Research Report

Effects of a 16-Week Multimodal Exercise Program on Physical Performance in Individuals With Dementia: A Multicenter Randomized Controlled Trial

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ABSTRACT

Background and Purpose: Dementia affects physical as well as cognitive performance. In individuals with dementia (IWD), decline in physical performance increases with disease progression and is associated with higher functional dependence and decreased quality of life. It is paramount to examine factors that potentially preserve physical performance in IWD, particularly in light of conflicting findings on the effectiveness of physical activity interventions on physical performance of IWD, mainly due to limited number of high-quality studies, large heterogeneity in methods used, or insufficient reporting of methods. The aim of this study was to investigate the effects of a 16-week multimodal exercise program (MEP) combining physical and cognitive tasks on physical performance in IWD, and to identify individual characteristics of MEP responders.

Methods: A multicenter randomized controlled trial with assessment methods identified by an expert panel was conducted. We included 319 IWD of mild to moderate severity, older than 65 years, who underwent a standardized MEP specifically designed for IWD. At baseline and immediately after the MEP, we assessed physical performance (ie, mobility, balance, and strength) and function of lower extremities (primary outcomes). Potential effects of the MEP on physical performance were identified using 2-factor analyses of variance with repeated measurements within 2 samples (ie, intention-to-treat and per-protocol sample). Additionally, we compared characteristics related to physical performance between positive, non-, and negative responders.

Results and Discussion: Neither analysis procedure revealed statistically significant time×group effects. However, 28% to 40% of participants were positive responders with regard to balance, and strength and function of lower extremities; and these persons had statistically significant lower baseline performance in the corresponding assessments.

Conclusions: This randomized controlled trial revealed no overall effects of the MEP on physical performance, probably due to high heterogeneity of the study sample. Findings in responder analysis showed that IWD with lower physical performance at baseline tended to benefit more than those with higher baseline performance. Thus, a higher degree of individualization of the MEP depending on baseline performance on IWD may improve overall MEP effectiveness.

Key Words: cognitive impacts, dementia, motor impacts, physical activity, physical performance

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INTRODUCTION

The successful completion of physically demanding tasks requires certain levels of mobility, balance, and strength. These basic abilities are summarized by the construct of "physical performance."[1] A decline in physical performance reduces the capacity to successfully perform activities of daily living (ie, eating and bathing). This decline is expected during aging but can be further accelerated by various aging-related disorders, thereby leading to an increased dependency in everyday life.[2] In contrast, maintenance of independency and individual autonomy is critical for quality of life in older adults.[3]

Decreased mobility or balance and consequently activities of daily living are particularly common in individuals with dementia (IWD).[4] Compared to cognitively unimpaired older adults and individuals with mild cognitive impairment, IWD have lower performance in balance and mobility.[6,7] With regard to gait, dementia is associated with decreased walking speed, shortened stride length, and increased double support time.[8] To date, less is known about strength and endurance in IWD.[9] Overall, the clinical symptoms of dementia are not restricted to decreasing cognitive skills, but also have an impact on patients' physical performance.

It has been postulated that there are causal relationships between declined physical performance and cognitive impairments, particularly as the pathological changes underlying Alzheimer's disease also affect regions known to subserve physical performance.[10] For example, control systems for motor regulation, initiation, planning, and execution are located in several cortical and subcortical regions known to be affected by Alzheimer's disease.[11] Furthermore, it is generally hypothesized that impairments in physical performance increase with disease progression,[12] and are also accompanied by a higher risk of falls.[13] In light of these associations, it is paramount to investigate whether multimodal interventions combining physical activity and cognitive tasks may impact physical performance in IWD.

In the absence of a cure for dementia and given the considerable side effects of currently prescribed drugs,[14] nonpharmacological interventions have gained increasing importance in recent years. Indeed, there is growing evidence that physical activity interventions may slow a decline in physical performance.[15] However, in IWD this evidence is less clear compared with institutionalized elderly persons with multiple diagnoses.[1] Previous reviews have mainly reported positive effects of physical activity on lower limb strength and activities of daily living in IWD.[15-17] Potential effects on mobility vary between studies, but are in general higher than for other motor skills.[15,17] However, conclusive evidence of the impact of physical activity interventions on physical performance in IWD does not exist. This may be due to limited numbers of high-quality studies and large heterogeneity in methods used, as well as insufficient reporting of methods, particularly with regard to intervention modalities (eg, intensity of exercise sessions or included tasks).[15,16,18] There is still a lack in trials that focus on multimodal exercise programs (MEPs) in a group setting of high aged IWD with physical impairments that can be implemented in care facilities.[23,35]

The aim of this study was therefore to examine the effects of an MEP that combined both physical and cognitive tasks on the primary outcomes of physical performance (ie, mobility, balance, and strength and function of lower extremities) in IWD. The secondary aim was to overcome existing methodological deficits by designing a multicenter randomized controlled trial (RCT) with assessment methods identified by an expert panel,[19] as well as designing and evaluating a sustainable multimodal intervention adjusted to the characteristics and needs of IWD. Our main hypothesis was that IWD would increase their physical performance after a 16-week MEP compared with a control group that received only conventional treatment. Additionally, we aimed at investigating the individual responses to the MEP as recommended by the Food and Drug Administration[20] (ie, a responder analysis allows for an assessment of clinical relevance and potentially helps to increase the translation of the results into clinical practice).

METHODS

Details of this study have been described previously in the study protocol,[21] and we followed the guidelines and recommendations of the Consolidated Standards of Reporting Trials statements.[22] The study was retrospectively registered in the German National Register of Clinical Trials (blinded) and was approved by the ethics committee of the blinded.

Study Design, Participants, and Randomization

The study included a multicenter parallel-group RCT with baseline and postassessments and an allocation ratio of 2:1 for the intervention (IG) and control groups (CG), respectively. A power analysis (G*Power 3, Version 3.1.9.2, 2-factor analysis of variance [ANOVA] with repeated measurement, 2 groups and 2 measurements, $\alpha = .05$, $1 - \beta = .80$, $\eta^2 = .01$) determined a required total sample size of 200 participants. The calculated sample size was based on the assumptions that even small effects are relevant with regard to the rapid disease progression expected in IWD.

Recruitment for this study took place in 36 care facilities for older persons located in South-Western Germany. Employees of the respective care facilities were asked to identify potential participants. Before entering the study, written consent of participants or their legal guardians was obtained. After baseline assessment, final inclusion or exclusion was determined according to the following criteria:

- *Inclusion criteria*: (*a*) diagnosis of dementia or "suspected" dementia (ie, person with dementia as suspected by the treating physician based on *International Classification of Diseases, Tenth Revision* [*ICD-10*] criteria and Mini-Mental State Examination [MMSE] performance but without a confirmed diagnosis or awaiting further clinical evaluation); (*b*) Alzheimer's disease, vascular dementia, or other primary dementia; (*c*) mild to moderate stage of dementia (MMSE 10-24); (*d*) older than 65 years; (*e*) walking ability of at least 10 m with or without walking aid; and (*f*) clearance from a general practitioner.
- *Exclusion criteria*: (*a*) secondary dementia; (*b*) other severe cognitive impairments; (*c*) other severe neurological conditions; (*d*) other severe acute diseases; and (*e*) severe motor impairments.

Baseline assessments were performed before participants were randomly allocated to the IG or CG by minimization (MinimPy, Version 0.3). Randomization was stratified by each care facility with an allocation ratio of 2:1 in favor of the IG. Investigators were blinded to group allocation.

Intervention

The MEP was specifically developed for IWD and thus combined both physical and cognitive tasks. The MEP was developed based on theoretical considerations, results from a previous pilot study,[23] and a literature review.[18] The main objective was to improve physical performance in IWD. The contents of the MEP were closely related to everyday activities and can be divided into tasks mainly requiring strength (43%), balance (25%), endurance (16%), flexibility (13%), and not further-specified tasks (3%).

The participants of the IG received the MEP in addition to conventional treatment for a duration of 16 weeks. Conventional treatment in the care facilities included, for example, individualized medication, standard care, or therapeutic applications and was maintained during the intervention period. Participants of the CG only received the conventional treatment for 16 weeks. The MEP was provided to the IG 2 times a week on nonconsecutive days by 2 skilled instructors, and delivered in a group setting of up to 12 participants. We opted for a frequency of 2 training sessions per week, as our previous literature review[18] showed that 2 sessions a week can induce changes in physical performance of IWD. Also, the decision for 2 training sessions per week was guided by 2 further reasons: first, we aimed to implement the MEP successfully and sustainably within the care facilities and a higher frequency of sessions would not have been feasible; second, the resources of the care facilities regarding room occupation, workload of nursing staff, or appropriate grouping were limiting and did not allow for a higher number of training sessions. Each session lasted for 60 minutes, with exercise time being about 45 minutes. The remaining time was spent for explanation of tasks and breaks in between tasks.

The MEP was not specifically tailored to individual baseline levels of physical performance of participants. Rather, all tasks were carried out with medium to submaximal intensity for all participants of the IG. Intensity was determined by the experienced instructors and was based on a literature review of geriatric exercise programs for older samples. The progression of the MEP with regard to intensity was predefined by an increase in the difficulty level of each exercise (see Appendix A, Table A2). Thus, intensity and difficulty levels of the participants were not individually increased throughout the intervention period but followed a predefined progression plan. Cognitive tasks included in the MEP mainly focused on the stimulation of memory, attention, language, and executive functions and also progressed in intensity and degree of difficulty from session to session.

In addition to certain didactic aspects such as adaptation to cognitive levels of participants or adjusted communication, the MEP aimed to provide the participants with orientation and familiarity, as well as a sense of security through ritualization. For this reason, each session was structured similarly and consisted of 3 parts (ie, arrival, destination, and departure), which were embedded in imagination journeys. Arrival and departure indicated the beginning and end of a session and remained consistent over the intervention period. The main aims of these 2 parts of the MEP, lasting about 5 minutes each, were to physically and cognitively prepare the participants for the exercise and cognitive tasks, and to cool down and relax body and mind after the main part of the session. The destination was the main part of the session, and changed from session to session with alternating physical and cognitive tasks. Prior to the first session, a social gathering session was held for all participants of the IG to become familiar with the instructors. A caregiver familiar to the participants additionally joined each MEP session to support the instructors, if and when needed.

To ensure standardization of the MEP as well as appropriate progression of intensity from session to session, we applied 2 strategies: (1) experienced and qualified instructors and (2) detailed schedules for all 32 training sessions that were followed by the instructors (see Appendix A, Table A3, and Trautwein et al[21]). All instructors had a background in sports and exercise science and received a specific training (see Appendix A, Table A1) on how to guide the MEP as well as consider and meet the specific demands and needs of IWD. Modifications of the schedules for each session were only allowed due to safety concerns (eg, to avoid falls). These modifications were based on individual decisions of the instructors, and mainly determined whether a task was carried out in sitting (safer) or standing position (less safe).

Outcomes and Assessments

Primary outcomes of this study were mobility, balance, as well as strength and function of lower limbs. These outcomes were measured using various assessments (Table 1).

The physical assessments were identified and selected by an international expert panel, which mainly focused on appropriateness and feasibility of the assessments for the purpose of this study. Details on this selection process and the final assessment battery can be found in Trautwein et al.[19] Before and after the 16-week intervention, baseline and postassessments were carried out with all participants of the IG and CG. The assessments took place within the care facilities by trained study staff. We deliberately aimed at testing a participant on the same day of the week during both baseline and postassessment, and also followed the same sequence of tests to decrease potential assessment bias.

Mobility was assessed using the Timed Up and Go test (TUG) and the 6-m walk test (6MWT). The TUG was conducted twice by asking participants to rise from a chair, walk 3 m, turn around, and then go back and sit down again on the chair. The 6MWT was administered twice. Participants were asked to walk from one side of the room to the other side, where a distance of 6 m was marked using

Table 1. Primary Outcome Measures

Primary Outcome	Assessments (at Baseline and After a 16-wk Intervention Period)
Mobility	Timed Up and Go test[24]
	6-m walk test[25]
Balance	Frailty and Injuries: Cooperative Studies of Intervention Techniques—subtest 4[26]
Strength and function of lower extremities	Modified 30-s chair-stand test[27,33]
	Modified Short Physical Performance Battery[28]

a line on the floor. When participants crossed the line, the time required to walk 6 m was measured. Before and after the line, participants had about 2 m for acceleration and deceleration. Walking aids were allowed for all assessments of mobility. Relative test-retest reliability for the 6MWT among IWD with mild to moderate dementia is documented from an intraclass correlation coefficient (ICC) = 0.83 to 0.89 and for the TUG from an ICC from 0.72 to 0.99. Absolute test-retest reliability presented with the minimal detectable change ($MDC_{95\%}$) amounts for the 6MWT 31.6% to 41.5% and for the TUG 15.8% to 39.6%.[33,31] Information about content and construct validity of the TUG and the 6MWT is currently not available for IWD.[31]

Static balance was determined using the Frailty and Injuries: Cooperative Studies of Intervention Techniques–subtest 4 (FICSIT-4), where participants were asked to perform 4 different standing positions (Romberg, semitandem, tandem, and single leg) for 10 seconds. The FICSIT-4 performance is rated on a scale of 0 to 5 points. If participants could not hold the first position for at least 3 seconds, a score of 0 was given. In contrast, participants received a score of 5 if they were able to stand in the most difficult (ie, single-leg position for at least 10 seconds).[26] Test-retest reliability of individuals with mild to moderate dementia for the FICSIT-4 is reported from an ICC from 0.79 to 0.82 and an $MDC_{95\%}$ from 59.4% to 71.1%,[33,31] To date, there is no information available about content and construct validity of the FICSIT-4 in IWD.[31]

Strength and function of lower limbs was assessed using the modified 30-second chair-stand test (30s CST) and the modified Short Physical Performance Battery (modified SPPB). For the modified 30s CST, participants were asked to stand up from a chair (height 46 cm, with armrests) as often as possible for 30 seconds. Time to perform 5 repetitions was recorded. The modified version allows the use of armrests,[27] which is essential for the majority of elderly IWD to safely perform this test. The SPPB[28] focuses on the lower extremities. The modified SPPB, like the SPPB, consists of the 3 subscales: FICSIT-4 for standing balance, walking speed (out of 6MWT) for mobility, and time required for 5 repetitions of the modified 30s CST for strength, and function of the lower limbs. The modified SPPB is scored on a scale of 0 to 12, with higher scores denoting better physical function. The SPPB is a reliable and valid measure in community-dwelling older adults.[29] In IWD living in care facilities, a pilot study concluded that relative reliability is acceptable, whereas absolute reliability is rather moderate.[30] No information is currently available about content and construct validity of modified 30s CST, or modified SPPB in IWD.[31] Criterion validity, however, was previously reported for the SPPB, and showed sufficient ability to identify individuals with low aerobic capacity based on correlations with peak oxygen consumption (assessed with a cycle ergometer test).[32] Test-retest reliability for the modified 30c CST in this setting varies from an ICC from 0.79 to 0.88 and an $MDC_{95\%}$ from 33.2% to 45.7%; for the SPPB it is currently unkonwn.[31,33]

The secondary outcome of this study was overall cognition determined by the MMSE. Moreover, body mass and height were measured (Seca 813 Robusta scale and Seca stadiometer, Hamburg, Germany), and the body mass index was calculated. Attendance of participants was documented by instructors for each session. Sample characteristics such as age, sex, use of walking aids, diagnosis, and etiology of dementia, as well as number of medications and the Cumulative Illness Rating Scale, were assessed using a questionnaire before baseline assessments. The questionnaire was completed by employees of the care facilities or the general practitioner.

Statistical Analysis

The statistical analyses to examine a potential impact of the MEP on physical performance were calculated within 2 samples:

1. The sample used for the per-protocol analysis was the original sample, including all participants of the IG who attended at least 75% of sessions and all participants of the CG. The sample size for this analysis was further reduced by missed assessments of participants, which may be due to lack of motivation.
2. A revised sample was generated for the intention-to-treat analysis. To this end, all participants who fulfilled the inclusion criteria and were randomized to either the IG or CG were considered, except for deceased participants. For this reason, a multiple-imputation procedure (fully conditional specification imputation method, 10 imputations, and 10 iterations) of the primary outcomes was applied to handle missing data. Several variables were considered as predictors for the multiple imputation (ie, all primary outcomes supplemented by attendance rate), as well as related physical and cognitive performance. To ensure plausibility of imputed data, further constraints were defined such as minimum and maximum values according to observed range in each variable, rounding according to original data, 100 maximal case draws, and 10 maximal parameter draws. We considered pooled results as provided by SPSS or reported ranges observed throughout the imputations as final estimates, if SPSS did not support pooled results.

Baseline characteristics of participants were compared between the IG and CG using χ^2 tests for categorical data, *t* tests for continuous data, and Mann-Whitney *U* tests for nonparametric variables. Normally distributed data (as confirmed by the Shapiro-Wilk test and relevant graphs) are presented as means and standard deviations. Treatment effects were analyzed and presented as within-group effects (differences from baseline to postassessments) and time×group effects (changes from baseline to postassessments between groups). Therefore, paired *t* tests and 2-factor ANOVA with repeated measurements were calculated for the primary outcomes of the intention-to-treat as well as the per-protocol analysis.

The responder analysis was conducted within the IG based on distribution-based methods (ie, information about the standard measurement error of the assessments within the per-protocol analysis). To this end, a positive change of 10% and more from baseline was defined as a positive responder. Changes between positive and negative 10% were defined as nonresponders, and negative changes of 10% or more were defined as negative responders. Selected sample characteristics were compared between positive, non-, and negative responders using Kruskal-Wallis tests and 1-factor ANOVA. For post hoc analyses, we used Dunn-Bonferroni tests and Tukey-Kramer post hoc tests, respectively. R and partial η^2 served as effect sizes. All statistical analyses were done using IBM SPSS, Version 25 (IBM Corporation, Armonk, New York). The significance level was set at $P < .05$ for all tests. Evaluation and data entry were conducted by trained and experienced investigators.

RESULTS

Sample Characteristics

Between March 2015 and March 2017, 600 IWD were screened for eligibility, and 319 persons were considered suitable for the study. After baseline assessments, 201 participants were randomly allocated to the IG and 118 to the CG. The overall dropout rate was 8%. The Figure shows the overall flow of participants.

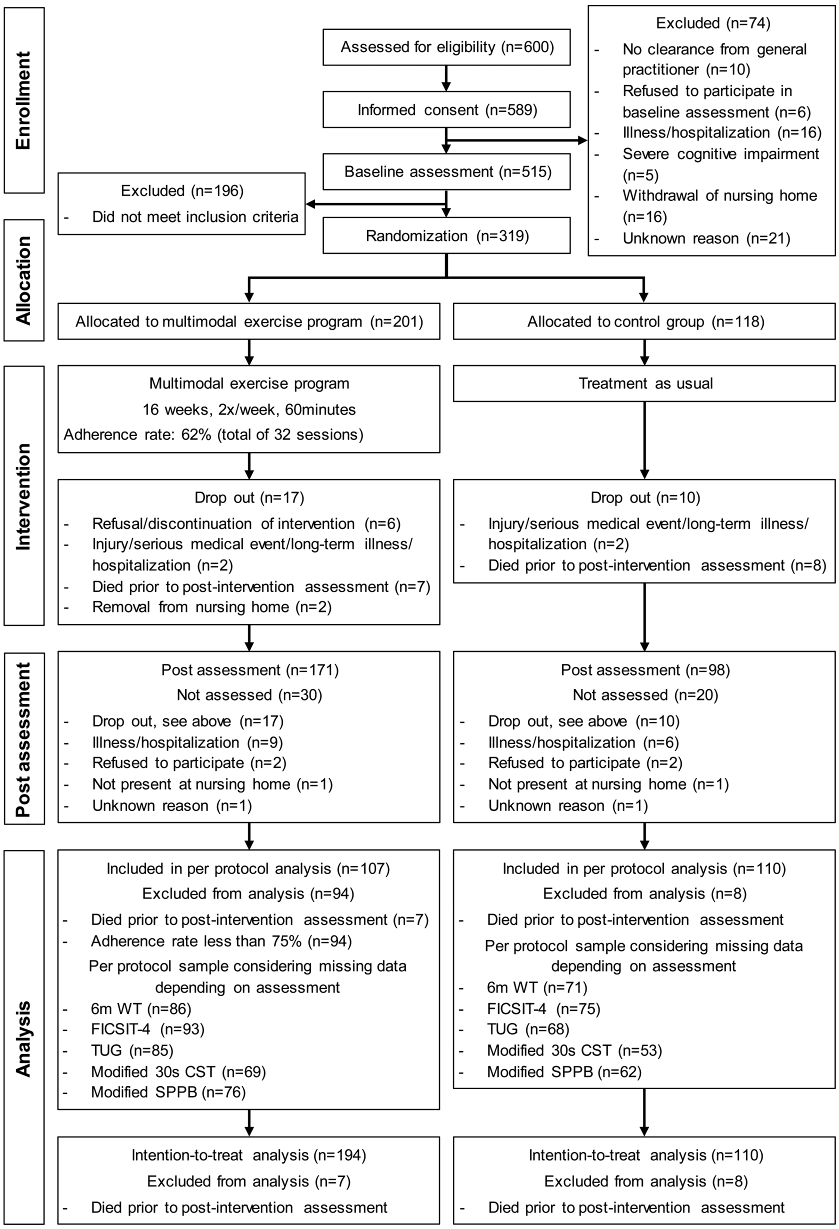

Figure. Flow of participants.

Table 2. Sample Characteristics of Participants at Baseline for the Intention to Treat Analysis

Characteristics	Total Sample N = 304 Mean (SD)	Intervention Group n = 194 Mean (SD)	Control Group n = 110 Mean (SD)	Group Differences $t(df)/\chi^2(df)$, P
Age, y	86.1 (6.1)	85.8 (6.3)	86.6 (5.8)	$t_{(302)} = 1.135$, $P = .257$
MMSE	17.0 (4.1)	16.9 (4.3)	17.1 (3.8)	$t_{(250.853)} = 0.389$, $P = .698$
BMI, kg/m² (n = 270)	28.0 (4.7)	28.5 (4.7)	27.2 (4.8)	$t_{(268)} = -2.307$, $P = .022$[a]
CIRS (n = 178)				
Morbidity index	9.3 (4.8)	9.2 (4.4)	9.5 (5.6)	$t_{(176)} = 0.469$, $P = .640$
Severity index	1.6 (0.4)	1.6 (0.4)	1.6 (0.4)	$t_{(176)} = 0.024$, $P = .981$
Number of medications (n = 234)	6.9 (3.9)	7.5 (3.8)	6.0 (4.0)	$t_{(232)} = -2.686$, $P = .008$
	n (%)	**n (%)**	**n (%)**	
Sex				$\chi^2(1) = 1.223$, $P = .269$
Female	262 (86.2)	164 (84.5)	98 (89.1)	
Male	42 (13.8)	30 (15.5)	12 (10.9)	
Diagnosis of dementia				$\chi^2(2) = 3.693$, $P = .158$
Yes	200 (65.8)	129 (66.5)	71 (64.5)	
No	55 (18.1)	39 (20.1)	16 (14.5)	
Unknown	49 (16.1)	26 (13.4)	23 (20.9)	
Type of dementia				$\chi^2(4) = 9.005$, $P = .050$
Alzheimer's disease	51 (16.8)	36 (18.6)	15 (13.6)	
Vascular dementia	45 (14.8)	34 (17.5)	11 (10.0)	
Mixed dementia	8 (2.6)	4 (2.1)	4 (3.6)	
Other	4 (1.3)	4 (2.1)	0 (0.0)	
Unknown	92 (30.3)	51 (26.3)	41 (37.3)	
No/unknown diagnosis	104 (34.2)	65 (33.5)	39 (35.5)	
Use of walking aid				$\chi^2(2) = 4.104$, $P = .128$
No walking aid	64 (21.5)	46 (24.5)	18 (16.5)	
Walker	216 (72.7)	134 (71.3)	82 (75.2)	
Waking stick/s	17 (5.7)	8 (4.3)	9 (8.3)	

Abbreviations: BMI, body mass index; CIRS, Cumulative Illness Rating Scale; *df*, degree of freedom; MMSE, Mini-Mental State Examination; SD, standard deviation.

After dropouts, a final sample of 304 participants was available for the intention-to-treat analysis (Table 2). The original sample for the per-protocol analysis was further reduced by 87 participants within the IG due to less than 75% attendance to the MEP (Table 3).

The sample characteristics of the original and revised samples can be found in Tables 2 and 3. Within both samples, no statistically significant differences at baseline between the IG and the CG were identified for most variables, except for the number of medications and body mass index.

Effects of the Multimodal Exercise Program on Physical Performance

Missing data ranged between 9.1% and 43.9%. Reasons for missing data besides death were medical constrains, refusal, or discontinuation of the assessment. Table 4 presents an overview of the effects of the MEP on physical performance in the revised sample. Participants in the IG had a mean attendance of 62%. No statistically significant differences in the primary outcomes between the 2 groups at baseline, or within the groups after the 16-week intervention period, were found. Similarly, we observed no statistically significant time×group effects.

The effects of MEP in the original sample are presented in Table 5. Participants in the IG had a mean attendance of 91%. Overall, the differences between the 2 groups at baseline, or within the groups after the 16-week intervention period, were not statistically significant. Similarly, no statistically significant time×group effects were found.

Table 3. Sample Characteristics of Participants at Baseline for the Per-Protocol Analysis

Characteristics	Total Sample N = 217 Mean (SD)	Intervention Group n = 107 Mean (SD)	Control Group n = 110 Mean (SD)	Group Differences $t(df)/\chi^2(df)$, P
Age, y	85.9 (6.3)	85.2 (6.7)	86.6 (5.8)	$t_{(215)} = 1.617$, $P = .107$
MMSE	16.9 (4.1)	16.8 (4.4)	17.1 (3.8)	$t_{(208.706)} = 0.603$, $P = .547$
BMI, kg/m² (n = 199)	27.8 (4.7)	28.4 (4.5)	27.2 (4.8)	$t_{(197)} = -1.960$, $P = .051$
CIRS (n = 124)				
Morbidity index	9.3 (5.0)	9.0 (4.4)	9.5 (5.6)	$t_{(122)} = 0.554$, $P = .581$
Severity index	1.6 (0.4)	1.5 (0.4)	1.6 (0.4)	$t_{(122)} = 0.835$, $P = .405$
Number of medication (n = 167)	6.8 (4.0)	7.5 (3.9)	6.0 (4.0)	$t_{(165)} = -2.347$, $P = .020$
	n (%)	**n (%)**	**n (%)**	
Sex				$\chi^2(1) = 1.161$, $P = .281$
Female	188 (86.6)	90 (84.1)	98 (89.1)	
Male	29 (13.4)	17 (15.9)	12 (10.9)	
Diagnosis of dementia				$\chi^2(2) = 4.154$, $P = .125$
Yes	145 (66.8)	74 (69.2)	71 (64.5)	
No	37 (17.1)	21 (19.6)	16 (14.5)	
Unknown	35 (16.1)	12 (11.2)	23 (20.9)	
Type of dementia				$\chi^2(4) = 6.563$, $P = .134$
Alzheimer's disease	29 (13.4)	14 (13.1)	15 (13.6)	
Vascular dementia	33 (15.2)	22 (20.6)	11 (10.0)	
Mixed dementia	6 (2.8)	2 (1.9)	4 (3.6)	
Other	2 (0.9)	2 (1.9)	0 (0.0)	
Unknown	75 (34.6)	34 (31.8)	41 (37.3)	
No/unknown diagnosis	72 (33.2)	33 (30.8)	39 (35.5)	
Use of walking aid				$\chi^2(2) = 4.674$, $P = .097$
No walking aid	48 (22.5)	30 (28.8)	18 (16.5)	
Walker	148 (69.5)	66 (63.5)	82 (75.2)	
Waking stick/s	17 (8.0)	8 (7.7)	9 (8.3)	

Abbreviations: BMI, body mass index; CIRS, Cumulative Illness Rating Scale; *df*, degree of freedom; MMSE, Mini-Mental State Examination; SD, standard deviation.

Differences in Characteristics Between Positive, Negative, and Nonresponders (Intervention Group Only, Per-Protocol Analysis)

The responder analysis was calculated for the IG based on the original sample. Between 28% and 40% of participants improved their physical performance by at least 10% (positive responders). Moreover, physical performance did not change in 26% to 37% of participants (nonresponders), while 34% to 44% showed a decline in physical performance by at least 10% (negative responders). The proportion of positive, non-, and negative responders and mean changes in physical performance is presented in Table 6.

Statistically significant differences were observed between positive, non-, and negative responders at baseline for the FICSIT-4 (FICSIT-4, modified SPPB), modified 30s CST (modified 30s CST, modified SPPB), and modified SPPB (modified SPPB, see Table 7). The post hoc analysis (see Table 7) revealed statistically significant lower performance of positive compared to negative responders for the FICSIT-4 (FICSIT-4) and the modified 30s CST (modified 30s CST); and lower performance of positive compared to nonresponders for the FICSIT-4 (modified SPPB), the modified 30s CST (modified SPPB), and the modified SPPB (modified SPPB).

In a further analysis (Appendix B), we compared 2 additionally drawn groups according to their attendance to the MEP (≥75% vs <75% of sessions). At baseline, the 2 groups differed statistically significant in the FICSIT-4 and the modified SPPB, whereas differences in the 30s CST were found in the postassessment.

Table 4. Results on the Impact of the Multimodal Exercise Program on Physical Performance in Individuals With Dementia (Intention-to-Treat Analysis)

	Baseline IG: n = 194 CG: n = 110 Mean (SE)	Group Differences at Baseline $t(df)$, P	Postintervention IG: n = 194 CG: n = 110 Mean (SE)	Difference Between Baseline and Postintervention Mean (SE), [CI_{95}]	Within-Group Time Effects $t(df)$, P	Time × Group Effects $F(df_{numerator}, df_{denominator})$, P	Effect Size η_p^2
6MWT, s							
IG	11.53 (0.44)	$t_{(8435)} = -0.154$, $P = .878$	10.81 (0.30)	0.72 (0.40), [−0.07, 1.51]	$t_{(199)} = 1.783$, $P = .076^{a}$	$F_{(1,302)} = 0.202$ to 3.468, $P = .064$ to $.653^{b}$	.001 to .011
CG	11.43 (0.47)		11.54 (0.44)	−0.10 (0.53), [−1.15, 0.95]	$t_{(39)} = -0.196$, $P = .846$		
FICSIT-4							
IG	1.97 (0.10)	$t_{(208)} = -0.505$, $P = .614$	2.06 (0.11)	−0.09 (0.11), [−0.31, 0.13]	$t_{(47)} = -0.832$, $P = .410$	$F_{(1,302)} = 0.024$ to 5.453, $P = .020$ to $0.876^{a,c}$	.000 to .018
CG	1.89 (0.12)		1.77 (0.15)	0.11 (0.16), [−0.20, 0.43]	$t_{(32)} = 0.711$, $P = .482$		
TUG, s							
IG	26.60 (1.23)	$t_{(532)} = -1.000$, $P = .318$	25.75 (1.05)	0.84 (1.26), [−1.66, 3.35]	$t_{(30)} = 0.673$, $P = .506^{a}$	$F_{(1,302)} = 1.183$ to 6.232, $P = .013$ to $.278^{a,b,c}$	.004 to .020
CG	24.74 (1.15)		26.54 (1.29)	−1.80 (1.13), [−4.04, 0.44]	$t_{(64)} = -1.590$, $P = .117^{a}$		
30s CST							
IG	7.67 (0.29)	$t_{(127)} = -0.118$, $P = .906$	7.41 (0.30)	0.26 (0.30), [−0.33, 0.85]	$t_{(26)} = 0.878$, $P = .388^{a}$	$F_{(1,302)} = 0.006$ to 2.281, $P = .132$ to .939	.000 to .007
CG	7.62 (0.35)		7.59 (0.36)	0.03 (0.37), [−0.71, 0.76]	$t_{(45)} = 0.074$, $P = .942$		
Modified SPPB							
IG	5.88 (0.20)	$t_{(1552)} = -0.313$, $P = .754$	6.04 (0.23)	−0.15 (0.18), [−0.52, 0.21]	$t_{(59)} = -0.841$, $P = .403$	$F_{(1,302)} = 0.758$ to 9.541, $P = .002$ to $.385^{a,b,c}$	.003 to .031
CG	5.78 (0.24)		5.43 (0.27)	0.35 (0.25), [−0.14, 0.85]	$t_{(48)} = 1.412$, $P = .165^{a}$		

Abbreviations: 6MWT, 6-m walk test; 30s CST, 30-second chair-stand test; CG, control group; CI_{95}, 95% confidence interval; *df*, degrees of freedom; FICSIT-4, Frailty and Injuries: Cooperative Studies of Intervention Techniques—subtest 4; IG, intervention group; SE, standard error; SPPB, Short Physical Performance Battery; TUG, Timed Up and Go test.
[a]Statistically significant in single imputations.
[b]Covariance homogeneity not fulfilled in all imputations.
[c]Variance homogeneity not fulfilled in all imputations.

Table 5. Results on the Impact of the Multimodal Exercise Program on Physical Performance in individuals With Dementia (Per-Protocol Analysis)

	Baseline Mean (SD)	Group Differences at Baseline $t(df)$, P	Postintervention Mean (SD)	Difference Between Baseline and Postintervention Mean (SD), [CI_{95}]	Within-Group Time Effects $t(df)$, P	Time×Group Effects $F(df_{numerator}, df_{denominator})$, P	Effect Size η_p^2
6MWT, s							
IG; n = 86	9.79 (3.15)	$t_{(155)} = -1.620$, $P = .107$	9.81 (3.52)	−0.02 (2.66), [−0.60, 0.55]	$t_{(85)} = -0.085$, $P = .933$	$F_{(1,155)} = 0.000$, $P = .986$[a]	.000
CG; n = 71	10.75 (4.28)		10.79 (3.74)	−0.03 (4.17), [−1.02, 0.95]	$t_{(70)} = -0.068$, $P = .946$		
FICSIT-4							
IG; n = 93	2.25 (1.44)	$t_{(172)} = -1.477$, $P = .141$	2.32 (1.42)	−0.07 (1.42), [−0.36, 0.22]	$t_{(92)} = -0.475$, $P = .636$	$F_{(1,166)} = 0.328$, $P = .567$	.002
CG; n = 75	1.87 (1.20)		1.81 (1.27)	0.05 (1.34), [−0.26, 0.36]	$t_{(74)} = 0.344$, $P = .732$		
TUG, s							
IG; n = 85	20.84 (9.99)	$t_{(151)} = 0.919$, $P = .360$	21.84 (10.64)	−1.01 (7.71), [−2.67, 0.66]	$t_{(84)} = -1.201$, $P = .233$	$F_{(1,151)} = 0.419$, $P = .518$	.003
CG; n = 68	22.32 (9.84)		24.11 (10.71)	−1.79 (7.16), [−3.52, −0.06]	$t_{(67)} = -2.065$, $P = .043$[b]		
30s CST							
IG; n = 69	8.29 (3.52)	$t_{(120)} = -0.374$, $P = .709$	8.17 (3.46)	0.12 (2.45), [−0.47, 0.71]	$t_{(68)} = 0.418$, $P = .678$	$F_{(1,120)} = 0.302$, $P = .584$	.003
CG; n = 53	8.05 (3.59)		8.21 (3.37)	−0.16 (3.25), [−1.06, 0.74]	$t_{(52)} = -0.359$, $P = .721$		
Modified SPPB							
IG; n = 76	6.78 (2.82)	$t_{(136)} = -1.245$, $P = .215$	6.87 (2.99)	−0.09 (2.16), [−0.59, 0.40]	$t_{(75)} = -0.372$, $P = .711$	$F_{(1,136)} = 0.980$, $P = .324$	.007
CG; n = 62	6.19 (2.63)		5.90 (2.61)	0.29 (2.37), [−0.31, 0.89]	$t_{(61)} = 0.964$, $P = .339$		

Abbreviations: 6MWT, 6-m walk test; 30s CST, 30-second chair-stand test; CG, control group; CI_{95}, 95% confidence interval; *df*, degrees of freedom; FICSIT-4, Frailty and Injuries: Cooperative Studies of Intervention Techniques—subtest 4; IG, intervention group; SD, standard deviation; SPPB, Short Physical Performance Battery; TUG, Timed Up and Go test.

[a]Covariance homogeneity not fulfilled.

[b]Statistically significant results appear underlined for $\alpha = .05$—no statistically significant results were observed considering adjusted significance levels using Bonferroni-Holm correction.

Table 6. Comparison of Positive, Non-, and Negative Responders in the Intervention Group and Mean Changes in Physical Performance From Baseline to Postintervention Assessment (Per-Protocol Analysis)

	All		Negative Responder		Nonresponder		Positive Responder	
	n	Mean Change, (SD), %	%	Mean Change, (SD), %	%	Mean Change, (SD), %	%	Mean Change, (SD), %
6MWT	86	0.0 (2.7)	34	2.9 (1.7)	31	−0.3 (0.5)	35	−2.5 (1.7)
FICSIT-4	93	0.1 (1.4)	38	−1.3 (0.6)	28	0 (0)	34	1.6 (0.9)
TUG	85	1.0 (7.7)	35	7.9 (6.5)	37	0 (1.1)	28	−6.3 (6.5)
30s CST	69	−0.1 (2.5)	44	−2.3 (1.4)	26	0.3 (0.5)	30	2.6 (1.4)
Modified SPPB	76	0.1 (2.2)	34	−2.2 (1.4)	26	0.0 (0.6)	40	2.1 (1.2)

Abbreviations: 6MWT, 6-m walk test; 30s CST, 30-second chair-stand test; FICSIT-4, Frailty and Injuries: Cooperative Studies of Intervention Techniques—subtest 4; SD, standard deviation; SPPB, Short Physical Performance Battery; TUG, Timed Up and Go test.

DISCUSSION

The aim of the present study was to examine the impact of the 16-week MEP on physical performance in IWD. No statistically significant time×group effects were observed in both the original (per-protocol analysis) and the revised sample (intention-to-treat analysis). Thus, our hypothesis that physical performance of IWD changes after a 16-week MEP could not be confirmed. One should not consider the lack of generalization of the results as indicating no treatment benefit. Rather this may indicate a lack of evidence against the null hypothesis between the groups of patients. Nevertheless, this RCT had a strong focus on methodological correctness and may thus expand on previous studies, which had some methodological limitations.[15] In line with this, we applied 2 analysis procedures. However, both procedures have limitations regarding the evaluation of the outcomes. The intention-to-treat analysis might underestimate the real effects, whereas the per-protocol analysis might overestimate them. One reason for the lack of significant overall effects might be the relatively high heterogeneity of our sample. High standard deviations were seen for all assessments in both the IG and the CG, probably due to the overall high age, differences in disease stage, other medical comorbidities, and constraints relating to the 3 basic abilities in participants. The high heterogeneity of samples of IWD has been reported as a limitation in prior studies.[34]

Similar to our observations, no effects in overall results of physical performance were reported in other RCTs.[35,36] Lamb et al[37] observed improved physical fitness after an aerobic and strength exercise training program of moderate to high intensity, but did not report any noticeable improvements in other clinical outcomes. A 3-month MEP showed improvements in mobility and executive function in people with mild cognitive impairment but not with Alzheimer's disease.[38] Even though some literature reviews concluded that there is a trend toward increased physical performance in IWD, the results of original research studies are still conflicting. In line with this, our study also could not establish a beneficial effect of the MEP on physical performance in IWD. There are several methodological limitations to consider, especially in terms of interventions and assessments, that need to be overcome by future studies. For example, physical activity interventions have several degrees of freedom, like motor skills (endurance, strength, etc) and training parameters (intensity, duration, etc), and it remains unclear which motor skills or training parameters may have the highest impact on physical performance. One key to success might be to perform most exercises in standing positions, as Netz et al[35] concluded. However, this is challenging for the target group of IWD given their increased risk of falling, which limits the selections of hands-free exercises that may be feasible for IWD.

As the response to physical exercise programs is known to vary individually,[39] a higher individualization might have improved the effects of our MEP on physical performance. It can be speculated that the proportion of nonresponders could have been diminished by an MEP with higher components of individualized intensity and/or dose of tasks.[40] Furthermore, especially in this sample, individualization with respect to high-intensity training is accompanied by several barriers, most notably motivation.[41] It remains uncertain whether higher effects can be achieved through a more individualized MEP, in particular with regard to higher frequency of sessions. Furthermore, assessing motor skills is challenging in IWD. The assessment might be biased by cognitive impairments, which may in turn lead to lower reliability.[33] Additionally, present assessments often do not measure the actual performance but are rather biased by mood or motivation of IWD. Thus, there is a high demand for appropriate assessment tools that are specifically developed for IWD.

Individuals with dementia who responded to our intervention, as identified by the responder analysis, revealed important insights that may be clinically meaningful. These findings are limited in their generalization. However, between 56% of participants with regard to the modified 30s CST and 66% of participants with regard to the 6MWT and the modified SPPB experienced no change, or even an

Table 7. Differences in Baseline Physical and Cognitive Performance Between Positive, Non-, and Negative Responders in the Intervention Group (Per-Protocol Analysis)

	Negative Responder Mean (SD)	Nonresponder Mean (SD)	Positive Responder Mean (SD)	Between-Group Difference $F(df_{numerator}, df_{denominator})/\chi^2(df)$, P	Post Hoc Analysis
*6*MWT					
MMSE (n = 86)	16.7 (4.1)	16.8 (4.3)	17.5 (4.9)	$F_{(2,83)} = 0.252$, $P = .777$, $\eta_p^2 = .006$	
6MWT (n = 86)	9.1 (2.9)	10.4 (3.4)	10.0 (3.1)	$F_{(2,83)} = 1.277$, $P = .284$, $\eta_p^2 = .030$	
Modified SPPB (n = 82)	7.5 (2.7)	6.4 (2.7)	6.7 (2.9)	$F_{(2,86)} = 1.199$, $P = .307$, $\eta_p^2 = .029$	
FICSIT-4					
MMSE (n = 93)	17.3 (4.5)	15.8 (3.9)	17.1 (4.5)	$F_{(2,90)} = 1.004$, $P = .370$, $\eta_p^2 = .022$	
FICSIT-4 (n = 93)	3.0 (1.3)	2.4 (1.5)	1.3 (1.1)	$\chi^2(2) = 23.083$, $P < .001$	$z = 4.722$, $P < .001$, $r = 0.58$[a] $z = 3.060$, $P = .007$, $r = 0.40$[b]
Modified SPPB (n = 88)	7.3 (2.9)	6.8 (3.0)	5.8 (2.5)	$F_{(2,85)} = 2.447$, $P = .093$, $\eta_p^2 = .054$	
TUG					
MMSE (n = 85)	16.6 (3.8)	17.7 (4.5)	17.0 (5.0)	$\chi^2(2) = 1.061$, $P = .588$	
TUG (n = 85)	19.8 (9.7)	19.3 (7.1)	24.1 (12.8)	$\chi^2(2) = 2.847$, $P = .241$	
Modified SPPB (n = 81)	7.3 (3.0)	6.8 (2.2)	6.8 (3.0)	$F_{(2,78)} = 0.305$, $P = .738$, $\eta_p^2 = .008$	
Modified 30s CST					
MMSE (n = 69)	17.0 (3.8)	17.8 (4.4)	18.0 (5.0)	$\chi^2(2) = 1.035$, $P = .596$	
30s CST (n = 69)	9.2 (3.9)	9.1 (2.6)	6.3 (2.8)	$F_{(2,66)} = 5.244$, $P = .008$, $\eta_p^2 = .137$	$P = .011$, MD = −2.81, CI_{95} [−5.08, −0.55][a] $P = .028$, MD = −2.81, CI_{95} [−5.36, −0.25][b]
Modified SPPB (n = 67)	7.5 (2.6)	7.6 (3.0)	5.9 (2.3)	$F_{(2,64)} = 2.668$, $P = .077$, $\eta_p^2 = .077$	
Modified SPPB					
MMSE (n = 76)	16.5 (3.8)	16.5 (4.3)	18.1 (4.7)	$\chi^2(2) = 2.805$, $P = .246$	
6MWT (n = 76)	10.5 (4.8)	8.7 (2.3)	9.8 (3.0)	$\chi^2(2) = 2.730$, $P = .255$	
FICSIT-4 (n = 76)	2.5 (1.3)	3.1 (1.3)	1.9 (1.5)	$\chi^2(2) = 9.446$, $P = .009$	$z = 3.051$, $P = .007$, $r = 0.43$[b]
Modified 30s CST (n = 69)	8.0 (3.5)	9.6 (4.3)	6.8 (2.7)	$F_{(2,66)} = 3.701$, $P = .030$, $\eta_p^2 = .101$	$P = .022$, MD = −2.86, CI_{95} [−5.39, −0.34][b]
Modified SPPB (n = 76)	6.9 (2.9)	8.3 (2.9)	5.7 (2.3)	$\chi^2(2) = 9.066$, $P = .011$	$z = 2.980$, $P = .003$, $r = 0.42$[b]

Abbreviations: 6MWT, 6-m walk test; 30s CST, 30-second chair-stand test; CI_{95}, 95% confidence interval; *df*, degrees of freedom; FICSIT-4, Frailty and Injuries: Cooperative Studies of Intervention Techniques—subtest 4; MD, mean difference; MMSE, Mini-Mental State Examination; SD, standard deviation; SPPB, Short Physical Performance Battery; TUG, Timed Up and Go test.
[a]Post hoc analysis: statistically significant lower performance of positive compared to negative responders.
[b]Post hoc analysis: statistically significant lower performance of positive compared to nonresponders.

improvement in their physical performance between baseline and postassessments. These findings reflect the positive, subjective feedback we received from several participants, relatives, or employees of care facilities. Even maintaining the level of physical performance over the 16-week study period may be a sign of a positive impact of the MEP, as rapid decline of physical performance is usually seen in IWD. Furthermore, our observations with regard to the increase in SPPB values may be of clinical relevance, as this assessment is related to mobility disability and may be a strong predictor of falls and death risk.

In addition, our results indicate that the potential benefit of the MEP varies depending on the level of physical performance at baseline. Those IWD who had low baseline performance in balance and strength and function of lower extremities had a higher likelihood of experiencing positive changes in the same variables after the MEP. This is clinically relevant, and one may conclude that physical activity treatment should particularly be recommended to IWD with poor physical performance. On the other hand, it is also possible that the intensity of our exercise sessions was too low to have a measurable impact on those IWD who had a higher level of physical performance at baseline. We cannot rule out this assumption, as the intervention was delivered in a group setting. Even though we deliberately had small group sizes, exercise instructors may have determined the intensity of the MEP sessions based on those participants with lowest physical fitness. However, of note, this was important and instructors were encouraged to do so to ensure safety for all participants during the MEP, including those with lower physical fitness. Nevertheless, the key to success may be a higher degree of individualization and potentially tailoring exercise intensities to baseline physical performance, which may also improve attendance (see Appendix B). There is a general assumption that lower levels of physical function are more pronounced in individuals with cognitive impairments compared with cognitively unimpaired persons. However, in our sample, we did not observe that poor physical function was associated with more severe cognitive impairment (ie, the responders in balance as well as strength and function of lower extremities that had lower performance levels at baseline did not differ in global cognition, MMSE]. To our knowledge, our study may be among the first to conduct a responder analysis, and more research is needed to confirm our observations.

The strengths of this study are the high-quality methodological approach, as well as the precise documentation and reporting. It is noteworthy that our RCT had a large sample size, as well as an MEP that proved to be a feasible and sustainable exercise program tailored to the characteristics and demands of IWD. This intervention was conducted in 36 care facilities, and most of these facilities decided to implement the MEP into their daily routine after the end of the study. Despite the methodological and planning efforts, our research still had some limitations. First, even though the MEP was carefully developed based on theoretical considerations, as well as the results of a pilot study[23] and a literature review,[18] it may not have been able to sufficiently consider the baseline physical performance level of participants. As the MEP was delivered in a group setting, some participants may not have reached the intensity threshold needed to induce any changes in physical fitness. Furthermore, the additional therapeutic interventions parallel with the administered program (ie, medication) were possibly different and biased the findings. Some of the effects we observed could be due to the group setting (ie, enhanced social interaction) or additional attention that participants received from the exercise instructors, rather than due to the MEP itself. This bias could be addressed in future studies by additional nonexercise groups that engage in social interventions. Another limitation pertains to the differences in sample sizes between the intention-to-treat and per-protocol analyses, which were relatively high, as several IWD did not complete the assessment battery. Reasons for not completing assessments were severe disease, impaired walking ability, or refusal due to appointment scheduling conflicts. It remained unclear whether this refusal was due to excessive demands of the MEP, reluctance or lacking motivation, or other daily conditions. Moreover, being a multicenter study, there is the problem of homogeneity of evaluations and interventions on the patients that can further bias the homogeneity of variance. Another major limitation is that assessments to measure physical function are often not specifically designed for IWD and the use of assistive aids is not described in detail. Assistive aids by some participants to ensure safety may have influenced test results. Thus, designing and evaluating tests to assess physical performance among IWD with the use of assistive aids are critically important and should be considered in future studies.

CONCLUSIONS

This multicenter RCT aimed to identify the effects of a multimodal physical and cognitive intervention on physical performance in IWD. Overall, there were no significant effects of the standardized program on physical performance. While keeping in mind the limitations of the responder analysis and the restrictions in terms of generalization, this analysis resulted in a considerable proportion of participants who responded to the MEP by maintaining or even improving their physical function between baseline and postintervention assessments. This may indicate the need to individualize physical activity interventions among IWD (eg, adjust exercise intensities or frequencies or selection of tasks based on baseline physical and/or cognitive performance). For this reason, we recommend to better adapt interventions by considering the individual needs and characteristics of IWD when planning an exercise training program.

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Appendix A. Additional and Exemplary as Well as Illustrative Information About the Multimodal Exercise Program and the Training for Instructors

Table A1. Contents of the Specific Training for Instructors and Investigators

Contents	Investigators	Instructors
Physiological basics of dementia	2 lesson units	2 lesson units
Communication with individuals with dementia	2 lesson units	2 lesson units
Implementation of cognitive tests with individuals with dementia	3 lesson units	
Implementation of motor tests with individuals with dementia	3 lesson units	
Theory and practice of the multimodal exercise program		4 lesson units
Work shadowing/accompanied implementation of the multimodal exercise program		2 lesson units
Handouts	Manual for testing	Manual for the planned sessions

Table A2. Examples of Exercises and Their Progression of the Multimodal Exercise Program

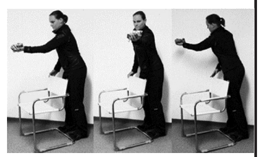
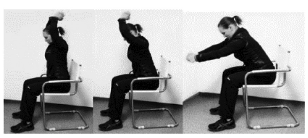
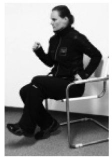
	Simple Performance	Progressive Performance Developed Within the 16 wk
Strength		
Motor task	Strengthening of upper limb and core: lateral flexion with pool noodle Starting position: seated, arms stretched above the head Sets and repetitions: 3 sets with 2 repetitions for each side 	Strengthening of upper limb, core, and lower limb: lateral flexion with rope Starting position: Standing upright behind the chair, arms stretched above the head Sets and repetitions: 2 sets with 3 repetitions for each side 
Cognitive task	No additional cognitive task	Answering questions about circus (topic of the session "Circus")
Balance		
Motor task	Slow and large arm movements in horizontal plane holding a small sandbag while leaning to left and right side Starting position: seated, one arm is horizontally stretched, flexion in hip joint to shift body weight to tiptoes Duration: 1 min, approximately 10 repetitions per side 	Slow and large arm movements in horizontal plane holding a small sandbag while leaning to left and right sides Starting position: standing upright behind the chair, one arm is horizontally stretched, flexion in hip joint to shift body weight to tiptoes Duration: 1:30 min, 15 repetitions per side 
Cognitive task	Answering questions about elephants (topic of the session "Safari in Namibia")	Counting back from 180 in steps of 6 (change hands at 90)
Endurance		
Motor task	"Walking" in seated position—lifting legs with active use of arms Starting position: seated Duration: 1 min 	"Walking" on the spot—lifting legs with active use of arms (if possible) Starting position: standing upright behind the chair Duration: 3 min 
Cognitive task	Answering questions about soccer and its rules (topic of the session "Soccer World Cup")	Naming animals living in the jungle. If a participant repeats an animal, he/she is asked to find another one
Flexibility		
Motor task	Extension and flexion of the trunk; bringing arms in extension with maximal personal range of motion Starting position: seated Sets and repetitions: 3 sets with 10 repetitions (5 repetitions slow, 5 repetitions fast) 	Extension and flexion of the trunk; bringing arms in extension with maximal personal range of motion (try to increase range of motion) Standing position: standing upright behind a chair Sets and repetitions: no repetitions defined; duration 3 min
Cognitive task	Performing in the same rhythm synchronous with other participants	Learning 3 different signals: 1 = moving fast; 2 = moving slow; 3 = change direction

Table A3. Sample Session of the Multimodal Exercise Program			
Imagination	**Motor Tasks**	**Cognitive Tasks**	**Time**
Arrival			
Destination: ask the participants for destination of this session	None.	If participants do not know destination, instructor gives explanations and descriptions about destination to create an imagination.	5 min
Pack your bag: take clothes out of the wardrobe	 Move your arms and upper body with straightened back to the right, middle, and left side and then down to the floor, respectively (in order to put the clothes into the bag).	Instructor asks where in the wardrobe trousers (in middle compartment), T-shirts, and pullovers (in left overhead compartment), swimsuit or swim trunks (in right overhead compartment), etc, are.	
Central station: walk to the central station (meet the other tourists)	 Alternately lift your legs and swing your arms to simulate walking.	None.	
Greet your fellow passengers	 Upper body rotates to the left/right side and shake hands with fellow passenger.	None.	
Take your ticket out of your pocket (trousers or shirt) or handbag and show it to the conductor	 Bend down to touch the chair leg (handbag) (alternatively touch the addressed pocket of your clothes), then stretch 1 arm with straightened back to the front and hold it.	Participants should remember where they have put the ticket after the last journey.	
The group reflects on packing and thinks about if everything important is included	 Resting and recovering.	Instructor asks participants what they packed in their bags a few minutes ago.	
Get out of the train and walk to the hotel for check-in	 Alternately lift your legs and swing your arms to simulate walking.	None.	

(*continues*)

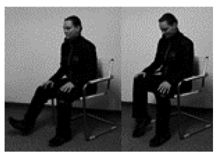
Table A3. Sample Session of the Multimodal Exercise Program (*Continued*)				
Imagination	**Motor Tasks**		**Cognitive Tasks**	**Time**
Main part: Visiting Scotland, joining the highland games				
First event: Cross-country running				
Leave the hotel and walk to the start	 Sit up straight.	 Alternately lift your legs with use of arms.	None.	1 min
Preparation for the cross-country run	 Sit up straight	1. Shaking out arms and legs 2. Circles of the shoulders and ankles  3. Stretch the arms and incline to the left and to the right.  4. Check your laces and take 3 deep breathes 	None.	2 min

(*continues*)

Table A3. Sample Session of the Multimodal Exercise Program (*Continued*)

Imagination	Motor Tasks		Cognitive Tasks	Time
Cross-country running		 Participants walk around the circle; possibly by holding the shoulders of the person in front. Additional movement variations: • Walking up the hill; large steps  • Walking over a root; high steps  • Walking under a branch; ducking upper body  • Walking around mud pools; steps to the right and to the left  Breaks are possible when needed (eg, walking 4 chairs further then make a break in seating position; 2-3 rounds should be done.	Instructor tells a story about the landscape where the described movement variations are integrated.	5 min

(*continues*)

Table A3. Sample Session of the Multimodal Exercise Program (*Continued*)				
Imagination		**Motor Tasks**	**Cognitive Tasks**	**Time**
Second event: Highland games				
Sawing tree trunks		 Two participants hold one pool noodle with one hand, and the other hand is on the back of the chair. Participants move the upper body simultaneously to the arm movement of sawing.	Instructor counts all odd numbers until 30 along with the participants.	2 min
Tree trunk competition		 Turn on its own axis. Imitate a throw and look behind the tree trunk. 	Instructor asks about the width each participant reaches.	3 min
Scottish dance		Dance 4/4 rhythm 1. Right leg: heel tip in front (1), toe tip next to the left foot (2), heel tip to the side (3), toe tip next to the left foot (4), heel tip in front (5), toe tip next to the left foot (6), knee lift (7), leg put down (8)  2. left leg: heel tip in front (1), toe tip next to the left foot (2), heel tip to the side (3), toe tip next to the left foot (4), heel tip in front (5), toe tip next to the left foot (6), knee lift (7), leg put down (8) Left and right legs in alternation for 2 times.	Instructor introduces the Scottish dance gradually and counts the rhythm.	4 min
Second run: sawing tree trunk		See above.	Instructor counts all even numbers until 30 along with the participants.	2 min
Second run: tree trunk competition		See above.	Instructor asks which participant reaches the highest width in the first round.	3 min

(*continues*)

Table A3. Sample Session of the Multimodal Exercise Program (*Continued*)				
Imagination		**Motor Tasks**	**Cognitive Tasks**	**Time**
Second run: Scottish dance		Same choreography as above.	Instructor remembers tot he learned choreography, starts with the guidance, and gives it up to a participant. Each participant should once guide/count for the choreography.	2 min
Break for drinking				
Third run: sawing tree trunk		See above.	Common counting of numerical series of +2, −1, +2, −1, … starting with 0, ending at 10 (0, 2, 1, 3, 2, 4, 3, 5, 4, 6, 5, 7, 6, 8, 7, 9, 8, 10)	2 min
Third run: tree trunk competition		See above.	Instructor asks about the width of the first run.	3 min
Third run: Scottish dance		Same choreography as above.	Instructor asks participants if they remember the choreography. Arm movements are added. Different participants count the rhythm.	3 min
Third event: Cycling tour				
Cycling tour		 Sitting on the edge of the chair, upper body is leaden back. Legs are lifted and move in the typical riding movement. 1. 2. Speed: normal pace, 1 min 2. 1. Speed: fast pace, 30 s 3. Short break, standing up, turn on its own axis (1 right, 1 left) 4. 3. Speed: slow pace, 1 min	Each speed is for a typical pace. Instructor calls a speed and each participant has to perform the respective pace.	4 min
Walk your bike up the hill to the hotel		Alternately lift your legs with use of arms.	None.	2 min

(*continues*)

Table A3. Sample Session of the Multimodal Exercise Program (*Continued*)			
Imagination	**Motor Tasks**	**Cognitive Tasks**	**Time**
Departure			
Pack your bag	None	Participants have to remember the clothes and other things they have put in the bag on the arrival. Instructor encourages them by asking explicit questions.	5 min
Walk to the central station	(See "Arrival")	None.	
Take your ticket out of your pocket (trousers or shirt) or handbag and show it to the conductor	(See "Arrival")	Participants have to remember where they have left the ticket after they have showed it to the conductor.	
Remembering	 Relax and shake your arms and legs.	Participants have to remember what the destination of the journey today was and what experiences they had. Instructor encourages group to talk about the training lesson and if needed give hints.	
Say goodbye to fellow passengers	 Wave your hands at other participants.	None.	
Announcing the next destination of the upcoming training lesson	None.	Instructor says goodbye to participants and gives a brief outlook to the next training session.	

Appendix B. Additional Analysis

Table B1. Differences Between the 2 Intervention Groups Divided by Their Attendance to the Multimodal Exercise Program

Characteristics	Intervention Group, ≥75% Attendance		Intervention Group, <75% Attendance		Group Differences $t(df)$, P
	n	Mean (SD)	n	Mean (SD)	
6MWT, s					
Baseline	100	10.43 (4.37)	74	11.93 (6.70)	$t_{(118)} = -1.687$, $P = .094$
Postintervention	89	9.78 (3.46)	43	10.96 (3.61)	$t_{(80)} = -1.788$, $P = .078$
FICSIT-4					
Baseline	101	2.22 (1.46)	78	1.77 (1.18)	$t_{(176)} = 2.276$, $P = .024$
Postintervention	97	2.27 (1.42)	51	1.87 (1.44)	$t_{(101)} = 1.633$, $P = .106$
TUG, sec					
Baseline	101	22.92 (12.89)	74	27.75 (17.82)	$t_{(126)} = -1.982$, $P = .050$
Postintervention	87	21.93 (10.56)	44	25.94 (11.47)	$t_{(181)} = -1.941$, $P = .056$
30s CST					
Baseline	91	8.06 (3.89)	61	7.53 (3.31)	$t_{(142)} = 0.903$, $P = .368$
Postintervention	78	8.35 (3.51)	40	6.84 (3.61)	$t_{(77)} = 2.178$, $P = .032$
Modified SPPB					
Baseline	96	6.61 (2.86)	67	5.55 (2.64)	$t_{(149)} = 2.443$, $P = .016$
Postintervention	83	6.63 (3.09)	46	5.54 (3.49)	$t_{(84)} = 1.756$, $P = .083$

Abbreviations: 6MWT, 6-m walk test; 30s CST, 30-second chair-stand test; *df*, degrees of freedom; FICSIT-4, Frailty and Injuries: Cooperative Studies of Intervention Techniques—subtest 4; SD, standard deviation; SPPB, Short Physical Performance Battery; TUG, Timed Up and Go test.