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Feasibility of reducing frailty components in older adults with Alzheimer's dementia: a randomized controlled home-based exercise trial (AD-HOMEX)

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ABSTRACT

Objectives: There is a need for interventions to reduce frailty in older people with Alzheimer's dementia (AD). The purpose of this study was to investigate the effect of a home-based multimodal exercise program for older adults with AD (AD-HOMEX) on frailty.

Design: A parallel single-blind randomized controlled trial comparing a home-based exercise program and usual care.

Setting and participants: A home-based program in Brazil. Forty individuals aged 65 years or older with mild to moderate AD.

Methods: The intervention group (IG) participated in a 16-week protocol involving three 60-minute sessions per week of progressive individualized physical exercises supervised by a physical therapist. The participants in the control group (CG) maintained their usual care. Frailty was assessed using the FRAIL questionnaire, the Edmonton Frail Scale (EFS) and a subjective assessment by the evaluator (SAE) at baseline and follow-up. Per-protocol analysis was performed.

Results: Thirty-five participants completed the program (IG = 16; CG = 19). Frailty improved in the IG based on the EFS ($P = .004$) and FRAIL ($P \leq .001$). An interaction between group and time ($P = .008$) and a significant difference between times ($P = .047$) were found for the SAE responsiveness domain. An improvement in the classification of frailty (EFS and FRAIL) was found between times in the IG ($P = .003$) and between groups at follow-up ($P = .027$). A significant difference in the SAE classification was found between groups at follow-up ($P = .034$), with a worsening between times in the CG ($P = .032$). Interestingly, a more favorable frailty transition pattern was found in the IG based on both the EFS and FRAIL.

Conclusions and implications: AD-HOMEX seems to reduce frailty and improve frailty transition patterns. Our findings provide a further theoretical basis for designing home-based physical interventions as routine practice for older frail adults with AD.

1. Introduction

Aging is a major risk factor for both Alzheimer's dementia (AD) and frailty (Alzheimer's Association, 2013; Clegg, 2013). According to a meta-analysis involving five international studies, the prevalence of frailty is as high as 31.9% among older people with mild to moderate AD

and higher when considering severe cases. Therefore, the coexistence of the two conditions is highly prevalent (Kojima et al., 2017). Moreover, frailty can be considered a risk factor for AD, as it increases the risk of cognitive geriatric disorders almost twofold (Borges et al., 2019). As neuropathological changes in AD are increased by a higher degree of frailty, clinical interventions should focus on diminishing frailty in this

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population (Wallace et al., 2019).

AD leads to cognitive, physical and functional impairments (LeDoux et al., 2020), requiring effective multimodal prevention and treatment strategies. The regular practice of physical exercise (Lobelo et al., 2018) can slow the progression of impairment (Cass, 2017; Panza et al., 2018; Hernández et al., 2015) and is comparable or even superior to pharmacological interventions (Lobelo et al., 2018). In frail older people, physical exercise results in less weakness and sedentarism and better motor performances (Liu and Fielding, 2011). Frail individuals commonly have impaired mobility, balance, strength, cognition, nutrition and physical activity (Ferrucci et al., 2004), exerting a negative impact on functioning and increasing the risk of falls (Zidan et al., 2012).

Although older people with dementia have motor and cognitive impairments that hinder access to treatment outside their home (See-matter-Bagnoud et al., 2012; Santos et al., 2013), there is a scarcity of home-based interventions for AD, especially those focusing on frailty (Santos et al., 2013). Home-based protocols improve adherence without increasing the cost of healthcare services and potentially reduce adverse events related to exercise (Pitkälä et al., 2013). Studies on home-based interventions in AD have analyzed the effects on cognition (Pitkälä et al., 2013; Holthoff et al., 2015; Vreugdenhil et al., 2012; Öhman et al., 2016a), functioning (Pitkälä et al., 2013; Vreugdenhil et al., 2012; Steinberg et al., 2009; Öhman et al., 2016b) and motor function (Pitkälä et al., 2013; Vreugdenhil et al., 2012; Suttanon et al., 2011). However, none of these studies analyzed frailty. Moreover, home-based exercise training is generally regarded as a responsibility of the caregiver (Holthoff et al., 2015; Vreugdenhil et al., 2012; Steinberg et al., 2009; Suttanon et al., 2013; Close et al., 2014). This is the first study to analyze the effect of a home-based program conducted by a physical therapist on the components of frailty in AD. The aim of this study was to investigate whether a home-based multimodal exercise program for older people with AD (AD-HOMEX) is effective at improving the components and transitions of frailty in mild to moderate AD.

2. Methods

2.1. Study design and setting

A parallel randomized controlled trial with two arms (AD-HOMEX) was conducted with an assessor blinded to the allocation of participants to the different groups. For such, the physiotherapists had no contact with the evaluators, and the caregiver and the participant were instructed not to mention the exercise protocol. AD-HOMEX was conducted at each participant's home. Evaluations were performed at the Federal University of São Carlos (UFSCar). This study received approval from the UFSCar Ethics Committee (CAAE: 89476318.0.0000.5504) and was registered in the Brazilian Clinical Trials Registry (RBR-2mhvvv). All caregivers signed consent forms and all identities will be kept confidential.

2.2. Participants

Community-dwelling individuals 65 years and older were recruited through posters and local media. The inclusion criteria were a diagnosis of mild to moderate AD based on the Clinical Dementia Rating scale, ability to walk at least 10 m and a medical certificate attesting the ability to practice exercise. The exclusion criteria were motor impairment due to stroke or similar condition affecting cognition or mobility, functional or sensory impairment, cardiovascular or infectious condition with an absolute contraindication to exercise (British Columbia Ministry Of Health, 2002), change of residence, hospitalization or institutionalization, and not wishing to continue in the study.

2.3. Randomization and blinding

Among the 159 older adults invited to participate in this study, 72

did not meet all inclusion criteria, 34 met some exclusion criterion and 13 declined to participate. Therefore, 40 people were eligible and randomized into two groups. The intervention group (IG) received the AD-HOMEX protocol and the control group (CG) received usual care. The allocation rate was 1:1 using blocks of 10 participants with a randomization plan generated at www.randomization.com. The randomization process was conducted by a researcher not otherwise linked to the study (L.M.M.). Opaque, sealed envelopes contained cards indicating the group to which the individual would be allocated. The envelopes were opened after the initial evaluation by L.M.M. to ensure the blind distribution of the participants.

2.4. Intervention

The three initial sessions in the first week were conducted by the physiotherapist responsible for each participant in the IG at his/her home to familiarize the participant with procedures, which is a useful tactic considering the participants' cognitive impairment. The AD-HOMEX protocol (Cezar et al., 2021) consisted of functional exercises directed at strength, balance, aerobic endurance and performance on dual tasks (cognitive and motor). Sixty-minute individual face-to-face sessions were held at the home three times a week on non-consecutive days by four protocol-trained physical therapists with experience in geriatrics. Although progressive load was planned after every six sessions, tolerance was respected considering the absence of self-reported pain and fatigue and the quality of exercise execution. Details on the protocol are published elsewhere (Cezar et al., 2021).

The participants of the CG were instructed to maintain their routine physical activity level and received telephone calls fortnightly to follow-up on their health and collect possible changes in their physical activity routine or usual care (medications and medical appointments). At the end of the 16 weeks, both groups were informed about their performances on the clinical tests and the caregivers and family members were invited to participate in a lecture on general care for older adults with AD to comply with ethical recommendations.

2.5. Data collection

Data measurements were performed by the same evaluators (M.P.B. O. and D.C.P.S.) at baseline and after 16 weeks. The following data were collected: sociodemographic characteristics (age, sex, schooling and physical activity), health-related variables (number of medications and falls, body mass index, waist-to-hip ratio, the Mini-Mental State Examination [MMSE], Pfeffer's Functional Activities Questionnaire, and Cornell Scale for Depression in Dementia) and frailty measures. These data were provided by the same caregiver/family member (who spent at least half the day with the older person at least four times weekly) at baseline and follow-up. The frailty measures and MMSE were administered to the participant.

2.6. Outcome measures

The primary outcome was a reduction in frailty components, scores or transitions in the IG. The secondary outcome was adherence to the program. Frailty was evaluated using the Edmonton Frail Scale (EFS) (Rolfson et al., 2006) and the FRAIL questionnaire (Malmstrom and Morley, 2013), which have different assessment approaches (objective, direct measures and subjective inference). Due to the degree of subjectivity in evaluations involving individuals with AD, the clinician who evaluated the participant and the caregiver answered questions addressing their perceptions in order to diminish social acceptability bias (answer from participants considered socially acceptable). The literature shows that this type of bias is a confounding factor that can result in the overestimation of data on subjective, self-administered instruments (Tracey, 2016; Adams et al., 2005; Mondal and Mondal, 2018).

The EFS addresses general health status, functional independence, social support, medication use, nutrition, mood, self-reported continence, cognition and functional performance (Fabrício-Wehbe et al., 2009). The EFS is derived from seven self-reported variables and four objective measures (Cezar et al., 2017). Individuals are classified as robust (0–4 points), vulnerable (5–6 points) or having mild (7–8 points), moderate (9–10 points) or severe frailty (11 or more points) (Fabrício-Wehbe et al., 2009). The EFS was administered to older people who passed the clock drawing test and to the caregivers of those who failed.

FRAIL is used to evaluate fatigue, endurance, aerobic fitness, disease burden and weight loss through five subjective questions with dichotomous answers (yes/no). The instrument classifies individuals as robust (0 points), pre-frail (1–2 points) or frail (3–5 points) (Malmstrom and Morley, 2013; Aprahamian et al., 2017). As the literature does not determine whether the scale should be administered to the older adult or caregiver when the former exhibits cognitive impairment, it was applied to both, incorporating their subjectivity and enabling comparisons.

To address other important aspects of frailty, the Subjective Assessment by the Evaluator (SAE) questionnaire was developed to be answered by the blinded assessor regarding cognitive performance, physical performance, responsiveness to verbal commands during evaluations, capacity to perform physical and cognitive tests and interaction between the participant and caregiver during the evaluations. Each aspect was judged “good” (0 points) or “poor” (1 point). The total score classified patient health as excellent (0 points), very good (1 point), good (2 points), fair (3 points) or poor (4–5 points).

2.7. Statistical analyses

The sample size was calculated using the G*Power 3.1. Considering the study type (two-way repeated-measures ANOVA), a 5% rate of type I error, an 80% statistical power and an effect size of 0.25 (Buto et al., 2019), a minimum of 28 participants was needed for the total sample. The sample was set at 40 individuals to compensate for a possible 40%

dropout rate (Steinberg et al., 2009).

The Shapiro-Wilk test was used to determine the distribution of the data. As the data had non-normal distribution, the z-score calculation was used to standardize quantitative data. Descriptive statistics as well as point and interval estimates were used for the variables of interest. Two-way repeated-measures ANOVA was used to test interactions between group and evaluation time, considering the covariate sex. Simple main effect analysis was used in the occurrence of a significant interaction. The chi-square test was used to compare the groups regarding categorical variables, such as frailty classification. The t-test was used to compare groups regarding continuous variables. Most sociodemographic and health-related data had normal distribution. Per-protocol analysis was performed with the inclusion of all randomly assigned participants. All participants were invited to the second assessment. The SPSS software was used for statistical analyses. *P*-values below .05 were considered statistically significant.

3. Results

3.1. Baseline characteristics

The total sample was composed of 22 participants with mild AD and 18 with moderate AD. After randomization, the IG and CG were each composed of 11 participants with mild AD and nine with moderate AD. After 16 weeks, 35 participants were evaluated. Dropouts were due to a change of address, hospitalization, institutionalization and refusal to continue in the study (Fig. 1).

The sociodemographic and health-related characteristics of the participants are shown in Table 1. A significant difference between the groups was found regarding sex ($P = .032$), with more women in the IG.

3.2. Primary outcomes

Figs. 2 and 3 present the transition patterns among the levels of

Fig. 1. CONSORT flow diagram.

Table 1

Sociodemographic and health characteristics of participants who completed the study.

	IG (n = 16)	CG (n = 19)	P-values
Age (years)	79.75 ± 5.87	79.05 ± 5.42	.717
Female, n (%)	14 (87.5)	9 (47.4)	.032
Education (years)	4.75 ± 3.7	7.89 ± 5.91	.074
Number of medications	5.94 ± 2.8	5.26 ± 3.23	.518
Number of falls			
Last 6 months	0.94 ± 1.65	1 ± 2.77	.937
Last 12 months	1.38 ± 2.28	2.05 ± 5.78	.663
Body mass index (kg/m ²)	25.97 ± 3.76	26.22 ± 3.6	.842
Waist-to-hip ratio (cm)	0.96 ± 0.1	0.91 ± 0.23	.411
Physical exercise practitioner, n (%)	2 (12.5)	8 (42.1)	.056
CDR			
Mild	9 (56.25)	11 (57.9)	.922
Moderate	7 (43.75)	8 (42.1)	
MMSE (0–30 ^a)	18.19 ± 3.51	18.42 ± 5.08	.878
Pfeffer (0–30 ^b)	15.44 ± 10.04	15.58 ± 8.8	.634
CSDD (0–38 ^b)	5.62 ± 4.47	6.42 ± 5.2	.628

Data are reported as mean ± standard deviation or total of individuals (percentage). IG: intervention group; CG: control group, CDR: Clinical Dementia Rating; MMSE: Mini-Mental State Examination; Pfeffer: Pfeffer's Functional Activities Questionnaire; CSDD: Cornell Scale for Depression in Dementia; n (%): number (percentage); kg/m², kilograms divided by meters squared; cm: centimeter.

^a Higher scores denote better performance.

^b Higher scores denote worse performance.

frailty from baseline to follow-up. The IG exhibited better frailty transitions after 16 weeks. Based on FRAIL, frailty improved after AD-HOMEX in 31.25% and 25% of the IG according to participants and caregivers, respectively. In contrast, 21.05% and 31.57% of the CG transitioned to a worse phenotype at follow-up according to participants and caregivers, respectively (Fig. 2). Based on EFS, the frailty phenotype improved in 37.5% of the IG after AD-HOMEX, whereas it worsened among 57.88% of the CG at follow-up (Fig. 3).

Table 2 shows the comparison of frailty scores and classification between groups and evaluation times. Regarding the total EFS score, significant group x time interactions were found regarding cognition ($P = .024$), subjective health ($P = .009$) and the total score ($P = .004$). A significant difference between evaluations was also found ($P = .004$), with improvement in the IG and worsening in the CG. A significant improvement occurred in the frailty classification in the IG based on EFS ($P = .003$), with an increase in the number of non-frail participants at follow-up, whereas the performance in the CG seems to have worsened, although not significantly ($P = .064$).

Regarding FRAIL, significant group x time interactions were found for the illness domain ($P = .040$) and total score ($P \leq .001$). Regarding the FRAIL classification according to the caregivers, a significant difference was found between groups at follow-up ($P = .027$), with improvement in the IG and worsening in the CG.

Regarding the SAE, a group x time interaction was found for responsiveness ($P = .008$) and a significant difference was found between evaluations ($P = .047$). According to this classification, the CG worsened significantly between the evaluations ($P = .032$), with

Fig. 2. Frailty transition patterns based on FRAIL classification.

Abbreviations: IG: intervention group; CG: control group.

Fig. 3. Frailty transition patterns based on EFS classification.

Abbreviations: IG: intervention group; CG: control group.

Table 2

Outcome measures of frailty between groups and evaluations times.

Variables	IG (n = 16)		CG (n = 19)		Time*sex interaction	Time*group interaction	Times	Groups (χ^2)	Times (χ^2)
	Baseline Mean $\pm$ SD ou n(%)	Follow-up Mean $\pm$ SD ou n(%)	Baseline Mean $\pm$ SD ou n(%)	Follow-up Mean $\pm$ SD ou n(%)					
EFS ^a									
Cognition	1.62 $\pm$ 0.72	1.88 $\pm$ 0.98	1.21 $\pm$ 0.92	1.47 $\pm$ 0.84	0.923	0.024	0.060		
Hospitalization	0.62 $\pm$ 0.25	–	0.10 $\pm$ 0.31	0.10 $\pm$ 0.31	0.803	0.255	0.298		
Subjective health	0.37 $\pm$ 0.50	0.19 $\pm$ 0.40	0.32 $\pm$ 0.48	0.53 $\pm$ 0.61	0.439	0.009	0.079		
Functional independence	1.31 $\pm$ 0.87	1.44 $\pm$ 0.81	1.42 $\pm$ 0.77	1.63 $\pm$ 0.68	0.644	0.797	0.653		
Social support	0.12 $\pm$ 0.34	0.06 $\pm$ 0.25	0.21 $\pm$ 0.42	0.10 $\pm$ 0.31	0.887	0.770	0.874		
Medication use (amount)	0.44 $\pm$ 0.51	0.50 $\pm$ 0.52	0.42 $\pm$ 0.51	0.63 $\pm$ 0.50	0.837	0.327	0.499		
Medication use (forgetfulness)	0.69 $\pm$ 0.48	0.69 $\pm$ 0.48	0.53 $\pm$ 0.51	0.63 $\pm$ 0.50	0.265	0.744	0.395		
Nutrition	0.31 $\pm$ 0.48	0.37 $\pm$ 0.50	0.47 $\pm$ 0.51	0.42 $\pm$ 0.51	0.753	0.456	0.667		
Mood	0.37 $\pm$ 0.50	0.25 $\pm$ 0.45	0.37 $\pm$ 0.50	0.42 $\pm$ 0.51	0.527	0.439	0.343		
Continence	0.31 $\pm$ 0.48	0.44 $\pm$ 0.51	0.21 $\pm$ 0.42	0.47 $\pm$ 0.51	0.329	0.597	0.349		
Functional performance	1.44 $\pm$ 0.51	1.44 $\pm$ 0.51	1.26 $\pm$ 0.45	1.31 $\pm$ 0.48	0.537	0.821	0.613		
Total score (0–17)	7.06 $\pm$ 2.89	6.56 $\pm$ 2.75	6.53 $\pm$ 2.91	7.74 $\pm$ 3.16	0.236	0.004	0.004		
Frailty classification by EFS, n (%)									
No frailty (0–5)	4 (25.0)	6 (37.5) ^b	7 (36.8)	3 (15.8)				0.753 (T1);	0.003 (IG);
Apparently vulnerable (6–7)	3 (18.8)	3 (18.8)	3 (15.8)	5 (26.3)				0.356 (T2)	0.064 (CG)
Mild frailty (8–9)	7 (43.8) ^b	5 (31.3)	7 (36.8)	4 (21.1)					
Moderate frailty (10–11)	1 (6.2)	2 (12.4) ^{xy}	2 (10.6)	6 (31.6)					
Severe frailty (12–17)	1 (6.2) ^{xy}	0 (0.0)	0 (0.0)	1 (5.2)					
FRAIL scale ^a									
Fatigue (P) (0–1)	0.37 $\pm$ 0.50	0.31 $\pm$ 0.48	0.10 $\pm$ 0.31	0.16 $\pm$ 0.37	0.140	0.917	0.383		
Fatigue (C) (0–1)	0.31 $\pm$ 0.48	0.25 $\pm$ 0.48	0.47 $\pm$ 0.51	0.63 $\pm$ 0.49	0.063	0.760	0.215		
Resistance (P) (0–1)	0.12 $\pm$ 0.34	–	–	–	–	–	–		
Resistance (C) (0–1)	–	–	–	–	–	–	–		
Ambulation (P) (0–1)	–	–	–	–	–	–	–		
Ambulation (C) (0–1)	–	–	0.06 $\pm$ 0.25	0.05 $\pm$ 0.23	–	–	–		
Illness (P) (0–1)	–	–	0.05 $\pm$ 0.23	0.05 $\pm$ 0.23	–	–	–		
Illness (C) (0–1)	0.06 $\pm$ 0.25	0.06 $\pm$ 0.25	0.10 $\pm$ 0.31	0.16 $\pm$ 0.37	0.040	0.632	0.463		
Loss of weight (P) (0–1)	0.25 $\pm$ 0.45	0.25 $\pm$ 0.45	0.16 $\pm$ 0.37	0.16 $\pm$ 0.37	0.484	0.768	0.892		
Loss of weight (C) (0–1)	0.44 $\pm$ 0.51	0.37 $\pm$ 0.50	0.42 $\pm$ 0.51	0.42 $\pm$ 0.51	0.266	0.967	0.576		
Total score (P) (0–5) (0–1)	0.75 $\pm$ 0.86	0.56 $\pm$ 0.63	0.32 $\pm$ 0.58	0.37 $\pm$ 0.60	0.179	0.950	0.443		
Total score (C) (0–5) (0–1)	0.81 $\pm$ 0.75	0.75 $\pm$ 0.93	1.00 $\pm$ 0.74	1.42 $\pm$ 1.17	<0.001	0.638	0.078		
Frailty classification by FRAIL (P), n (%)									
Non-frail (0)	7 (43.8)	8 (50.0)	14 (73.7)	13 (68.4)				0.150 (T1);	0.565 (IG);
Pre-frail (1–2)	8 (50.0)	8 (50.0)	5 (26.3)	6 (31.6)				0.268 (T2)	1.00 (CG)
Frail (3–5)	1 (6.2)	–	–	–					
Frailty classification by FRAIL (C), n (%)									
Non-frail (0)	6 (37.5)	9 (56.3)	4 (21.1)	4 (21.1)				0.402 (T1);	0.091 (IG);
Pre-frail (1–2)	10 (62.5)	7 (43.7)	14 (73.7)	10 (52.6)				0.027 (T2)	0.212 (CG)
Frail (3–5)	0 (0.0)	0 (0.0)	1 (5.2)	5 (26.3) ^b					
SAE ^a									
Cognitive performance (0–1)	0.19 $\pm$ 0.40	0.12 $\pm$ 0.34	0.21 $\pm$ 0.42	0.37 $\pm$ 0.50	0.646	0.185	0.410		
Physical performance (0–1)	0.19 $\pm$ 0.40	–	0.21 $\pm$ 0.42	0.21 $\pm$ 0.42	0.410	0.064	0.057		
Responsiveness (0–1)	0.37 $\pm$ 0.50	–	0.26 $\pm$ 0.45	0.26 $\pm$ 0.45	0.699	0.008	0.047		
Ability to tests (0–1)	0.19 $\pm$ 0.40	–	0.32 $\pm$ 0.58	0.32 $\pm$ 0.48	0.307	0.427	0.242		
Interaction (0–1)	0.12 $\pm$ 0.34	–	0.05 $\pm$ 0.23	0.16 $\pm$ 0.37	0.154	0.204	0.081		
Total score (0–5)	1.06 $\pm$ 0.77	0.12 $\pm$ 0.34	0.95 $\pm$ 1.02	1.32 $\pm$ 1.33	0.981	0.992	0.996		
Classification SAE, n (%)									
Poor (4–5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)				0.222 (T1);	0.230 (IG);
Fair (3)	0 (0.0)	0 (0.0)	1 (5.3)	4 (21.1) ^{xy}				0.034 (T2)	0.032 (CG)
Good (2)	5 (31.2)	0 (0.0)	6 (31.6) ^b	2 (10.5)					
Very good (1)	7 (43.8)	2 (12.5)	3 (15.8)	5 (26.3)					
Great (0)	4 (25.0)	14 (87.5)	9 (47.3) ^{xy}	7 (36.8) ^b					

Data are reported as mean $\pm$ standard deviation or total of individuals (percentile). IG: intervention group; CG: control group, B: baseline; F: follow-up; T1: initial evaluation, T2: final evaluation, EFS: Edmonton Frail Scale, P: participant, C: caregiver, (–): analysis was not possible because values were 0, SAE: subjective assessment by evaluator, SD: standard deviation, n (%): number (percentage), bold type: significant difference between groups or evaluation times.

^a Higher scores denote worse performance.

^b Residual adjustment >2.0.

increasing and decreasing numbers of participants with health classified as fair and good, respectively. Moreover, a significant difference was found between groups at follow-up ($P = .034$), with the IG improving in the frailty classification, whereas the CG worsened.

3.3. Secondary outcome: adherence to treatment

Among the 20 participants in the IG, 80% completed training and 93.75% completed more than 70% of the 48 sessions. The main reasons for missing sessions were family commitment, holiday, malaise, uncontrolled blood pressure, travel and temporary health problem or indisposition. The possible adverse effects related to AD-HOMEX included mild muscle pain and dizziness.

4. Discussion

The present study investigated the effects of a home-based multimodal exercise program on frailty scores and transitions in older adults with mild to moderate AD. AD-HOMEX led to improvements in the total score of the instruments and transition patterns of frailty among the participants who performed the program, as demonstrated by both the EFS and FRAIL instruments.

A recent meta-analysis of randomized controlled trials on frailty management demonstrated that physical activity was the only treatment to reduce frailty, with a standardized mean difference of -0.92 (Negm et al., 2019). International evidence-based guidelines for the identification and management of frailty reinforce strong evidence regarding multi-component physical activity with resistance-based training as a first line of treatment (Dent et al., 2019). However, no previous trial was published regarding the effects of exercise on frailty in AD. One study involved a multimodal exercise protocol for frail older people with cognitive decline (mild cognitive impairment or dementia) (Casas-Herero et al., 2019). However, the program was not home-based and not specific to individuals with AD. Associations between frailty severity, functioning and number of falls among older adults with AD were investigated (Perttinen et al., 2016). However, many participants performed physical exercise in groups, were not stratified into different groups and frailty components/transition patterns were not evaluated. This highlights the importance of the present study, which implemented a multimodal exclusively home-based exercise program to reduce frailty in older adults with mild to moderate AD.

Pooling the participants with mild, moderate and severe frailty, a 12.5% reduction in frailty (EFS) occurred in the IG and a 10.5% increase occurred in the CG (23% difference between groups). An interdisciplinary intervention focused on frailty characteristics in older people with a MMSE score higher than 18 points found a 14.7% difference between groups after 12 months (Cameron et al., 2013), which is in line with our findings. Another multimodal exercise trial for 24 weeks was effective at reducing the frailty phenotype and improving cognition among community-dwelling older adults (Tarazona-Santabalbina et al., 2016).

A previous study involving 12 weeks of exercise, cognitive training and board games for pre-frail older people found a significant reduction in frailty (FRAIL), with an increase in frailty among controls (Yu et al., 2020), as occurred herein. Moreover, 83.3% of pre-frail participants transitioned to non-frailty compared to only 1.6% of controls. We also identified transitions from pre-frail to non-frail in 25% and 10.5% of the participants in the IG and CG, respectively. Thus, the present results follow the same trend but more subtly, possibly because the sample involved older people with AD.

High adherence to AD-HOMEX was found; 80% of the participants in the IG remained in the program and 93.75% completed at least 70% of the sessions. Previous trials involving home-based exercises with AD

reported adherences between 58.01% and 90% (Pitkälä et al., 2013; Holthoff et al., 2015; Steinberg et al., 2009; Suttanon et al., 2013). Only one of these studies (Pitkälä et al., 2013) was supervised by a physical therapist. It is important to supervise physical exercise, especially considering this population, to correct positioning, ensure safety and avoid possible adverse events (e.g., falls). It is worth mentioning that supervised training is more effective, compared to unsupervised training (Halabchi et al., 2017). Moreover, studies involving physical exercises for older people with frailty reported adherence rates of 26 to 50% (Cameron et al., 2013), 63% (Losa-Reyna et al., 2019; Aas et al., 2020), 70% (Clegg et al., 2014), 73% (Arrieta et al., 2019), 78% (Hsieh et al., 2019), 82% (Tarazona-Santabalbina et al., 2016) and 94% (Yu et al., 2020). As these studies were not home-based, the presence of a professional was not the only factor that influenced adherence.

Due to the lack of a diagnostic consensus for frailty, several instruments have been used for this assessment in clinical trials (Cameron et al., 2013; Tarazona-Santabalbina et al., 2016; Losa-Reyna et al., 2019; Aas et al., 2020; Arrieta et al., 2019; Hsieh et al., 2019; Doody et al., 2019). The present study used two common instruments. EFS was used in clinical trials conducted by Tarazona-Santabalbina and colleagues (Tarazona-Santabalbina et al., 2016) and Clegg and colleagues (Clegg et al., 2014) and FRAIL was used by Yu and colleagues (Yu et al., 2020). These instruments were selected because EFS is used to assess frailty in older people with cognitive impairment (Mondal and Mondal, 2018) and FRAIL is correlated with dementia and is a friendly instrument for clinical practice (Ruiz et al., 2020). Despite being the most widely used in the literature, Fried's seminal phenotype criteria (Fried et al., 2001) do not include cognitive impairment in the assessment. No previous study has included a subjective assessment of the evaluator, although subjective evaluations of AD patients are common in clinical practice.

Home-based multimodal exercise seems to be a good non-pharmacological treatment modality to combat frailty in older people with AD. The multimodal protocol was chosen because the literature highlights it for older adults with dementia (Blankevoort et al., 2010; American College of Sports Medicine, 2009), given the induction of greater activity in the frontal and parietal regions, which are involved in the control of attention (Foster et al., 2011). Nonetheless, the present study has limitations that should be considered, such as the inclusion of two AD stages due to recruitment difficulties, which increased heterogeneity in the sample. However, the groups were similar regarding the different stages of AD. Another limitation regards the impossibility of the progression of exercises in all participants of the IG, as the individuality of the participants was considered. Thus, future studies should consider revising the proposed protocol. Finally, there was a small number of men in the IG, which could limit the generalization of the results.

This study has also several strengths, such as a previous published exercise protocol conducted by trained physical therapists based on the CONSORT and SPIRIT guidelines; the evaluator was blinded to the allocation of the participants to the groups; strategies were employed to minimize dropouts, such as fortnightly telephone calls; and validated instruments were employed to assess the outcome measures. This is the first randomized controlled trial on a home-based exercise program for older people with AD performed in a developing country and the first study to encompass the analysis of frailty in older people with AD including an innovative subjective assessment. Future studies should enrich the evidence by including other frailty measures with objective tests, adding intermediate and follow-up evaluations or analyzing three groups separately (AD, frailty and AD + frailty). Regarding the feasibility of the protocol, it would be interesting to include exercises for strengthening the upper limbs and walking, which are important to reducing frailty.

5. Conclusions and implications

AD-HOMEX appears to reduce frailty and improve frailty transition patterns. The results provide the theoretical basis for designing home-based physical interventions in routine practice for older frail adults with AD.

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CRediT authorship contribution statement

Natália Oiring de Castro Cezar: conceptualization, methodology, data curation, formal analysis, writing (original draft, revision & editing). Ivan Aprahamian: conceptualization, writing (revision & editing). Juliana Ansai: conceptualization, formal analysis, writing (revision & editing). Marcos Oliveira, Danielle Silva, Wildja de Lima Gomes, Bruna Barreiros, Tamiris de Cássia Oliva Langelli: data curation, writing (revision). Larissa Andrade: conceptualization, methodology, writing (revision & editing), supervision.

Sponsor's role

No sponsor.

Trial registration

Brazilian Clinical Trials Registry (RBR-2mhvvv).

Brief summary

A home-based multimodal physical exercise program for older people with mild to moderate Alzheimer's disease is an effective intervention strategy that reduces frailty and improves frailty transition patterns.

Declaration of competing interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.exger.2021.111390>.

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