday Memory Questionnaire, MMSE, Logical memory I&II (WMS-R), category fluency test, letter fluency test, Digit symbol (WAIS-III), and Trail making test-part A&B[33]. The quality of life (QOL) component was measured with the life satisfaction index[34]. Details of all FI variables are presented in Supplementary Table S1. Additionally, instrumental ADL assessed with Tokyo Metropolitan Institute of Gerontology Index of Competence (TMIG index) was another outcome measure[35]. All participants were evaluated at baseline before randomization, at week 26 (the end of the intervention period), and at week 52 (post-intervention follow-up).

Statistical analysis

We estimated that with a sample size of 82 subjects in each group, the study would have more than 80% power at the alpha level of 0.05 to detect a between-group difference for measurement at three time-points that was equivalent to a clinically significant difference for a small-to-medium effect size (Cohen's d=0.33, f=0.15)[36]. Allowing for a 20% loss to follow-up at week 52, we aimed to recruit 103 subjects in each group. We used a general estimating equation on an intention-to-treat basis to analyze mean score change on the FI and its components[37]. Cohen's d was used to describe the standardized mean difference of an effect[38]. The estimated intervention effects were adjusted for age and sex. Multiple imputation analyses with 15 iterations and 5 imputations were used to manage missing values. We analyzed data using IBM SPSS Statistics for Windows, Version 25.0. (IBM Corp., Armonk, NY).

Results

Participant characteristics

A total of 415 participants (53% men, 47% women) were randomized into 4 groups (Figure 1). Participant characteristics are listed in Table 1. The mean age ± SD at baseline was 72.3±4.6 years, with 28.9% of participants aged ≥75 years. A total of 19.4% participants had completed more than 12 years of education. The mean baseline FI was 0.3±0.1 with a slight right-skewed distribution (supplementary Figure S1). Average number of deficits in FI at baseline was 30.3 out of 95 items. Logical memory II (scoring from 0 to 50, with a higher score indicating better delayed recall memory) and MMSE scores at baseline were 10.1±6.2 and 26.3±2.6, respectively. The baseline characteristics were similar in all four groups, except for BMI (p=0.04).

Participants' session attendance rates in AT, RT, and AT+RT group were 82.5%, 85.9%, and 83.5%, respectively. In total, 70% and 74.1% participants have reached their target heart rates and RPE. A total of 37 (8.9%) participants completed the intervention but did not attend follow-up sessions at week 26 and 52, and 8 (1.9%) participants completed the intervention and follow-up session at week 26 but did not attend the final follow-up session at week 52. Compared with participants who completed the study, those who were lost to follow-up were older (p<0.001), with lower hand grip strength (p=0.03), lower normal (p<0.001) and maximum gait speeds (p=0.01), longer time to complete the Timed Up and Go test (p<0.001), and higher FI score (p=0.03) (Supplementary Table S2).

Effects of intervention on frailty index

Changes in FI at weeks 26 and 52, with the model unadjusted and adjusted for age and sex, are shown in Table 2 and Fig 2, respectively. Compared with the control group in the overall unadjusted analysis, the AT group showed reduced FI by −0.024 (p=0.02) at week 26 (Table 2). In the fully adjusted model, participants in the AT group still showed reduced FI at week 26 (mean difference −0.020, CI −0.039 to −0.001, effect size −0.275) but not at week 52 (Fig 2). No significant differences in FI were found in RT and AT+RT groups at week 26 and 52. There were no significant differences in TMIG index among all intervention groups (Supplementary Table S3).

When divided into two groups by frailty severity at baseline (FI≤0.21 and >0.21)[39], results showed that only participants with FI more than 0.21 benefited from AT (mean difference −0.024, CI −0.045 to −0.002) and RT (mean difference −0.030, CI −0.054 to −0.006) at week 26 (supplementary Table S4). Additionally, when divided by cognition at baseline, AT demonstrated improved FI at week 26 (mean difference −0.024, CI −0.044 to −0.004) in non-MCI participants (supplementary Table S5).

Effects of intervention on components of frailty index

Changes in components of the FI at weeks 26 and 52, adjusted for age and sex, are shown in Table 3. AT changed the depression and anxiety component of the FI at week 26 by −0.051 (CI −0.084 to −0.018, effect size −0.469) after adjusting for age and sex; however, there was no significant change in any component of FI at week 52.

Discussion

This randomized controlled trial involving older adults with memory concerns indicated that aerobic exercise could reduce frailty. However, the benefits of intervention wane over time. Interestingly, resistance and combined training failed to provide more benefits than aerobic exercise alone.

AT has been shown to improve depression without relying on it being a risk for dementia[40]. Our findings suggest that AT potentially reduce frailty by a small extent, especially in the depression and anxiety component. However, our results failed to demonstrate the AT effects on other FI components (e.g., physical and functional component) or instrumental ADL. A pilot randomized controlled trial reported the evidence that a 26-week AT could benefit functional ability (Disability Assessment for Dementia) in patients with early-stage Alzheimer's disease. The major difference to our study was that target training duration was titrated to 150 minutes per week, which was 30 minutes longer than that in our protocol[41]. On the other hand, as more evidence suggested the combined benefits of nutritional support and exercise training[42], exercise alone is unlikely to be sufficient to reduce frailty. The present study confirmed that the multifaceted frailty intervention with a longer training duration might yield greater improvements.

Only participants with subjective memory concerns were recruited for our study because the aim was to advance current knowledge for people at risk of cognitive impairment. In a previous study, a multicomponent physical activity intervention improved working cognition and physical function in MCI patients[43]. Our findings demonstrate that physical activity decreases frailty at weeks 26, providing further evidence of the benefits of physical activity in individuals with subjective memory concerns. On the other hand, non-significant differences in the cognitive component of FI among the 4 exercise groups, which were consistent with the results of the LIFE Study[44], may underscore that (a) early intervention is needed at the stage before subjective memory impairments, which might be determined by biomarkers[45], (b) the optimal dose, duration, and period of exercise is not yet understood; and (c) specific types of cognitive training (e.g., cognicise[46]) are worth investigating further. Future studies are warranted to confirm the benefits of physical activity in individuals with subjective memory concerns.

Contrary to our hypothesis, both RT and AT+RT failed to decrease FI scores. One possible reason is that the 40-min core training time might be insufficient to build muscle and improve frailty. Moreover, the transition time between AT and RT sessions in the AT+RT group reduced the total training period, which could diminish the effects of training. The complexity of practicing both training types may compromise proficiency and offset the effects of training, especially for our participants with memory concerns.

Another possible explanation is that the RT was designed to be adaptable to real-life settings with minimal equipment. The intensity and duration of resistance-band and bodyweight exercises may be not strong and long enough to achieve detectable improvement in physical performance. To balance the beneficial and adverse effects (e.g., muscle ache, injury, pain in joints) induced by exercise, future studies are warranted to determine the optimal type, intensity, duration, and frequency of individualized home-based training for older adults with memory concerns.

There are several additional limitations to this study. First, because the characteristics of subjective cognitive impairment are manifested variably and heterogeneously, three screening questions in the Kihon checklist may not be sufficient to identify all subtypes of subjective cognitive impairment[47]. In addition, recruitment by mail, unknown age at onset of subjective cognitive impairment, and unknown elapsed time between onset of subjective cognitive impairment and recruitment limit the generalizability of the findings. Second, a lack of data on exercise habits at baseline and daily self-training records at home meant we could not assess exercise adherence and self-motivation during and after the intervention program. Finally, a physical intervention, instead of an integrative approach including nutritional support, might have limited effectiveness and validity for improving frailty. However, the present study underscores the importance of investigating the optimal, applicable, and feasible physical activity training model for community-dwelling older adults with subjective cognitive impairments to prevent and delay the occurrence of frailty.

Conclusion

This study suggests that aerobic exercise modestly reduces frailty for older adults with subjective cognitive impairments, especially in the depression and anxiety component; but shows no effects on instrumental activities of daily living. Resistance training and combined training have no favorable effects on frailty. To reverse frailty and improve management, implementation of aerobic exercise training is recommended to be an integral part of comprehensive intervention strategies.

References

1. Ensrud KE, Ewing SK, Cawthon PM, Fink HA, Taylor BC, Cauley JA, et al. A comparison of frailty indexes for the prediction of falls, disability, fractures, and mortality in older men. J Am Geriatr Soc. 2009 Mar;57(3):492-8.
2. Dent E, Lien C, Lim WS, Wong WC, Wong CH, Ng TP, et al. The Asia-Pacific Clinical Practice Guidelines for the Management of Frailty. J Am Med Dir Assoc. 2017 Jul 1;18(7):564-75.
3. Churchward-Venne TA, Tieland M, Verdijk LB, Leenders M, Dirks ML, de Groot LC, et al. There Are No Nonresponders to Resistance-Type Exercise Training in Older Men and Women. J Am Med Dir Assoc. 2015 May 1;16(5):400-11.
4. Nagai K, Miyamato T, Okamae A, Tamaki A, Fujioka H, Wada Y, et al. Physical activity combined with resistance training reduces symptoms of frailty in older adults: A randomized controlled trial. Arch Gerontol Geriatr. 2018 May - Jun;76:41-7.
5. Oh SL, Kim HJ, Woo S, Cho BL, Song M, Park YH, et al. Effects of an integrated health education and elastic band resistance training program on physical function and muscle strength in community-dwelling elderly women: Healthy Aging and Happy Aging II study. Geriatr Gerontol Int. 2017 May;17(5):825-33.
6. Lamb SE, Mistry D, Alleyne S, Atherton N, Brown D, Copsey B, et al. Aerobic and strength training exercise programme for cognitive impairment in people with mild to moderate dementia: the DAPA RCT. Health Technol Assess. 2018 May;22(28):1-202.
7. Jongsiriyanyong S, Limpawattana P. Mild Cognitive Impairment in Clinical Practice: A Review Article. Am J Alzheimers Dis Other Demen. 2018 Dec;33(8):500-7.
8. Margioti E, Kosmidis MH, Yannakoulia M, Dardiotis E, Hadjigeorgiou G, Sakka P, et al. Exploring the association between subjective cognitive decline and frailty: the Hellenic Longitudinal Investigation of Aging and Diet Study (HELIAD). Aging Ment Health. 2019 Jan 9:1-11.
9. Yoon DH, Kang D, Kim HJ, Kim JS, Song HS, Song W. Effect of elastic band-based high-speed power training on cognitive function, physical performance and muscle strength in older women with mild cognitive impairment. Geriatr Gerontol Int. 2017 May;17(5):765-72.
10. Lipardo DS, Aseron AMC, Kwan MM, Tsang WW. Effect of Exercise and Cognitive Training on Falls and Fall-Related Factors in Older Adults With Mild Cognitive Impairment: A Systematic Review. Archives of physical medicine and rehabilitation. 2017 Oct;98(10):2079-96.
11. Anderson-Hanley C, Stark J, Wall KM, VanBrakle M, Michel M, Maloney M, et al. The interactive Physical and Cognitive Exercise System (iPACES): effects of a 3-month in-home pilot clinical trial for mild cognitive impairment and caregivers. Clin Interv

Aging. 2018;13:1565-77.

12. Karssemeijer EGA, Bossers WJR, Aaronson JA, Sanders LMJ, Kessels RPC, Olde Rikkert MGM. Exergaming as a Physical Exercise Strategy Reduces Frailty in People With Dementia: A Randomized Controlled Trial. J Am Med Dir Assoc. 2019 Dec;20(12):1502-8 e1.

13. Van Roie E, Walker S, Van Driessche S, Baggen R, Coudyzer W, Bautmans I, et al. Training load does not affect detraining's effect on muscle volume, muscle strength and functional capacity among older adults. Exp Gerontol. 2017 Nov;98:30-7.

14. Ng TP, Feng L, Nyunt MS, Feng L, Niti M, Tan BY, et al. Nutritional, Physical, Cognitive, and Combination Interventions and Frailty Reversal Among Older Adults: A Randomized Controlled Trial. Am J Med. 2015 Nov;128(11):1225-36 e1.

15. Schouten HJ. Adaptive biased urn randomization in small strata when blinding is impossible. Biometrics. 1995 Dec;51(4):1529-35.

16. Aisen PS, Petersen RC, Donohue MC, Gamst A, Raman R, Thomas RG, et al. Clinical Core of the Alzheimer's Disease Neuroimaging Initiative: progress and plans. Alzheimers Dement. 2010 May;6(3):239-46.

17. Arai H, Satake S. English translation of the Kihon Checklist. Geriatr Gerontol Int. 2015 Apr;15(4):518-9.

18. Umegaki H, Makino T, Uemura K, Shimada H, Hayashi T, Cheng XW, et al. The Associations among Insulin Resistance, Hyperglycemia, Physical Performance, Diabetes Mellitus, and Cognitive Function in Relatively Healthy Older Adults with Subtle Cognitive Dysfunction. Front Aging Neurosci. 2017;9:72.

19. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol. 1999 Mar;56(3):303-8.

20. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc. 1982;14(5):377-81.

21. Strath SJ, Swartz AM, Bassett DR, Jr., O'Brien WL, King GA, Ainsworth BE. Evaluation of heart rate as a method for assessing moderate intensity physical activity. Med Sci Sports Exerc. 2000 Sep;32(9 Suppl):S465-70.

22. Hayashi T, Umegaki H, Makino T, Cheng XW, Shimada H, Kuzuya M. Association between sarcopenia and depressive mood in urban-dwelling older adults: A cross-sectional study. Geriatr Gerontol Int. 2019 Jun;19(6):508-12.

23. Umegaki H, Makino T, Shimada H, Hayashi T, Wu Cheng X, Kuzuya M. Cognitive Dysfunction in Urban-Community Dwelling Prefrail Older Subjects. J Nutr Health Aging. 2018;22(4):549-54.

24. Umegaki H, Makino T, Uemura K, Shimada H, Cheng XW, Kuzuya M. Objectively measured physical activity and cognitive function in urban-dwelling older adults. Geriatr

Gerontol Int. 2018 Jun;18(6):922-8.

25. Umegaki H, Makino T, Uemura K, Shimada H, Hayashi T, Cheng XW, et al. Association between insulin resistance and objective measurement of physical activity in community-dwelling older adults without diabetes mellitus. Diabetes Res Clin Pract. 2018 Sep;143:267-74.

26. Umegaki H, Makino T, Yanagawa M, Nakashima H, Kuzuya M, Sakurai T, et al. Maximum gait speed is associated with a wide range of cognitive functions in Japanese older adults with a Clinical Dementia Rating of 0.5. Geriatr Gerontol Int. 2018 Sep;18(9):1323-9.

27. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005 Aug 30;173(5):489-95.

28. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. BMC Geriatr. 2008 Sep 30;8:24.

29. Schreiner AS, Hayakawa H, Morimoto T, Kakuma T. Screening for late life depression: cut-off scores for the Geriatric Depression Scale and the Cornell Scale for Depression in Dementia among Japanese subjects. Int J Geriatr Psychiatry. 2003 Jun;18(6):498-505.

30. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Archives of internal medicine. 2006 May 22;166(10):1092-7.

31. Helbostad JL, Taraldsen K, Granbo R, Yardley L, Todd CJ, Sletvold O. Validation of the Falls Efficacy Scale-International in fall-prone older persons. Age Ageing. 2010 Mar;39(2):259.

32. Satake S, Shimada H, Yamada M, Kim H, Yoshida H, Gondo Y, et al. Prevalence of frailty among community-dwellers and outpatients in Japan as defined by the Japanese version of the Cardiovascular Health Study criteria. Geriatr Gerontol Int. 2017 Dec;17(12):2629-34.

33. Kazui H, S Watamori T, Honda R, Mori E. The validation of a Japanese version of the Everyday Memory Checklist [Japanese]2003.

34. Neugarten BL, Havighurst RJ, Tobin SS. The measurement of life satisfaction. J Gerontol. 1961 Apr;16:134-43.

35. Koyano W, Shibata H, Nakazato K, Haga H, Suyama Y. Measurement of competence: reliability and validity of the TMIG Index of Competence. Arch Gerontol Geriatr. 1991 Sep-Oct;13(2):103-16.

36. Hindin SB, Zelinski EM. Extended practice and aerobic exercise interventions benefit untrained cognitive outcomes in older adults: a meta-analysis. J Am Geriatr Soc. 2012 Jan;60(1):136-41.

37. Zeger SL, Liang KY, Albert PS. Models for longitudinal data: a generalized estimating equation approach. Biometrics. 1988 Dec;44(4):1049-60.

38. Aarts S, van den Akker M, Winkens B. The importance of effect sizes. European Journal of General Practice. 2014 2014/03/01;20(1):61-4.

39. Hoover M, Rotermann M, Sanmartin C, Bernier J. Validation of an index to estimate the prevalence of frailty among community-dwelling seniors. Health Rep. 2013 Sep;24(9):10-7.

40. Morres ID, Hatzigeorgiadis A, Stathi A, Comoutos N, Arpin-Cribbie C, Krommidas C, et al. Aerobic exercise for adult patients with major depressive disorder in mental health services: A systematic review and meta-analysis. Depress Anxiety. 2019 Jan;36(1):39-53.

41. Morris JK, Vidoni ED, Johnson DK, Van Sciver A, Mahnken JD, Honea RA, et al. Aerobic exercise for Alzheimer's disease: A randomized controlled pilot trial. PLoS One. 2017;12(2):e0170547.

42. Liao CD, Lee PH, Hsiao DJ, Huang SW, Tsauo JY, Chen HC, et al. Effects of Protein Supplementation Combined with Exercise Intervention on Frailty Indices, Body Composition, and Physical Function in Frail Older Adults. Nutrients. 2018 Dec 4;10(12).

43. Bae S, Lee S, Lee S, Jung S, Makino K, Harada K, et al. The effect of a multicomponent intervention to promote community activity on cognitive function in older adults with mild cognitive impairment: A randomized controlled trial. Complementary therapies in medicine. 2019 Feb;42:164-9.

44. Sink KM, Espeland MA, Castro CM, Church T, Cohen R, Dodson JA, et al. Effect of a 24-Month Physical Activity Intervention vs Health Education on Cognitive Outcomes in Sedentary Older Adults: The LIFE Randomized Trial. JAMA. 2015 Aug 25;314(8):781-90.

45. Lee JC, Kim SJ, Hong S, Kim Y. Diagnosis of Alzheimer's disease utilizing amyloid and tau as fluid biomarkers. Experimental & molecular medicine. 2019 May 9;51(5):53.

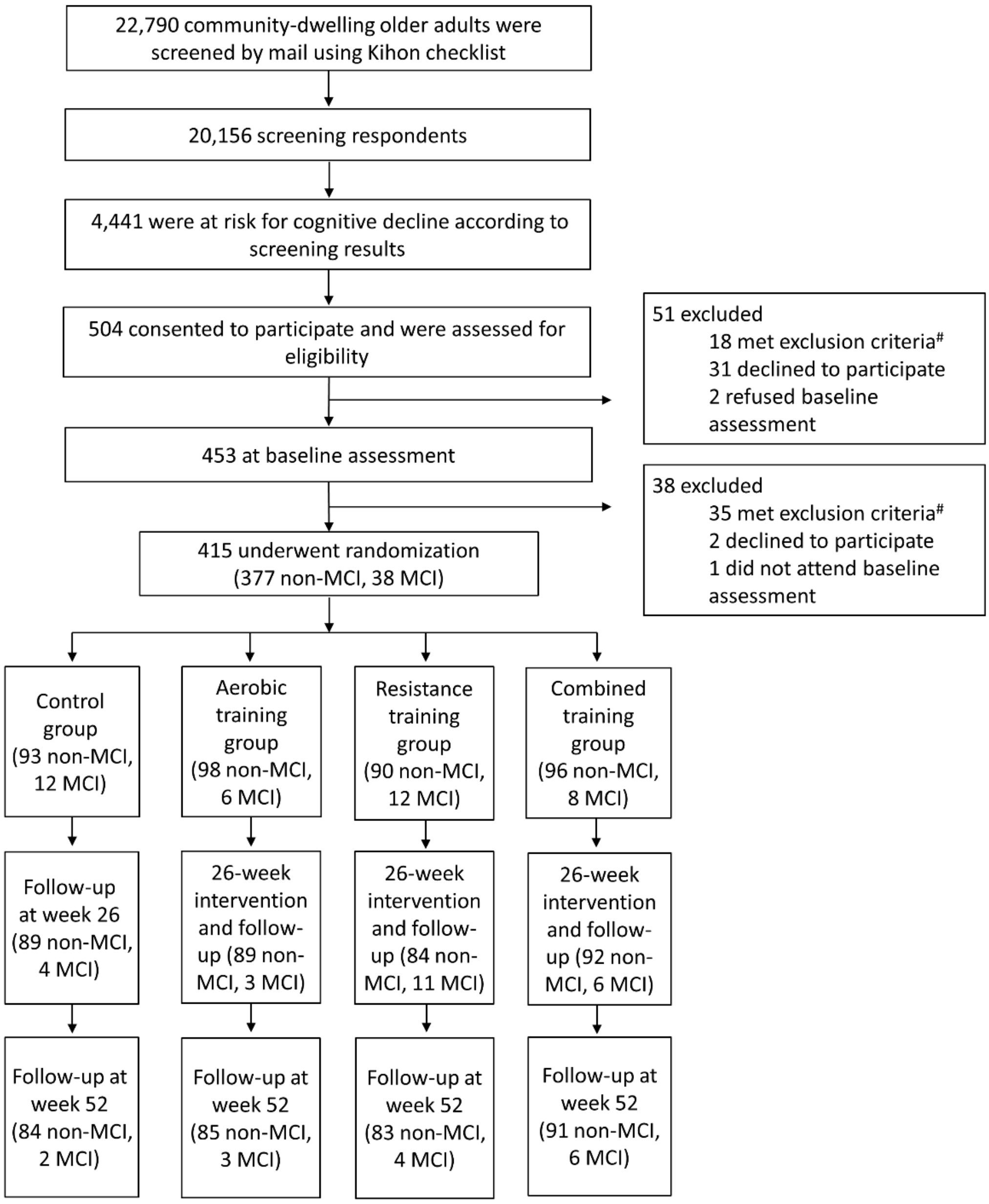
46. Suzuki T, Makizako H, Doi T, Park H, Lee S, Tsutsumimoto K, et al. Community-Based Intervention for Prevention of Dementia in Japan. The journal of prevention of Alzheimer's disease. 2015;2(1):71-6.

47. Jessen F, Amariglio RE, van Boxtel M, Breteler M, Ceccaldi M, Chetelat G, et al. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. Alzheimers Dement. 2014 Nov;10(6):844-52.

Figure

Figure 1.

Flowchart of study participants and group allocation



#Exclusion criteria:

(1) Clinical diagnosis of dementia according to the Diagnostic and Statistical

Manual of Mental Disorders, 4th Edition criteria

(2) Impaired activities of daily living (ADL) or instrumental activities of daily living (IADL)

(3) Requiring support or care from the Japanese public long-term care insurance system

(4) Mini-Mental State Examination (MMSE) score of ≤ 19

(5) Severe visual impairment

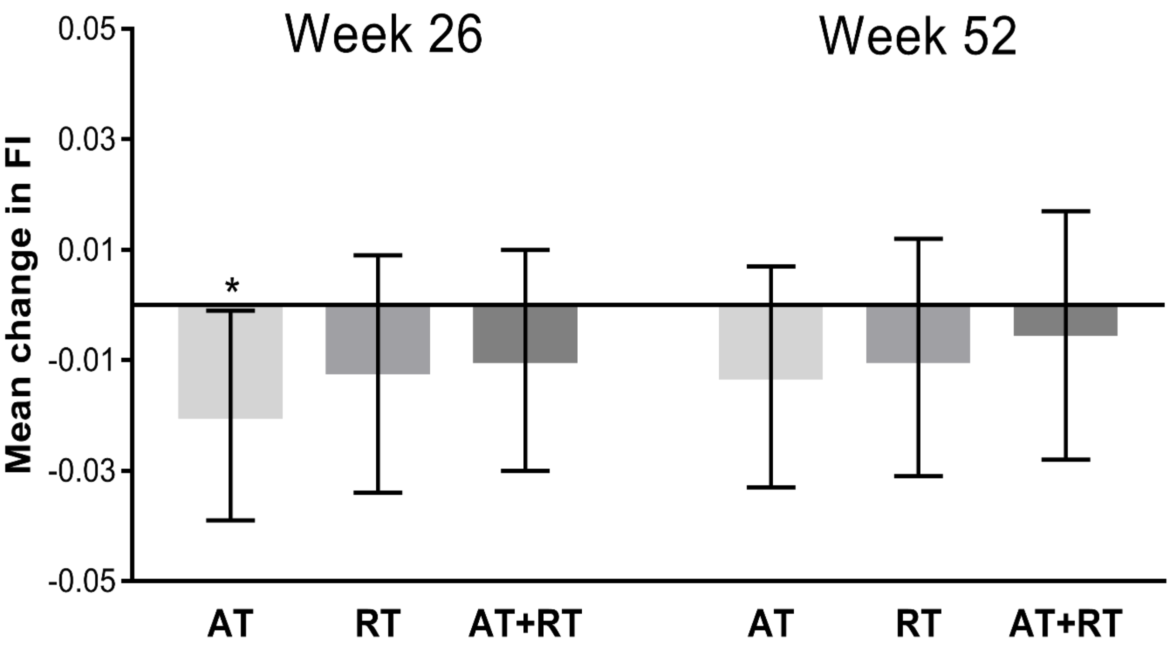
(6) Any diagnosis of a neurodegenerative disorder (e.g., Parkinson’s disease)

(7) Psychiatric disease (e.g., major depressive disorder)

(8) Medical contraindications to exercise

(9) A history of serious cardiovascular, musculoskeletal, respiratory, or cerebrovascular disease or other severe health issue

Figure 2. Mean change in frailty index adjusted for age and sex in all participants



Notes: FI, frailty index; AT, aerobic training; RT, resistance training; AT+RT, aerobic training plus resistance training. Error bars represent 95% confidence interval. The asterisk indicates $p<0.05$ for the comparison with the control group.

TABLES

Table 1. Participant characteristics at baseline

Characteristics§	All (N=415)	AT (N=98)	RT (N=90)	AT+RT (N=96)	Control (N=93)	*p* value*
Sex, no. (%)						0.53
Female	195(47%)	49(47.1%)	49(48%)	43(41.3%)	54(51.4%)	
Male	220(53%)	55(52.9%)	53(52%)	61(58.7%)	51(48.6%)	
Age (years)	72.3±4.6	72.3±4.6	72.3±4.8	72.6±4.5	72.1±4.6	0.88
Education level						0.95
0–9 years	137(33.3%)	37(35.6%)	34(33.3%)	30(28.8%)	36(34.3%)	
10–12 years	195(47.3%)	45(43.3%)	49(48%)	52(50%)	49(46.7%)	
>12 years	80(19.4%)	22(21.2%)	19(18.6%)	20(19.2%)	19(18.1%)	
Height (cm)	157.3±8.3	157±7.6	158.4±9	156.5±8.1	158.3±8.3	0.47
Weight (kg)	56.7±9.3	56.7±10	56.3±8.8	58.7±9.6	55.3±8.5	0.06
BMI (kg/m^2)	22.8±2.8	22.6±2.8	22.9±2.8	23.4±2.8	22.4±2.8	0.04
Abdominal circumference (cm)	82.8±7.8	82.3±8.4	82.7±7.4	84.5±7.8	81.5±7.6	0.05
SMI (kg/m^2)	6.5±0.9	6.5±1	6.5±1	6.6±1	6.5±0.9	0.48
Hand grip (kg)	28.3±7.8	28±7.3	28±8	28.8±8.5	28.3±7.5	0.86
Usual gait speed (m/s)	1.4±0.2	1.5±0.2	1.5±0.2	1.4±0.2	1.4±0.2	0.10
Maximum gait speed (m/s)	1.8±0.3	1.8±0.3	1.8±0.3	1.8±0.2	1.8±0.3	0.74
TUG (sec)	7.8±1.3	7.8±1.4	7.8±1.3	7.9±1.3	7.8±1.3	0.77
MMSE (score)	26.3±2.6	26.4±2.5	26.1±2.5	26.4±2.7	26.3±2.7	0.77
Logical Memory form II (score)#	10.1±6.2	10.8±6.2	9.9±6.1	9.8±5.5	10.2±6.9	0.65
GDS-15 (score)	4.0±2.8	4.1±2.7	3.4±2.5	4.1±3.0	4.3±3.1	0.15
GAD-7 (score)	4.7±2.7	4.6±2.4	4.9±2.8	4.8±2.7	4.6±2.9	0.85
Frailty index	0.30±0.10	0.31±0.11	0.29±0.09	0.31±0.11	0.30±0.10	0.34

Notes: AT, aerobic training; RT, resistance training; AT+RT, aerobic training plus resistance training; BMI, body mass index; SMI, skeletal muscle index; TUG, Timed Up and Go test; MMSE, Mini-Mental State Examination, ranging from 0 to 30, with higher scores indicating better cognitive functioning; GDS-15, Geriatric Depression Scale-15, ranging from 0 to 15, with higher scores indicating greater severity of depression; GAD-7, Generalized Anxiety Disorder scale, ranging from 0 to 21, with higher scores indicating greater severity of anxiety

§ Continuous variables are presented as means ± standard deviation

Scores range from 0 to 50, with a higher score indicating better delayed recall memory

*Chi-square test for proportions and ANOVA for continuous measures.

Table 2. Changes in unadjusted frailty index at weeks 26 and 52 compared with baseline

All (N=415)	Raw score change§	Estimated effect of intervention vs. control (95% CI)	*p* value
Week 26			
AT	−0.023±0.064	−0.024 (−0.044 to −0.004)	0.02
RT	−0.012±0.083	−0.014 (−0.036 to 0.009)	0.24
AT+RT	−0.013±0.077	−0.014 (−0.036 to 0.070)	0.19
Control	0.001±0.076	0	
Week 52			
AT	−0.014±0.072	−0.017 (−0.038 to 0.004)	0.11
RT	−0.005±0.081	−0.010 (−0.033 to 0.013)	0.38
AT+RT	−0.009±0.092	−0.008 (−0.032 to 0.015)	0.48
Control	0.001±0.069	0	

Notes: AT, aerobic training; RT, resistance training; AT+RT, aerobic training plus resistance training; CI, confidence interval

§Values are presented as means ± standard deviation

Table 3. Changes in components of the frailty index in all participants (N = 415) at weeks 26 and 52 compared with baseline*

	Estimated effect of intervention vs. control (95% CI) *	*p* value
Week 26		
Depression and anxiety component		
AT	−0.051 (−0.084 to −0.018)	<0.01
RT	−0.012 (−0.044 to 0.020)	0.46
AT+RT	−0.025 (−0.059 to 0.008)	0.14
Control	0	
Physical component		
AT	−0.010 (−0.052 to 0.031)	0.64
RT	−0.003 (−0.048 to 0.042)	0.89
AT+RT	0.007 (−0.038 to 0.053)	0.75
Control	0	
Disease component		
AT	−0.001 (−0.009 to 0.007)	0.79
RT	−0.004 (−0.011 to 0.003)	0.23
AT+RT	−0.002 (−0.010 to 0.005)	0.56
Control	0	
Cognition component		
AT	0.019 (−0.033 to 0.070)	0.48
RT	−0.005 (−0.058 to 0.047)	0.85
AT+RT	0.001 (−0.049 to 0.05)	0.99
Control	0	
QOL component		
AT	−0.026 (−0.58 to 0.006)	0.11
RT	−0.016 (−0.052 to 0.020)	0.39
AT+RT	−0.031 (−0.064 to 0.003)	0.07
Control	0	
Week 52		
Depression and anxiety component		
AT	−0.021 (−0.055 to 0.014)	0.25
RT	−0.009 (−0.045 to 0.028)	0.64
AT+RT	−0.003 (−0.040 to 0.034)	0.88
Control	0	

Physical component		
AT	−0.032 (−0.081 to 0.018)	0.20
RT	−0.025 (−0.072 to 0.023)	0.31
AT+RT	−0.020 (−0.071 to 0.032)	0.45
Control	0	
Disease component		
AT	−0.003 (−0.013 to 0.007)	0.58
RT	−0.003 (−0.013 to 0.007)	0.55
AT+RT	−0.001 (−0.011 to 0.010)	0.91
Control	0	
Cognition component		
AT	0.022 (−0.035 to 0.079)	0.45
RT	0.044 (−0.015 to 0.102)	0.14
AT+RT	0.030 (−0.029 to 0.089)	0.32
Control	0	
QOL component		
AT	−0.008 (−0.040 to 0.025)	0.65
RT	−0.008 (−0.043 to 0.028)	0.67
AT+RT	−0.015 (−0.051 to 0.021)	0.40
Control	0	

Notes: AT, aerobic training; RT, resistance training; AT+RT, aerobic training plus resistance training; QOL, quality of life; CI, confidence interval

* Adjusted for age and sex