Experimental Gerontology 156 (2021) 111590

Contents lists available at ScienceDirect

Experimental Gerontology

journal homepage: www.elsevier.com/locate/expgero

Short- and long-term effects of different exercise programs on the gait performance of older adults with subjective cognitive decline: A randomized controlled trial

Kosuke Fujita [a,b], Hiroyuki Umegaki [a,b], Taeko Makino [a], Kazuki Uemura [a], Takahiro Hayashi [a], Aiko Inoue [a], Chiharu Uno [a], Tomoharu Kitada [a], Chi Hsien Huang [b,c], Hiroyuki Shimada [d], Masafumi Kuzuya [a,b,*,**]

[a] Institute of Innovation for Future Society, Nagoya University, Nagoya, Japan
[b] Department of Community Healthcare and Geriatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan
[c] Department of Family Medicine, E-Da Hospital, Kaohsiung City, Taiwan, ROC
[d] Department of Preventive Gerontology, Center for Gerontology and Social Science, National Center for Geriatrics and Gerontology, Obu, Japan

ARTICLE INFO

Section Editor: Christiaan Leeuwenburgh

Keywords:
Cognition
Gait-biomechanics
Rehabilitation

ABSTRACT

Background: Older adults, especially those with cognitive decline, often have poor gait performance, which results in poor clinical outcomes due to falls or decreased daily physical activity. The effects of various exercises on gait performance have been studied, whereas the short-term and long-term effects of different exercise modalities remain unknown.
Objective: To compare the short- and long-term effects of aerobic training (AT), resistance training (RT), and combined training (CT) on the gait performance of community-dwelling older adults with subjective cognitive decline (SCD).
Design: A four-arm, randomized controlled trial.
Setting and subjects: 388 community-dwelling older adults with SCD (mean age, 72.3 years).
Methods: Participants attended an exercise or education class twice a week for 26 weeks. 10 gait performance parameters were examined at baseline, post-intervention (Week 26), and after 26 weeks of follow-up (Week 52) using an electronic walkway system.
Results: The mean adherence of exercise sessions was 82.5 to 85.9%. All exercise intervention induced an improvement in gait speed, stride time, cadence, stride length, and double-support time at Week 26 ($p < .05$), without significant intergroup differences among exercise interventions. However, only RT showed a significant effect on some spatiotemporal gait parameters at Week 52. The analyses for the gait variability parameters showed mild effects of all exercise interventions.
Conclusion: All of the exercise programs examined had a positive short-term effect on spatiotemporal gait parameters of older adults with SCD, despite no effect on gait variability parameters. RT are most recommended when long-lasting effects are the primary aim.

1. Introduction

A gait disorder is one of the common geriatric syndromes (Sudarsky, 1990). Gait disorder such as small stride length and increased variability confers a high risk of falls or restriction of daily physical activity on older adults (≥65 years old) (Marques et al., 2018; Rubenstein, 2006). Approximately 29% of older adults suffer a fall at least once a year, and approximately 10% of falls would be the cause of major injuries, such as hip fractures (Guirguis-Blake et al., 2018). As gait disorder itself, falls, or decreased physical activity are one of the most major causes of future loss of independence, lower quality of life (QoL), and mortality in older adults (2020 Alzheimer's disease facts and figures, 2020; Fried et al.,

* Corresponding author at: Institute of Innovation for Future Society, Nagoya University, 65 Tsuruma-cho, Showa-ku, Nagoya, Aichi 466-8550, Japan.
** Corresponding author at: Department of Community Healthcare and Geriatrics, Nagoya University Graduate School of Medicine, 65 Tsuruma-cho, Showa-ku, Nagoya, Aichi 466-8550, Japan.
E-mail address: kuzuya@med.nagoya-u.ac.jp (M. Kuzuya).

https://doi.org/10.1016/j.exger.2021.111590
Received 29 June 2021; Received in revised form 8 September 2021; Accepted 7 October 2021
Available online 12 October 2021

2001; van Kan et al., 2009), it is necessary to implement preventive measures against gait disorders in this vulnerable population.

Impaired cognitive function is associated with gait abnormality in older adults (Zhang et al., 2019). Recent research has indicated that cognitive pathways, such as those for executive function and attention, are the predominant mediators of gait control (Parihar et al., 2013). The impairment of these cognitive functions is considered to be the cause of gait abnormality in patients with dementia (Zhang et al., 2019). Older adults with dementia have slow gait speed, small stride length, prolonged double limb support time, and increased stride variability when compared to healthy individuals (Visser, 1983). Gait disorders are present even in patients with mild cognitive impairment and become increasingly severe with the progression of cognitive dysfunction (Allali & Verghese, 2017; Bahureksa et al., 2017).

Effective interventions for gait disorders would improve the QoL and mortality risk of older adults by supporting their safer and independent mobility, especially in patients with cognitive impairment (Hardy et al., 2007; Zhang et al., 2019). Several studies have examined the effect of pharmacological and non-pharmacological interventions on gait disorders in older adults with cognitive decline (Beauchet et al., 2011, 2014). Pharmacotherapy, using memantine or acetylcholinesterase inhibitors, are reported to be effective for improving gait variability in patients with dementia (Beauchet et al., 2015). On the other hand, exercise training is an established non-pharmacological intervention for improving gait performance in older adults, including patients with dementia (Kemoun et al., 2010; Schwenk et al., 2014). Aerobic training (AT), resistance training (RT), and balance training have been shown to improve gait parameters, such as gait speed and stride length (Kao et al., 2018; Kemoun et al., 2010; Schwenk et al., 2014). A meta-analysis and systematic review revealed that RT with gradually increasing intensity, functional mobility training such as walking, or combination of various exercise modality are effective for improving gait speed or performance on the timed up and go test (TUG) in older adults (Kokkinos et al., 2017; Zhang et al., 2019). However, the most effective exercise modality for improving spatiotemporal gait and gait variability parameters has not been identified. Moreover, as only a few studies included follow-up investigations (Hauer et al., 2012; Kao et al., 2018), the long-term effect of exercise intervention on gait performance remains unclear. Since the effect on exercise intervention for patients with moderate to severe dementia is uncertain (Lamb et al., 2018), we have decided to target older adults with subjective cognitive decline (SCD) as subjects who are at a high risk of cognitive decline.

The primary objective of this study was to compare the effect of different exercise programs with same duration (2session per week for 26 weeks), that is, AT, RT, and both (combined training, CT), on improving gait parameters in older adults with SCD. The secondary objective was to investigate the long-term (26 weeks after the end of intervention) effects of the abovementioned exercise interventions on older adults with SCD. Considering the previous systematic review (Zhang et al., 2019), we hypothesized that CT is most effective in improving both short- and long-term gait performance.

2. Methods

2.1. Study design

This four-arm, assessor-blinded, randomized controlled trial, named the TOyota Prevention Intervention for Cognitive decline and Sarcopenia (TOPICS) trial, was conducted between October 2014 and October 2015. From this trial TOPICS, the effects of AT, RT, and CT on the frailty and intrinsic capacity are already investigated and published elsewhere (Huang et al., 2020a,b; Makino et al., 2021). We estimated that with at least 80 participants in each intervention group, this study would have 80% statistical power to detect a significant difference of less than 0.05 with a medium effect size of 0.45 SD, without for multiple comparison (Cohen, 1992). Eligible participants were randomly and equally assigned to one of the three intervention groups or a control group by using a computer-based minimization algorithm, where the stratification factors included age, sex, duration of education (in years), presence or absence of amnesia (defined by the Alzheimer's Disease Neuroimaging Initiative criteria), and the Mini-Mental State Examination (MMSE) scores. The allocation list was provided by an independent statistician and concealed until the randomization process finished.

The study protocol was approved by the local ethics committee (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.

2.2. Study population

A mail-based, 25-item self-reported questionnaire (the Kihon Checklist) was conducted for 22,790 community-dwelling older adults (age range 65–85 years) to screening SCD. Subjects who were determined to having SCD were invited to participate in the study through a postal invitation and examined further eligibility (Arai & Satake, 2015; Maki et al., 2012). We used all three items consist of the cognitive domain of the Kihon Checklist. The questionnaires were following: "Q18: Do your family or friends point out your memory loss?" (e.g., "You ask the same question repeatedly"); "Q19: Do you make a call by looking up phone numbers?"; and "Q20: Do you find yourself not knowing today's date?" Residents who responded either "yes" to Q18 or Q20, or "no" to Q19, were considered to be having SCD. The exclusion criteria of the TOPICS trial were: (1) fulfilling the clinical criteria for dementia (including anti-dementia drugs use); (2) having any disability that affected the basic and instrumental activities of daily living; (3) indicated to require support or care from the Japanese public long-term care insurance system; (4) MMSE score $\leq$ 19; (5) having severe visual impairment; (6) diagnosed with a neurodegenerative disease (e.g., Parkinson's disease); (7) with any medical contraindications to exercise; (8) psychiatric disease (i.e., major depressive disorder); (9) a history of serious cardiovascular, musculoskeletal, respiratory, or cerebrovascular disease with paralysis or other severe health issues; or (10) having gait disorder or need of walking aid. Participants who had a cerebrovascular disease without paralysis were excluded from the current analysis to avoid the possible confounding effects of exercise intervention on the gait performance.

2.3. Interventions

The duration, frequency and intensity of the exercise interventions were determined by the meta-analyses about exercise and cognitive function (Gates et al., 2013); participants conducted exercise 2 days a week for 26 weeks, with 52 sessions in total. Each session consisted of a 50-minute exercise program and a 5-minute medical checkup before and after the exercise. The exercise program includes a 10-minute warm-up followed by 30 min of core training, and a 10-minute cool-down at the end. Trainers took adequate intervals in each session and paid attention to the fatigue of the participants. The intensity of the program was increased gradually in conformance with the American College of Sports Medicine guidelines (Thomas et al., 2016). The detail of each exercise was presented in the supplementary file (Supplementary Table S3). Participants in the control group received information about healthy aging, healthy diet, disease prevention, and health management during the 26-week intervention period. The control subjects did not receive specific instructions about exercise, physical activity, or cognitive health.

2.3.1. Aerobic training

Subjects assigned to the AT group undertook a step-on-the-spot exercise in a chair or standing position for 10–15 min followed by a 15-min walking exercise after a 5-min rest interval. The exercise intensity was set according to the percent heart rate reserve (%HRR) estimated by the Karvonen method (Strath et al., 2000). The target heart rate zone was 40% HRR in weeks 1 to 2, 50% HRR in weeks 3 to 8, 60% HRR in weeks 9 to 12, and 70% HRR in the remainder of the session. Besides the supervised program in the class, the participants were recommended to practice home-based training, such as walking outdoors, by themselves.

2.3.2. *Resistance training*

The participants assigned to the RT group undertook resistance band exercise, including bicep curls, chest presses, side raises, seated rowing, leg presses, hip abduction, and side bends, for 10–15 min followed by a 15-minute bodyweight exercise that comprised shrugs, knee-ups, trunk curls, squats, kneeling kickbacks, toe raises, and calf raises after a 5-minute rest interval. All movements were performed with 10 repetitions for a set, and 2 sets per session. The exercise intensity was set according to the ratings of perceived exertion by using the Borg Scale. The target Borg Scale ratings were set as 10–12, 12–14, and 14–16 in weeks 1–2, 3–12, and the remainder of the session, respectively. Home-based training was recommended to all participants in the RT group.

2.3.3. *Combined training*

The CT group conducted RT followed by AT in the same modality and intensity, but for only half of the duration of the other two interventions. The two types of exercise included in AT (stepping exercise and walking) were each performed in turns during one week. Walking outdoors and RT were recommended as home-based training.

2.4. *Measures*

Trained physicians, nurses, physical therapists, and clinical psychologists were in charge of the study measurements using standardized protocols at three time points (baseline, Week 26, and Week 52). The procedure of measurements in demographic, health, physical, mental, and social assessments are detailed in supplemental file.

2.4.1. *Gait performance*

Six spatiotemporal gait parameters (i.e., gait speed, stride time, cadence, double support, and step width) and 4 gait variability parameters (i.e., stride-time variability, stride-length variability, double-support variability, and step-width variability) (Montero-Odasso et al., 2011) were assessed using an electronic walkway system, the MV-1000 (Anima Co. Ltd., Japan), which comprised a sheet-type pressure sensor (240 × 60 cm) with a sampling rate of 100 Hz. Spatiotemporal gait parameters were calculated using an average of 4 to 5 steps included in one trial, and gait variability parameters were defined as a coefficient of the variation (standard deviation divided by mean value) of each step. To exclude the effects of the acceleration and deceleration phase, participants started walking 1.5 m prior to reaching the electronic walkway and stopped 1.5 m beyond it. After the familiarization session, participants performed the usual gait with self-selected speed 5 times (Kressig et al., 2006), and the mean value of 5 trials was used for statistical analysis.

2.5. *Statistical analysis*

The results of continuous variables with normal distribution are presented as the mean and standard deviation, and variables with non-normal distribution are reported as median and interquartile range. Categorical variables are presented as number and percentage.

We compared the baseline characteristics among the groups by one-way analysis of variance or Kruskal–Wallis test for continuous variables and chi-square or Fisher exact test for dichotomous variables, as appropriate. All analyses were conducted on an intention-to-treat basis. The analysis of prospective changes in the gait performance was conducted by applying generalized estimating equations (GEE) with repeated measures. The dependent variables were the spatiotemporal gait parameters and gait variability parameters, and the independent variables were the intervention group, time, and the interaction of group and time. The GEE analysis yields coefficient values that represent the associations between a factor score and the variables included in the model. The main coefficients of interest in each model presented an interaction term for the time point and the intervention group. A significant *p*-value for the interaction coefficient indicates a difference in the change in a factor score depending on each intervention group. No prespecified adjustment was implemented in the entire analysis.

Statistical analyses were performed by using R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria). A two-tailed $p <$ .05 indicated statistical significance for all analyses.

3. Results

3.1. *Study population*

Of the total of 415 eligible study participants, 388 (AT: $n = 95$; RT: $n = 93$; CT: $n = 98$, and control: $n = 102$) participants were used in this analysis according to the exclusion criteria. Among these 388 participants, 36 dropped out before the completion of Week 26 and 25 dropped out during the follow-up period (before the completion of Week 52) (withdrawal rate: 9.3% and 15.7%, respectively; Fig. 1).

The average adherence of participation in exercise sessions was 82.5%, 85.9%, and 83.5% in the AT, RT, and CT groups, respectively. The participants in this study had a mean (SD) age of 72.3 (4.6) years, and 51.8% were men. There were no significant intergroup differences for all of the study variables at the baseline (Table 1 and Supplementary Table S1). At both week 26 and week 52, there was no statistically significant difference in the background of dropouts and continuing participants other than age in the analysis for each group.

3.2. *Effects of exercise intervention on the gait performance*

In the analyses of changes in the longitudinal spatiotemporal gait parameters between the baseline and Week 26, compared with the control group, all three exercises significantly improved all parameters (gait speed, stride time, cadence, stride length, and double-support time) except the step width. The longitudinal analysis between the values at

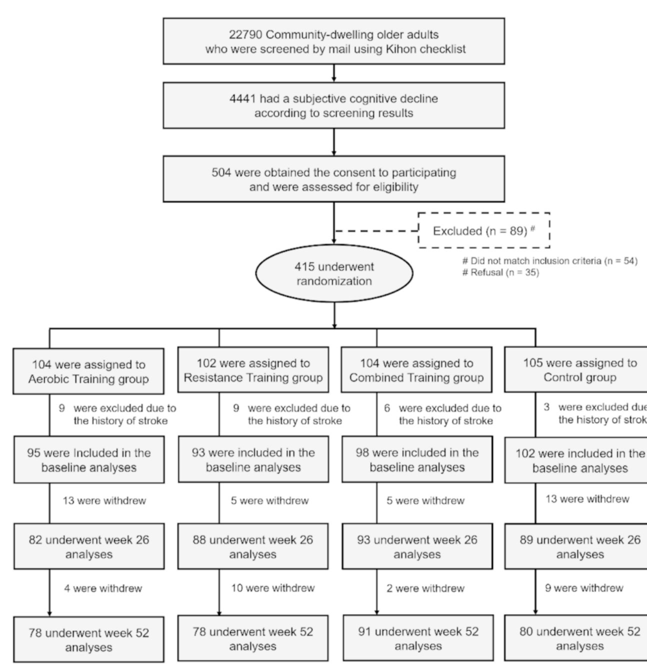

Fig. 1. Flowchart of participant selection.

Table 1
Baseline characteristics of the four intervention groups.

	Overall (n = 388)	AT (n = 95)	RT (n = 93)	CT (n = 98)	Control (n = 102)	p-Value
Age (years)	72.3 ± 4.6	72.2 ± 4.6	72.3 ± 4.8	72.6 ± 4.5	72.1 ± 4.6	0.900
Male (n, %)	201 (51.8)	47 (49.5)	47 (50.5)	57 (58.2)	50 (49.0)	0.538
BMI (kg/m^2)	22.8 ± 2.8	22.6 ± 2.9	22.8 ± 2.8	23.4 ± 2.8	22.4 ± 2.8	0.094
SBP (mmHg)	154.5 ± 19.7	155.1 ± 22.9	155.2 ± 19.1	156.2 ± 19.0	151.6 ± 17.5	0.361
DBP (mmHg)	78.9 ± 11.7	78.2 ± 11.8	79.0 ± 11.3	80.7 ± 13.4	77.7 ± 10.3	0.286
Heart rate (bpm)	77.7 ± 12.1	78.0 ± 12.2	77.6 ± 11.6	77.4 ± 12.7	78.0 ± 12.0	0.985
Medication (n, %)						0.202
0	82 (21.2)	16 (17.0)	22 (23.7)	17 (17.3)	27 (26.5)	
1–2	165 (42.5)	47 (49.5)	39 (41.9)	42 (42.9)	37 (36.3)	
3–4	90 (23.2)	21 (22.1)	14 (15.1)	26 (26.5)	29 (28.4)	
5–6	29 (7.5)	5 (5.3)	11 (11.8)	9 (9.2)	4 (3.9)	
≥7	21 (5.4)	5 (5.3)	7 (7.5)	4 (4.1)	4 (3.9)	
Grip strength (kg)	28.1 ± 7.8	27.5 ± 7.1	27.9 ± 8.2	28.8 ± 8.5	28.4 ± 7.5	0.709
TUG (s)	7.3 ± 1.2	7.3 ± 1.2	7.2 ± 1.2	7.4 ± 1.2	7.2 ± 1.2	0.475
SMI (kg/m^2)	6.5 ± 0.9	6.5 ± 1.0	6.4 ± 1.0	6.6 ± 0.9	6.5 ± 0.9	0.465
Previous fall (n, %)						0.834
Never	284 (73.2)	73 (76.8)	64 (68.8)	73 (74.5)	74 (72.5)	
1 time	65 (16.8)	15 (15.8)	17 (18.3)	17 (17.3)	16 (15.7)	
≥2 times	39 (10.1)	7 (7.4)	12 (12.9)	8 (8.2)	12 (11.8)	
MMSE (points)	26.4 ± 2.6	26.5 ± 2.5	26.1 ± 2.4	26.4 ± 2.7	26.4 ± 2.7	0.793
GDS (points)	3.9 ± 2.9	4.0 ± 2.8	3.4 ± 2.6	4.1 ± 3.0	4.2 ± 3.1	0.229
Comorbidity (n, %)						
Diabetes mellitus	56 (14.4)	12 (12.6)	15 (16.1)	18 (18.4)	11 (10.8)	0.631
Cancer	44 (11.3)	8 (8.4)	11 (11.8)	13 (13.3)	12 (11.8)	0.746
Heart failure	52 (13.4)	13 (13.7)	16 (17.2)	9 (9.2)	14 (13.7)	0.353
Hyperlipidemia	114 (29.4)	33 (34.7)	30 (32.3)	28 (28.6)	23 (22.6)	0.317
Hypertension	163 (42.0)	40 (42.1)	39 (41.9)	45 (45.9)	39 (38.2)	0.911
Osteo-arthropathy	39 (10.1)	7 (7.4)	12 (12.9)	12 (12.2)	8 (7.8)	0.640
Osteoporosis	39 (10.1)	10 (10.5)	10 (10.8)	12 (12.2)	7 (6.9)	0.178
Education (years)	11.5 ± 2.4	11.4 ± 2.5	11.6 ± 2.5	11.5 ± 2.2	11.3 ± 2.7	0.908

Note: Values are expressed as means ± SD, n (%), or median [interquartile range]. Abbreviations: AT = aerobic training; BMI = body mass index; CT = combined training; DBP = diastolic blood pressure; GDS = Geriatric Depression Scale; MMSE = mini-mental state examination; RT = resistance training; SBP = systolic blood pressure; SMI = skeletal muscle index; TUG = Timed Up-and-Go test. p-Values from one-way analysis of variance for continuous variables and the chi-square test for categorical variables are presented.

the baseline and at Week 52 revealed a significant improvement in gait speed, stride length, and double-support time only in the RT group (Table 2 and Fig. 2).

In the analyses of the changes in the gait variability parameters for the three exercise programs between the baseline and Week 26, we observed an improvement of the step-width variability only with CT. There were no significant improvements in the gait variability parameters between the baseline and Week 52 in any exercise program (Table 3).

Table 2
The estimated changes in spatiotemporal gait parameters that were calculated by generalized estimating equations.

	From baseline to Week 26		From baseline to Week 52	
	Change (95% CI)	p-Value	Change (95% CI)	p-Value
Gait speed (cm/s)				
AT	11.1 (5.9 to 16.3)	<0.001	4.6 (−0.9 to 10.1)	0.099
RT	6.5 (1.6 to 11.4)	0.009	5.4 (0.0 to 10.7)	0.049
CT	10.2 (5.5 to 14.9)	<0.001	5.5 (−0.1 to 11.1)	0.053
Control	0		0	
Stride time (ms)				
AT	−34.8 (−56.6 to −13.1)	0.002	−10.8 (−32.9 to 11.3)	0.338
RT	−21.7 (−41.4 to −2.1)	0.030	−11.5 (−30.7 to 7.8)	0.243
CT	−33.7 (−52.9 to −14.4)	0.001	−21.2 (−44.3 to 1.9)	0.073
Control	0		0	
Cadence (step/min)				
AT	4.9 (2.3 to 7.5)	<0.001	1.8 (−1.0 to 4.6)	0.214
RT	2.8 (0.4 to 5.2)	0.020	1.4 (−1.0 to 3.7)	0.264
CT	4.4 (2.2 to 6.7)	<0.001	2.1 (−0.4 to 4.6)	0.106
Control	0		0	
Stride length (cm)				
AT	5.1 (1.8 to 8.3)	0.003	1.9 (−2.4 to 6.2)	0.387
RT	3.3 (0.2 to 6.4)	0.039	4.1 (0.5 to 7.8)	0.028
CT	4.7 (1.7 to 7.7)	0.002	2.3 (−1.8 to 6.2)	0.271
Control	0		0	
Double support time (ms)				
AT	−8.9 (−14.7 to −3.1)	0.003	−3.8 (−9.1 to 1.4)	0.155
RT	−5.6 (−11.1 to −0.1)	0.047	−5.9 (−11.4 to −0.4)	0.037
CT	−6.9 (−12.6 to −1.2)	0.017	−3.9 (−9.5 to 1.7)	0.170
Control	0		0	
Step width (cm)				
AT	0.1 (−0.7 to 0.9)	0.843	−0.3 (−1.2 to 0.7)	0.559
RT	−0.1 (−0.9 to 0.7)	0.812	−0.1 (−1.1 to 0.9)	0.823
CT	0.1 (−0.6 to 0.9)	0.724	0.2 (−0.8 to 1.1)	0.755
Control	0		0	

Note: Reference group of intervention: control; Reference group of time: baseline. The model was adjusted for age, sex, and body mass index.
Abbreviations: AT = aerobic training; CT = combined training; CI = confidence interval; RT = resistance training.

Differences in the changes in various exercise parameters between the intervention groups from the pre- and post-intervention assessments were examined; however, there was no apparent difference in any of the parameters between the different exercise groups (Supplementary Table S2). Short- and long-term changes in physical and cognitive functions other than gait performance have already been reported in elsewhere (Makino et al., 2021).

4. Discussion

The primary objective of this study was to compare the effect of AT, RT, and CT on the gait parameters in older adults with SCD. The secondary objective was to investigate the long-term effects of the above-mentioned exercise interventions. We hypothesized CT is most effective in improving both short- and long-term gait performance.

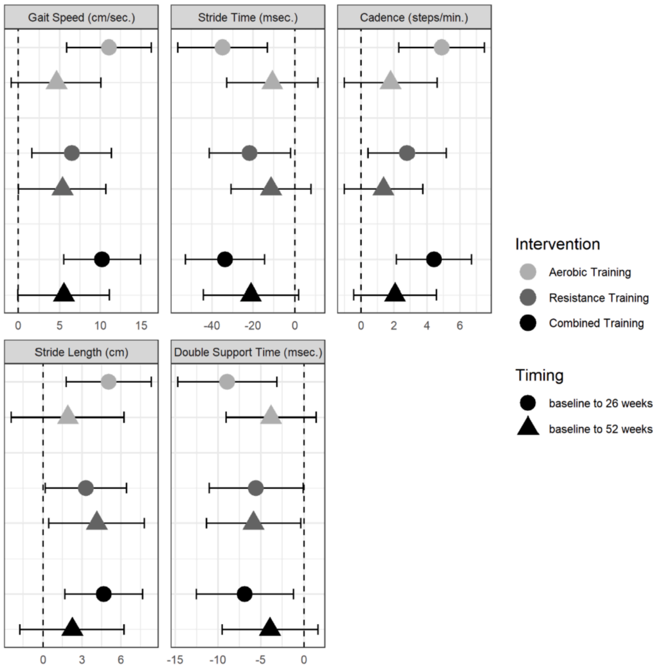

Fig. 2. Estimated gait performance change from the baseline to Week 26 (circle), and to Week 52 (triangle). The horizontal line indicates the 95% confidence interval.

This study demonstrated that the AT, RT, and CT had a short-term effect on the spatiotemporal gait parameters, except for step width, in older adults with SCD. As consistency with a systematic review by Zhang et al. (Zhang et al., 2019), the short-term effectiveness of exercise training on the gait performance are shown. The first novelty of this research is target of intervention; the effectiveness of exercise training was found in older adults with SCD. The second novelty of this research is an insight on the long-term effect of exercise on gait performance; only RT intervention maintained a beneficial effect on spatiotemporal gait parameters until Week 52.

The beneficial effect of AT on gait parameters in this study is considered to have two separate aspects: training for cardiorespiratory fitness and functional mobility training related to walking (Bossers et al., 2014). The mechanism of the beneficial effect of training for cardiorespiratory fitness and functional mobility training on the improvements of gait performance are not elucidated sufficiently. However, some previous studies found evidence of functional and structural brain change which is generated by a repeated walking exercise in healthy individuals (Erickson et al., 2011; Mang et al., 2016; McDonnell et al., 2013). Further investigation using functional magnetic resonance imaging or functional near-infrared spectroscopy is needed to reveal the association among AT, brain structure/function, and gait performance in the future study. The relationships between gait parameters such as gait speed or stride length and the muscle strength are already known (Miyazaki et al., 2013), and previous studies have shown that RT improves the gait parameter (Schwenk et al., 2014; Uematsu et al., 2018), which is in agreement with the results of this study.

The exercise interventions in the current study had little effect on the step width and almost all gait variability parameters, which were in agreement with the findings of Schwenk et al. that a combination of RT and functional mobility training for older adults with dementia had no effect on the step width and the gait variability parameters (Schwenk et al., 2014). Besides, a novel finding of this study was that other exercises such as AT and CT had little effect on the step width and almost all of the gait variability parameters.

Step width and gait variability parameter reflect the control imposed by cognitive factors (Zhang et al., 2019). According to research using

Table 3
The estimated changes in gait variability parameters that were calculated by generalized estimating equations.

	From baseline to Week 26		From baseline to Week 52	
	Change (95% CI)	*p*-Value	Change (95% CI)	*p*-Value
Stride time variability (%)				
AT	−0.3 (−0.7 to 0.2)	0.283	−0.1 (−0.5 to 0.4)	0.765
RT	−0.1 (−0.6 to 0.3)	0.641	0.1 (−0.4 to 0.5)	0.771
CT	−0.1 (−0.6 to 0.4)	0.606	0.2 (−0.3 to 0.6)	0.477
Control	0		0	
Stride length variability (%)				
AT	−0.1 (−0.7 to 0.6)	0.877	−0.2 (−0.8 to 0.5)	0.575
RT	0.5 (−0.1 to 1.0)	0.074	−0.2 (−0.7 to 0.3)	0.480
CT	0.1 (−0.6 to 0.8)	0.801	−0.1 (−0.8 to 0.6)	0.726
Control	0		0	
Double support time variability (%)				
AT	1.1 (−0.5 to 2.7)	0.173	0.5 (−1.0 to 2.0)	0.530
RT	0.9 (−0.7 to 2.5)	0.253	0.9 (−0.7 to 2.5)	0.257
CT	0.9 (−0.7 to 2.4)	0.268	1.2 (−0.3 to 2.7)	0.105
Control	0		0	
Step width variability (%)				
AT	1.4 (−3.3 to 6.1)	0.562	−1.9 (−7.3 to 3.4)	0.479
RT	4.1 (−1.0 to 9.2)	0.116	4.0 (−2.0 to 10.0)	0.195
CT	4.6 (0.4 to 8.9)	0.032	5.0 (−1.2 to 11.2)	0.114
Control	0		0	

Note: Reference group of intervention: control; Reference group of time: baseline. The model was adjusted for age, sex, and body mass index.
Abbreviations: AT = aerobic training; CT = combined training; CI = confidence interval; RT = resistance training.

SPECT for investigating the association of the gait abnormalities and the brain blood flow in older adults with dementia, lower blood flow in the frontal lobes might be responsible for gait disorders (Nakamura et al., 1997). Moreover, another study which investigated the association of the gait abnormalities and specific cognitive functions found that executive function (e.g., cognitive flexibility and processing speed), focus, and switch attention, as well as the inhibition of distractions during walking, are responsible for controlling step width and gait variability parameters (Montero-Odasso et al., 2012; Zhang et al., 2019), which are considered to reflect gait disorders in older adults with cognitive decline, for which we found a mildly significant improvement in this study.

Because some studies have indicated that AT may have positive effects on cognitive functions, such as memory and executive function (Baker et al., 2010; Duzel et al., 2016), the improvements on the step width and gait variability parameters by AT intervention are expected. However, the result did not support our hypothesis, which may have been due to the ceiling effect. Studies have previously shown that abnormalities in gait variability parameters become apparent as the cognitive function deteriorates (Muir et al., 2012). It is possible that there was no or only a minor abnormal gait variability in the SCD participants such that an improvement effect of the exercise intervention could be confirmed. In fact, in the previous studies of older adult patients with dementia, the stride-time variability was approximately 5.2% (MMSE score = 21.0) and 4.8–6.1% (MMSE score = 14.7–20.8) (Beauchet et al., 2013; Schwenk et al., 2014). In our study, the stride-time variability was 2.8% on average, which is much smaller than the variability reported in above studies. Further evaluation, including the measurement of actual cognitive function, of subjects with more severe cognitive impairment is needed to clarify the effect of AT on the gait variability parameters.

The short-term effects on spatiotemporal gait parameters of AT and CT did not find in 52 weeks, whereas the short-term effects on gait speed and stride length of RT persisted at 52 weeks. A systematic review showed that exercise program, including RT, could improve the short-term and long-term gait speeds, although the short-term improvement of exercise interventions without RT disappeared within 3 months after the intervention (Van Abbema et al., 2015). This suggests that incorporating RT into training is essential for long-term beneficial effects on gait speed. In contrast with our hypothesis, CT did not show a long-term effect. It may be because the CT intervention performed only half the duration of RT, which was not sufficient to improve muscle strength. On the other hands, long-term effects on other spatiotemporal gait parameters such as stride length and cadences for patients with dementia are controversial. Kao et al. reported that 8 weeks of intervention, including balance and strength training improved the stride length which was maintained for 12 months (Kao et al., 2018). In contrast, Hauer et al. found that 12 weeks of exercise, with a combination of RT and functional training had long-term improvement only in cadence (Hauer et al., 2012). Because RT in this study had a long-term effect on the stride length but not on the cadence, the result partly supports the results of Kao et al. (Kao et al., 2018). Further research investigating the mechanisms contributing to the improvement of gait performance by RT or the effect of detraining would be expected in the future.

This study had some limitations. First, because the AT in this study focused on stepping and walking, we could not conclude whether the improvement in gait performance from AT is due to the result of an increase in cardiorespiratory fitness or the result of functional mobility training. Second, not all aspects of gait function have been evaluated in this study. Examining the effects of exercise on other gait analysis parameters, such as joint angle (Ritt et al., 2017), joint power, and trunk acceleration (Doi et al., 2012) will provide deeper insights into the mechanisms of gait improvement. Third, since this study is a secondary, exploratory analysis of the TOPICS trial, the correction for multiple comparisons did not perform. Future research with a stricter design is needed. Fourth, since we have not obtained the information about the quantity and quality of the home-based training or daily physical activity during the intervention period (baseline to Week 26) and the post-intervention period (Week 26 to Week 52), the result of the short- and long-term effect may be biased. Fifth, although the intensity of RT was evaluated using the Borg scale following the American College of Sports Medicine guideline (Thomas et al., 2016), such an index based on participants' subjective fatigue may not ensure sufficient objectivity for the intervention. Further examination based on more objective indices such as 1RM is needed. Finally, it is unclear whether the exercise trainings examined in this study have beneficial effects on clinical outcomes, such as the incidence of frailty or falls, following improvements in the gait parameters. Long-term prospective studies are needed to resolve this question.

In conclusion, this study demonstrated that: (1) three different exercise interventions showed effectiveness in all spatiotemporal parameters of older adults with SCD, except for step width. However, only limited effects were found on gait variability parameters. (2) Only RT intervention was able to maintain a sustained beneficial effect on spatiotemporal gait parameters until Week 52. AT, RT and CT may all have the effect of improving the spatiotemporal gait parameters of older adults with SCD. However, RT would be recommended if sustained effects are expected.

CRediT authorship contribution statement

Conceptualization, K.F., H.U., T.M., K.U. and M.K.; Methodology, K. F., T.M., K.U., C.H.H., H.S. and M.K.; Software, K.F. and C.H.H.; Validation, H.U., T.M., K.U., T.H. and T.K.; Formal analysis, K.F. and C.H.H.; Investigation, H.U., K.U. and T.K.; Resources, A.I., C.U., H.S. and M.K.; Data Curation, T.M., T.H, A.I. and C.U.; Writing - Original Draft, K.F., H. U., C.H.H. and M.K.; Writing - Review & Editing, K.F. and M.K.; Visualization, K.F. and C.H.H.; Supervision, H.U., T.M., T.H., A.I., C.U. and H.S.; Project administration, T.M., K.U., H.S. and M.K.; Funding acquisition, H.S. and M.K.

Declaration of competing interest

None.

Acknowledgments

The authors would like to acknowledge all the participants in the TOPICS trial.

Funding

This work was supported by the Center of Innovation (COI) program of Japan Science and Technology (JST) Agency for funding [grant number JPMJCE1317].

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.exger.2021.111590.

References

2020 Alzheimer's disease facts and figures, 2020. Alzheimers Dement. 16, 391–460.
Allali, G., Verghese, J., 2017. Management of gait changes and fall risk in MCI and dementia. Curr. Treat. Options Neurol. 19, 29.
Arai, H., Satake, S., 2015. English translation of the Kihon checklist. Geriatr. Gerontol. Int. 15, 518–519.
Bahureksa, L., Najafi, B., Saleh, A., et al., 2017. The impact of mild cognitive impairment on gait and balance: a systematic review and meta-analysis of studies using instrumented assessment. Gerontology 63, 67–83.
Baker, L.D., Frank, L.L., Foster-Schubert, K., et al., 2010. Effects of aerobic exercise on mild cognitive impairment: a controlled trial. Arch. Neurol. 67, 71–79.
Beauchet, O., Allali, G., Launay, C., Fantino, B., Annweiler, C., 2011. Does memantine improve the gait of individuals with Alzheimer's disease? J. Am. Geriatr. Soc. 59, 2181–2182.
Beauchet, O., Launay, C.P., Allali, G., et al., 2013. Anti-dementia drugs and changes in gait: a pre-post quasi-experimental pilot study. BMC Neurol. 13, 184.
Beauchet, O., Launay, C.P., Allali, G., Herrmann, F.R., Annweiler, C., 2014. Gait changes with anti-dementia drugs: a prospective, open-label study combining single and dual task assessments in patients with Alzheimer's disease. Drugs Aging 31, 363–372.
Beauchet, O., Launay, C.P., Montero-Odasso, M., Annweiler, C., Allali, G., 2015. Anti-dementia drugs-related changes in gait performance while single and dual tasking in patients with Alzheimer disease: a meta-analysis. Curr. Alzheimer Res. 12, 761–771.
Bossers, W.J.R., Scherder, E.J.A., Boersma, F., Hortobagyi, T., van der Woude, L.H.V., van Heuvelen, M.J.G., 2014. Feasibility of a combined aerobic and strength training program and its effects on cognitive and physical function in institutionalized dementia patientsA pilot study, 9 (10), e97577.
Cohen, J., 1992. A power primer. Psychol. Bull. 112 (1), 155–159.
Doi, T., Makizako, H., Shimada, H., et al., 2012. Brain atrophy and trunk stability during dual-task walking among older adults. J. Gerontol. A Biol. Sci. Med. Sci. 67, 790–795.
Duzel, E., van Praag, H., Sendtner, M., 2016. Can physical exercise in old age improve memory and hippocampal function? Brain 139, 662–673.
Erickson, K.I., Voss, M.W., Prakash, R.S., et al., 2011. Exercise training increases size of hippocampus and improves memory. Proc. Natl. Acad. Sci. U. S. A. 108 (7), 3017–3022.
Fried, L.P., Tangen, C.M., Walston, J., et al., 2001. Frailty in older adults: evidence for a phenotype. J. Gerontol. A Biol. Sci. Med. Sci. 56, M146–M156.
Gates, N., Fiatarone Singh, M.A., Sachdev, P.S., Valenzuela, M., 2013. The effect of exercise training on cognitive function in older adults with mild cognitive impairment: a meta-analysis of randomized controlled trials. Am. J. Geriatr. Psychiatry 21, 1086–1097.
Guirguis-Blake, J.M., Michael, Y.L., Perdue, L.A., Coppola, E.L., Beil, T.L., 2018. Interventions to prevent falls in older adults updated evidence report and systematic review for the US preventive services task force. JAMA 319, 1705–1716.
Hardy, S.E., Perera, S., Roumani, Y.F., Chandler, J.M., Studenski, S.A., 2007. Improvement in usual gait speed predicts better survival in older adults. J. Am. Geriatr. Soc. 55 (11), 1727–1734.

Hauer, K., Schwenk, M., Zieschang, T., Essig, M., Becker, C., Oster, P., 2012. Physical training improves motor performance in people with dementia: a randomized controlled trial. J. Am. Geriatr. Soc. 60, 8–15.
Huang, C.H., Umegaki, H., Makino, T., et al., 2020. Effect of various exercises on frailty among older adults with subjective cognitive concerns: a randomised controlled trial. Age Ageing afaa086.
Huang, C.H., Umegaki, H., Makino, T., et al., 2020. Effect of various exercises on intrinsic capacity in older adults with subjective cognitive concerns. J. Am. Med. Dir. Assoc. S1525–8610 (20), 30570–30573.
Kao, C.C., Chiu, H.L., Liu, D., et al., 2018. Effect of interactive cognitive motor training on gait and balance among older adults: a randomized controlled trial. Int. J. Nurs. Stud. 82, 121–128.
Kemoun, G., Thibaud, M., Roumagne, N., et al., 2010. Effects of a physical training programme on cognitive function and walking efficiency in elderly persons with dementia. Dement. Geriatr. Cogn. Disord. 29, 109–114.
Kokkinos, P.F., Faselis, C., Myers, J., et al., 2017. Cardiorespiratory fitness and incidence of major adverse cardiovascular events in US veterans: a cohort study. Mayo Clin. Proc. 92, 39–48.
Kressig, R.W., Beauchet, O., European GAITRite Network Group, 2006. Guidelines for clinical applications of spatio-temporal gait analysis in older adults. Aging Clin Exp Res 18, 174–176.
Lamb, S.E., Sheehan, B., Atherton, N., et al., 2018. Dementia and physical activity (DAPA) trial of moderate to high intensity exercise training for people with dementia: randomised controlled trial. BMJ 361, k1675.
Maki, Y., Ura, C., Yamaguchi, T., et al., 2012. Effects of intervention using a community-based walking program for prevention of mental decline: a randomized controlled trial. J. Am. Geriatr. Soc. 60, 505–510.
Makino, T., Umegaki, H., Ando, M., et al., 2021. Effects of aerobic, resistance, or combined exercise training among older adults with subjective memory complaints: a randomized controlled trial. J. Alzheimers Dis. 82, 701–717.
Mang, C.S., Brown, K.E., Neva, J.L., Snow, N.J., Campbell, K.L., Boyd, L.A., 2016. Promoting motor cortical plasticity with acute aerobic exercise: A role for cerebellar circuits. Neural Plast 6797928.
Marques, N.R., Spinoso, D.H., Cardoso, B.C., Moreno, V.C., Kuroda, M.H., Navega, M.T., 2018. Is it possible to predict falls in older adults using gait kinematics? Clin. Biomech. (Bristol, Avon) 59, 15–18.
McDonnell, M.N., Buckley, J.D., Opie, G.M., Ridding, M.C., Semmler, J.G., 2013. A single bout of aerobic exercise promotes motor cortical neuroplasticity. J. Appl. Physiol. 114, 1174–1182.
Miyazaki, J., Murata, S., Horie, J., Uematsu, A., Hortobágyi, T., Suzuki, S., 2013. Lumbar lordosis angle (LLA) and leg strength predict walking ability in elderly males. Arch. Gerontol. Geriatr. 56, 141–147.
Montero-Odasso, M., Muir, S.W., Hall, M., et al., 2011. Gait variability is associated with frailty in community-dwelling older adults. J. Gerontol. A Biol. Sci. Med. Sci. 66, 568–576.
Montero-Odasso, M., Verghese, J., Beauchet, O., Hausdorff, J.M., 2012. Gait and cognition: a complementary approach to understanding brain function and the risk of falling. J. Am. Geriatr. Soc. 60, 2127–2136.
Muir, S.W., Speechley, M., Wells, J., Borrie, M., Gopaul, K., Montero-Odasso, M., 2012. Gait assessment in mild cognitive impairment and Alzheimer's disease: the effect of dual-task challenges across the cognitive spectrum. Gait Posture 35, 96–100.
Nakamura, T., Meguro, K., Yamazaki, H., et al., 1997. Postural and gait disturbance correlated with decreased frontal cerebral blood flow in Alzheimer disease. Alzheimer Dis. Assoc. Disord. 11, 132–139.
Parihar, R., Mahoney, J.R., Verghese, J., 2013. Relationship of gait and cognition in the elderly. Curr. Transl. Geriatr. Exp. Gerontol. Rep. 2:10.1007/s13670-013-0052-7.
Ritt, M., Schulein, S., Lubrich, H., Bollheimer, L.C., Sieber, C.C., Gassmann, K.G., 2017. High-technology based gait assessment in frail people: associations between spatio-temporal and three-dimensional gait characteristics with frailty status across four different frailty measures. J. Nutr. Health Aging 21, 346–353.
Rubenstein, L.Z., 2006. Falls in older people: epidemiology, risk factors and strategies for prevention. Age Ageing 35 Suppl 2, ii37-ii41.
Schwenk, M., Zieschang, T., Englert, S., Grewal, G., Najafi, B., Hauer, K., 2014. Improvements in gait characteristics after intensive resistance and functional training in people with dementia: a randomised controlled trial. BMC Geriatr. 14, 73.
Strath, S.J., Swartz, A.M., Bassett, D.R., O'Brien, W.L., King, G.A., Ainsworth, B.E., 2000. Evaluation of heart rate as a method for assessing moderate intensity physical activity. Med. Sci. Sports Exerc. 32, S465–S470.
Sudarsky, L., 1990. Current concepts - gait disorders in the elderly. N. Engl. J. Med. 322, 1441–1446.
Thomas, D.T., Erdman, K.A., Burke, L.M., 2016. American college of sports medicine joint position statement. nutrition and athletic performance. Med. Sci. Sports Exerc. 48, 543–568.
Uematsu, A., Hortobágyi, T., Tsuchiya, K., et al., 2018. Lower extremity power training improves healthy old adults' gait biomechanics. Gait Posture 62, 303–310.
Van Abbema, R., De Greef, M., Craje, C., Krijnen, W., Hobbelen, H., Van der Schans, C., 2015. What type, or combination of exercise can improve preferred gait speed in older adults? A meta-analysis. BMC Geriatr 15, 72.
van Kan, G.A., Rolland, Y., Andrieu, S., et al., 2009. Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people an international academy on nutrition and aging (IANA) task force. J. Nutr. Health Aging 13 (10), 881–889.
Visser, H., 1983. Gait and balance in senile dementia of Alzheimer's type. Age Ageing 12, 296–301.
Zhang, W.H., Low, L.F., Gwynn, J.D., Clemson, L., 2019. Interventions to improve gait in older adults with cognitive impairment: a systematic review. J. Am. Geriatr. Soc. 67, 381–391.