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The cost effectiveness of a multidomain intervention on physical, cognitive, vascular, dietary and psychosocial outcomes among community dwelling older adults with cognitive frailty in Malaysia: The AGELESS Trial

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Abstract

Background Cognitive frailty (CF) in older adults is a potentially reversible syndrome that may benefit from lifestyle-based multidomain interventions. This study assessed the AGELESS intervention's impact on cognitive, physical, vascular, dietary, and psychosocial outcomes, along with its cost-effectiveness, in a Low-Middle-Income Country (LMIC).

Methods The AGELESS randomized controlled trial recruited 106 older adults (above 60 years) from Klang Valley, Malaysia, with (pre)-CF (≥ 1 Fried's criteria and Clinical Dementia Rating scale = 0.5). Participants were randomly assigned to a 24-month multidomain intervention (physical activity, cognitive training, nutritional and psychological counselling, cardiovascular care) or control group (educational module). Primary outcomes, assessed at baseline, 12 and 24 months, included the modified Neuropsychological Tests Battery (mNTB) and physical performance measures. Intervention costs were calculated to determine Incremental Cost-Effectiveness Ratios (ICERs). An intention-to-treat analysis was conducted to account for attrition.

Results The trial occurred during the COVID-19 pandemic. Despite a 50% dropout rate, adherence among remaining participants was over 50% for all intervention components (range 53%-91%). The intervention led to significant improvements in selected parameters of cognitive function, physical performance, anthropometry, and dietary patterns (for all parameters, $p < 0.05$ for interaction time*group in repeat-measures ANOVA). The cost per participant was RM 1592.74 (≈USD 355.05) in the multidomain arm, and RM 488.21 (≈USD 108.83) in the control arm. The ICER computation indicated the 2-min step test as the most cost-effective measure (ICER RM 149.19 ≈USD33.26).

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Conclusion The AGELESS trial demonstrates that a multidomain, lifestyle-based intervention can improve cognitive and physical function in older adults with (pre)-CF. This cost-effective approach highlights CF as a modifiable health condition and supports its potential inclusion in health policy to promote healthy aging and reduce health risks in LMICs, where there is a larger prevention potential due to prevalent lifestyle-related risk factors.

Keywords Cognitive frailty, Multidomain, Intervention, Community dwelling, Older adults

Introduction

Alongside the rapid, global growth of the ageing population, frailty has become a common issue among older individuals [1]. Cognitive impairment is another common syndrome in advanced age [2]. The coexistence of frailty and cognitive impairment, conceptualized as 'cognitive frailty' (CF), has been identified as a precursor to dementia [3].

Several modifiable factors have been linked to CF. Older persons with lower socioeconomic status are at higher risk of frailty due to factors such as poor nutrition and physical inactivity, and they are also more prone to poor cognitive health [4]. Particularly, poor diet has been classified as an indicator of frailty and cognitive impairment due to oxidative damage and harmful neuroinflammation [5, 6]. Poor health outcomes and increased risk of frailty are also affected by psychosocial well-being such as lack of support [7]. In Malaysia, the prevalence of CF is reported to be 39.6% [8]. Increasing age, reduced niacin intake, lack of social support, lower functional status, and depression have been identified to increase risk of CF in the Malaysian older adults aged 60 years and above [8].

CF is described as a condition with potential for reversibility through appropriate measures. Physical exercise has been identified as crucial for improving frailty and cognitive symptoms, as well as delaying the progression of cognitive impairments [9]. Cognitive abilities in older individuals could also be enhanced through task-specific training that involves multisensory integration [10].

Compared with single-domain interventions, multidomain interventions can align with the multifactorial nature of CF, promoting synergistic benefits. While evidence on interventions specifically targeting CF is limited, there are studies suggesting that multidomain interventions can improve physical performance and cognition in older adults, such as the seminal Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER). This study demonstrated that implementing a 2-year multidomain intervention including exercise, diet, cognitive training, social stimulation, and good control of cardiometabolic disorders, resulted in improved cognitive function and maintained daily functioning in older adults at higher risk of dementia [11, 12]. A more recent analysis from the FINGER trial showed that the 2-year intervention could reverse the first signs of frailty among older men, but not in women [13].

A feasibility study in Malaysia, WE-RISE, included a multidomain intervention for people with CF and lower socioeconomic status, reporting a cost of approximately RM 194.74 (≈USD 43.39) per participant for 48 sessions over 24 weeks [14]. WE-RISE showed improvements in cognition, physical function, body composition, and quality of life, but it did not include vascular or psychosocial parameters [14]. Knowledge gaps remain, on the benefit of multidomain interventions on the CF phenotype, particularly regarding the scalability and long-term impact of multidomain interventions, their cost-effectiveness, and their applicability in low- and middle-income countries (LMICs) such as Malaysia.

Addressing CF aligns with Malaysia's national health priorities, which emphasize "healthy aging" and the reduction of non-communicable diseases (NCDs) to ease the burden on the healthcare system and promote healthy longevity among elderly people [15].

Building on the FINGER and WE-RISE results, the Multidomain Intervention to Reverse Cognitive Frailty among Community Dwelling Older Adults (AGELESS Trial) tested a multidomain intervention in the Malaysian population with CF. As part of the World-Wide FINGERS (WW-FINGERS) Network of multidomain trials for risk reduction and prevention of dementia [12], the AGELESS trial aimed to develop and deliver culturally appropriate interventions comprising of physical activity, cognitive training, dietary, psychosocial counselling and vascular management, to assess their effectiveness in improving physical and cognitive function (primary outcomes), and several secondary outcomes among older adults with CF. Additionally, the trial assessed cost-effectiveness to inform scalable health interventions for CF management in Malaysia and other LMICs, supporting national goals of promoting healthy lifestyles and extending life expectancy among aging populations.

Methodology

Study design

The AGELESS study protocol, baseline characteristics of participants, and preliminary findings have been described earlier [16–18]. Some minor discrepancies exist between the earlier publications and the current

report, due to extensive data cleaning processes conducted after the study completion and for this analysis. The AGELESS Trial began recruitment in November 2019, but the onset of the COVID-19 pandemic soon required adjustments to the recruitment process, which was conducted in phases to adapt to lockdown restrictions, with participants being gradually enrolled as conditions allowed. A full intervention schedule was only initiated after lockdowns ended, which led to a revised timeline for intervention delivery and follow-up assessments. Ethical approval was obtained from the Research Ethics Committee of Universiti Kebangsaan Malaysia with approval number UKM PPI/111/8/JEP-2020–347. The study was registered with the National Medical Research Register (NMRR) and the International Standard Randomized Controlled Trial Registry (Trial ID: ISRCTN75429638, dated 1st June 2021). The AGELESS Trial comprised of 2 phases as depicted in Fig. 1. Phase 1 aimed to develop a culturally relevant multidomain intervention module, and phase 2 was the randomized controlled trial to determine the effectiveness of the developed module.

Study participants

Participants in the AGELESS trial were registered members of the Activity Centers for Older Persons (PAWE), strategically located in low-cost housing areas across the Klang Valley in the center of Malaysia (Kuala Lumpur and Selangor) and a rural area of Seremban (further South of Klang Valley). A team of researchers conducted screenings at these centers to identify individuals aged 60 and above who exhibited cognitive frailty (CF). The operational definition of CF followed the criteria outlined by the IANA/IAGG international consensus group [3] and has been previously published [16, 18]. Briefly, CF was based on the Fried´s phenotype for frailty [19], consisting of 5 components—unintentional weight loss, exhaustion, low physical activity, weak hand grip strength and slow gait speed – and the Clinical Dementia Rating (CDR) scale for the cognitive aspect [20]. People were eligible for the trial if they had score 19–25 on the Mini Mental State Examination (MMSE) [21], 0.5 on the CDR, and had ≥ 1 Fried's criteria. Participants were classified either as having pre-CF (1–2 Fried's criteria and CDR = 0.5) or with CF (≥ 3 Fried's criteria and CDR = 0.5) [3]. The exclusion criteria included major depression, other major psychiatric disorders, severe cognitive impairment or dementia, malignant diseases, or other conditions that would prevent safe participation in the study as judged by the researcher, or concurrent participation in any intervention trial.

The trial sample size initially calculated [16] was reassessed, due to pandemic-related challenges in recruitment, to ensure a sufficient number of participants, and accounting also for new data from ongoing WW-FINGERS trials [22, 23]. Additionally, only participants from the urban area were selected for the intervention due to logistic reasons that allowed the intervention programme to be effectively conducted, due to pandemic-related travel restrictions [18]. The sample size was determined

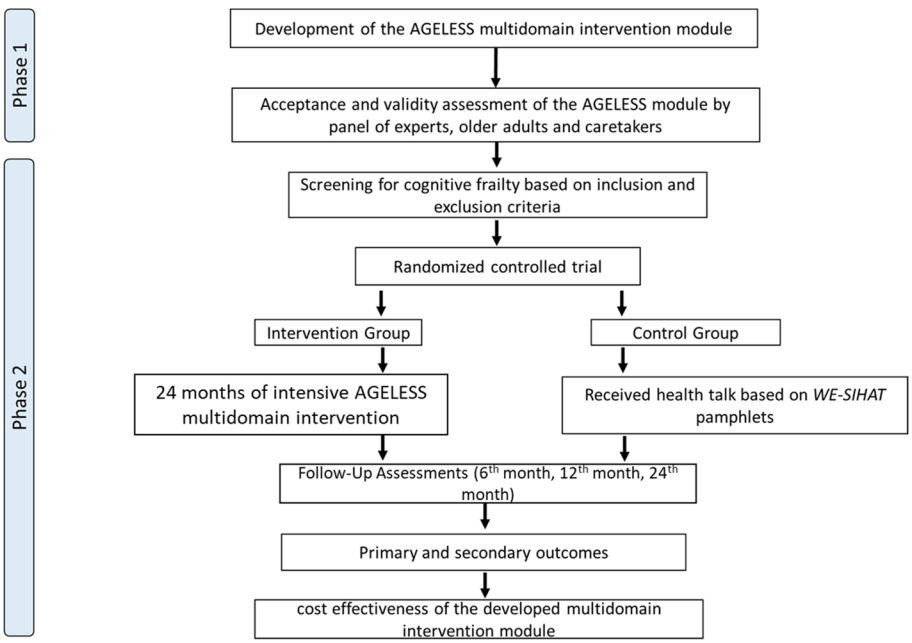


Fig. 1 The AGELESS trial flowchart

using G-Power Statistical power analysis, incorporating a medium effect size (Cohen's d = 0.38), which is recommended for detecting medium effects in gerontology studies [24]. Anticipating a dropout rate of 40%, a total of 106 participants were initially recruited: 53 in the intervention group and 53 in the control group.

Randomization and intervention

Participants were randomly assigned to the intervention or control group using Research Randomizer software by a trial manager, employing a simple randomization approach. The group receiving the intervention underwent a multidomain 24-month program, which was adapted from the FINGER trial protocol, as well as the local WE-RISE trial [11, 14, 16]. To facilitate adherence, the multidomain intervention was introduced in a stepwise manner, commencing with vascular management, nutritional and psychological counselling, followed by exercise and cognitive training (Fig. 2). Vascular management sessions were conducted every 6 months, with physician consultations based on blood test results. Dietary and psychological counseling sessions were held monthly in groups for the first 12 months, transitioning to once every three months thereafter, with 8–10 participants per group. Dietary consultations were led by a dietitian and nutritionist, addressing healthy eating among older adults, based on the Malaysian Dietary Guidelines for Older Adults [25] and Malaysian Recommended Nutrient Intake for individuals aged 60 years and above [26]. Psychological counseling was delivered through group sessions and individual sessions, focusing on stress, coping mechanisms, social support, self-efficacy, and depression. The exercise was carried out as a multi component group exercise that included progressive resistance, endurance, flexibility, coordination and balance training. Whereas the cognitive training was administered as paper and pencil routines that were designed specifically to enhance the cognitive domains such as memory, executive function, processing speed, language, visuospatial reasoning and attention. Both exercise and cognitive training were conducted 2 to 3 times a week for a stretch of 24 months.

Control group

Participants in the control group attended a series of structured health talks every five months over the 24-month study period, totaling five sessions. These health talks were designed to provide general health information, covering topics relevant to aging populations but without the personalized, multidomain focus of the intervention group. Each session lasted approximately 60 min and was led by a healthcare professional or guest speaker with expertise in the respective topic (Fig. 3). This design ensured that control participants received some general health support without the interactive components central to the AGELESS intervention.

Outcome measures

The primary outcome included cognitive and physical function [16]. Cognitive function comprised of tests which are part of the modified Neuropsychological Tests Battery (mNTB), including the digit span forward, digit span backward, digit span overall, verbal paired

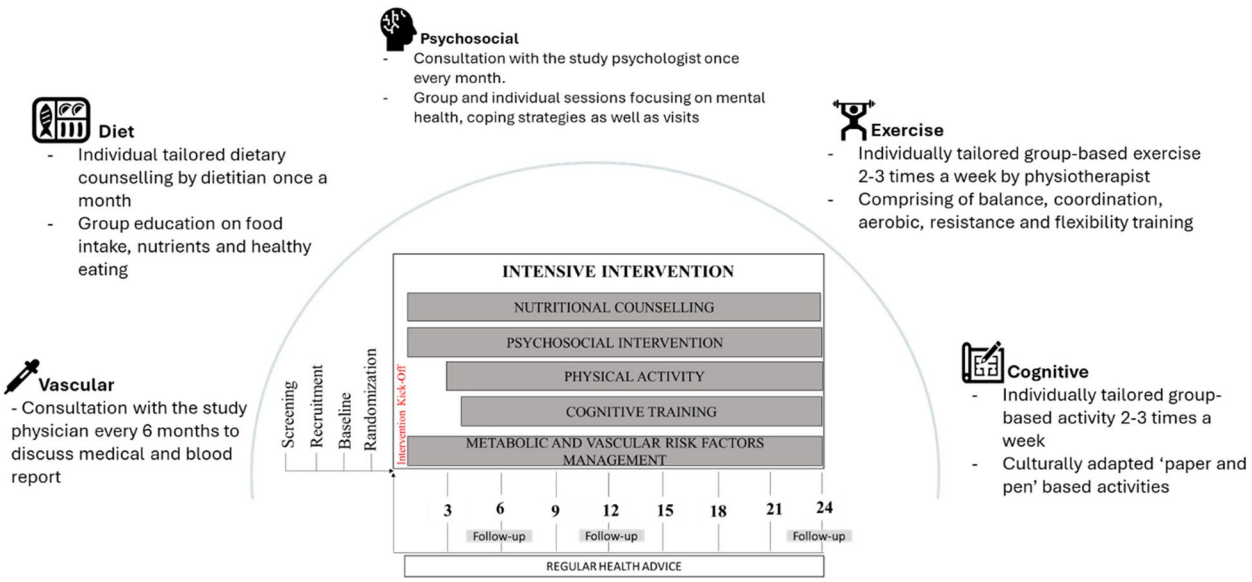


Fig. 2 Intervention Protocol of the AGELESS Trial (adapted and modified from [16])

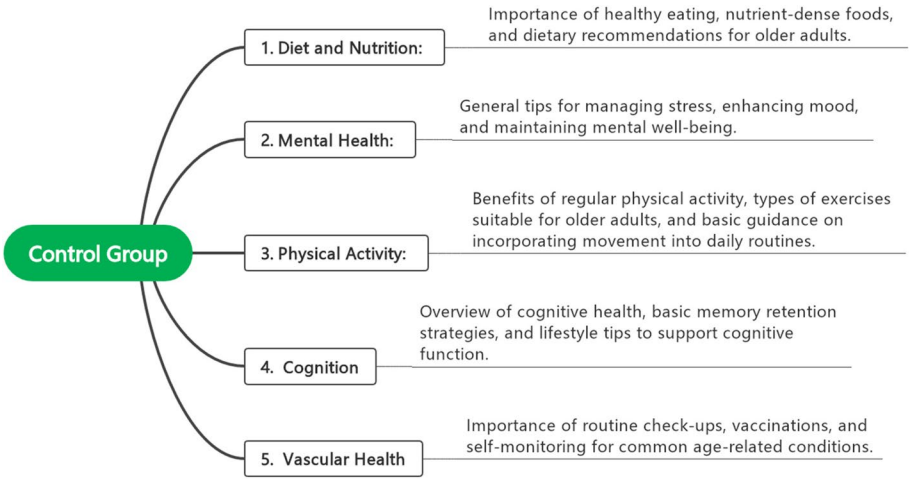


Fig. 3 Health talks received by the control group

associates (immediate and delayed recall), visual paired associates (immediate and delayed recall), Ray Auditory Verbal Learning Test (RAVLT), and Categorical Fluency Test. Physical function comprised of chair sit and react test, back scratch test, timed up and go test, 30 s sit to stand, 6 min walk test and 2 min step test. The secondary outcomes were anthropometry and body composition measures, vascular measures, psychosocial variables, dietary intake, and functional magnetic resonance imaging (fMRI). We also examined changes in CF status. The outcomes were measured at baseline, 6th month, 12th month and 24th month.

fMRI Assessment

The fMRI assessment involved a subsample that was calculated using the formula proposed by Zhong (2009) [27] and was based on findings from Lau (2020) [28], which reported a mean difference in brain activation of 0.7 between the control and intervention groups, with a pooled standard deviation of 0.26. Using these data, the required sample size was estimated to be 13 participants per group, accounting for a 40% dropout rate, 80% statistical power, and a 95% confidence interval. Participants were screened for eligibility at baseline, and those with claustrophobia or metal implants were excluded from the fMRI assessment. A total of 28 eligible participants provided consent to participate, 14 from the intervention group and 14 from the control group. The fMRI scans were conducted at the Department of Radiology, UKM Specialist Children's Hospital, at baseline, 12th month and 24th month.

Task-based fMRI was employed in relation to cognitive function assessment, using the N-back task and the Stroop Colour Word Task (SCWT). Imaging was performed using a 3.0 Tesla MRI scanner (Magnetom Skyra, Siemens, Erlangen, Germany). High-resolution T1-weighted anatomical images were acquired with a repetition time (TR) of 1,900 ms (ms), an echo time (TE) of 2.27 ms, a voxel size of 1.0×1.0×1.0 mm (mm), 176 slices, and a slice thickness of 1 mm. Functional scans for the N-back task were obtained using T2*-weighted imaging with a TR of 3,000 ms, a TE of 30 ms, 3-mm isotropic voxels, 29 slices, and a slice thickness of 4 mm. For the SCWT, the acquisition parameters included a TR of 2,000 ms, a TE of 30 ms, a flip angle of 90°, and a slice thickness of 4 mm, using an interleaved sequence with 29 slices per volume.

a. N-back

A qualified radiologist explained the N-back task procedures to the participants, ensuring that they understood the task by providing diagrams and a detailed explanation of the protocol. The task was designed and displayed using SuperLab 5 (Cedrus, Los Angeles, CA, United States) and included two conditions: 0-back and 1-back [29].

In the 0-back condition, participants were required to respond to a stimulus by determining whether it matched a predefined target presented at the beginning of the block. In the 1-back condition, participants had to decide whether the current stimulus matched the one immediately before it. Each condition consisted of four blocks, with each block lasting 30 s, followed by a 30-s rest interval. The total duration of the task was 510 s. Before beginning the task, participants underwent a 5.42-min anatomical brain scan, which was followed by approximately 9.11 min of N-back task performance.

b. Stroop Colour Word Task (SCWT)

The Stroop Colour Word Task (SCWT) was implemented using E-PRIME 3.0 (Psychological Software Tools, Inc., Sharpsburg, Philadelphia). During the fMRI scan, participants were presented with a continuous series of colour-related stimuli designed to assess cognitive control. The task began with a neutral baseline condition in which the symbol "XXXX" was displayed in different colours, and participants were required to respond based on the colour shown. This was followed by the congruent condition, where colour words were displayed in matching ink colours, such as the word "red" appearing in red ink. Finally, the task progressed to the incongruent condition, where colour words were presented in mismatched ink colours, such as the word "red" displayed in yellow ink. Four colours; red, blue, yellow, and green were used in various congruent and incongruent combinations, following the approach of [29].

Adherence

Participants´ adherence was calculated by dividing their total number of attended intervention sessions by the total number of sessions offered, and then multiplying the result by 100 to determine the percentage.

Cost effectiveness

The costs of various components for the multidomain intervention were determined using Activity-Based Costing (ABC), a method designed to provide a detailed understanding of costs associated with specific activities and processes [30]. In this study, expenses were categorized into materials (including printed materials, stationery, cognitive stimulation tools, and exercise equipment), logistics (such as meals and participant honorariums), and fieldworker costs (encompassing wages, transportation, and telecommunication charges).

The calculations were based on a structured schedule where 53 participants attended 168 sessions of exercise and cognitive training, 24 sessions of dietary and psychological training, and 4 sessions of vascular consultation each. Since exercise and cognitive training sessions were held consecutively on the same day, transportation costs were combined for both domains. A similar approach was applied to vascular, psychosocial, and dietary consultation sessions. The cost for control group comprised of the expenditure for the 5 sessions of health talk including transportation and charges for the speaker. Total costs were computed by aggregating expenses across all sessions conducted during the trial period.

The costing analysis of the AGELESS trial utilized the Incremental Cost-Effectiveness Ratio (ICER), which allows for a comprehensive comparison of the economic value of a healthcare intervention relative to an alternative. ICER is determined by dividing the difference in costs between the intervention and control groups by the difference in their outcomes ($Cost_{intervention} - Cost_{control}$)/($Outcome_{intervention} - Outcome_{control}$). Only primary outcomes that showed significant differences between groups were included in the ICER calculation to ensure a meaningful assessment of cost-effectiveness.

Statistical analysis

All analyses were performed using IBM Statistical Package for the Social Sciences (IBM SPSS), version 23.0 (SPSS Inc., Chicago, IL, USA). A significance level of alpha < 0.05 was used for all tests. Descriptive and frequency analyses were conducted to report characteristics of the participants, including CF status (pre-CF and CF). To compare sociodemographic profiles between control and multidomain groups, chi-squared (χ^2) tests were used for categorical variables, and independent t-tests were used for continuous variables. Repeat measures ANOVA was employed to examine the within-group effect (time effect), between-group effect (group effect), and interaction effect (time x group). We based the primary efficacy analysis on the intention-to-treat population (ITT).

Results

Recruitment

A total of 957 community-dwelling older adults from urban ($n=764$) and rural ($n=193$) areas were screened for eligibility across Klang Valley and Seremban, respectively. However, only participants screened in urban area in Klang Valley proceeded with the intervention trial due to commuting restrictions to rural areas at that time. Among the 764 individuals screened in Klang Valley, 650 completed the screening process, of whom 275 met the eligibility criteria for CF. Ultimately, 106 participants (36.1%) consented to participate in the trial (Fig. 4). The majority were classified as pre-CF ($n=91$, 85.9%), while the remaining 15 participants (14.1%) met the criteria for CF. People were randomly assigned to either intervention ($n=53$) or control group ($n=53$). Throughout the 24-month intervention period, an average of 50% participants dropped out from the trial due to various reasons, such as health issues and medical appointments ($n=10$), loss of contact ($n=15$), personal commitments ($n=7$), relocated ($n=6$), family did not grant permission ($n=1$), work commitments ($n=3$) and withdrawn without reason ($n=11$). Therefore, the study conducted an intention-to-treat analysis to account for these dropouts.

Participant characteristics

As shown in Table 1, majority of the participants were aged between 60 to 69 years old (63.2%), predominantly female (58.5%), of Malay ethnicity (83%), living with others (85.8%), unmarried or widowed (52.8%), and no

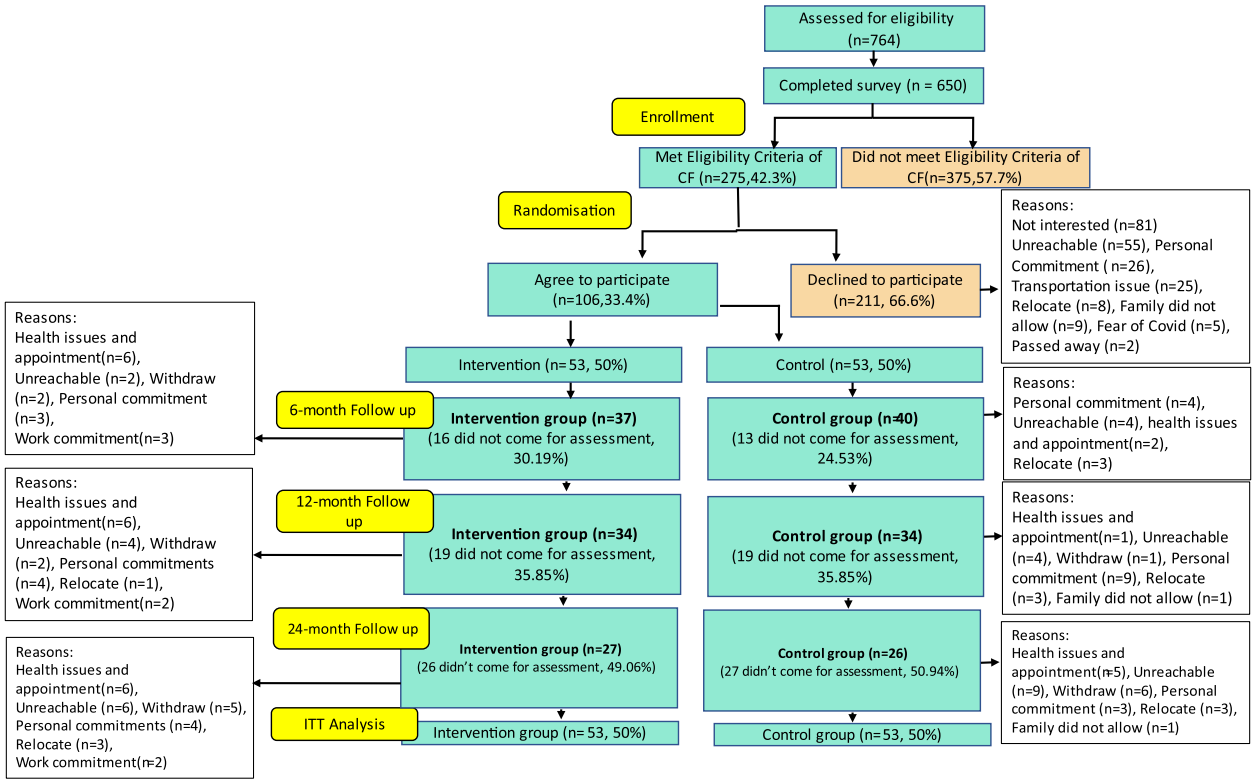


Fig. 4 Consort Flow Diagram for AGELESS Multidomain Intervention Trial Recruitment

longer working (87.74%). Many participants also exhibited multimorbidity (59.4%), with hypertension (66%), hypercholesterolemia (56.6%) and diabetes (56.6%) as the most common chronic diseases reported. There were no significant disparities between the intervention and control groups in terms of sociodemographic or clinical profiles ($p > 0.05$ for all parameters). Most of the participants (85.9%) were classified as pre-CF, with no significant differences between the multidomain and control group.

The adherence rate of participants towards the multidomain intervention was satisfactory (>50% for all domains) throughout the 24 months (Fig. 5). The adherence rate was the highest for vascular consultation (91%) and was the lowest for exercise and cognitive training (53%).

Primary outcomes

As tabulated in Table 2, a significant intervention effect on cognitive change (time*group interaction) was observed for most of neuropsychological tests, including digit span forward ($p < 0.05$, $n^2 = 0.18$), digit span overall ($p < 0.005$, $n^2 = 0.16$), visual paired immediate recall (($p < 0.05$, $n^2 = 0.10$), visual paired delayed recall ($p < 0.05$, $n^2 = 0.15$) verbal paired immediate recall ($p < 0.001$, $n^2 = 0.23$) verbal paired delayed recall ($p < 0.05$, $n^2 = 0.29$). Though no significant interaction effect was noted for category fluency test and RAVLT (delay), but significant effect of time within group effect was observed ($p < 0.05$). Mean score of the cognitive tests in the intervention group showed improvement at 6th and 12th month, and a reduction in mean score at 24th month.

Physical measures that showed significant intervention effects were chair sit and reach test ($p < 0.005$, $n^2 = 0.01$), 6-min walk test ($p < 0.05$, $n^2 = 0.01$), and 2-min step test ($p < 0.05$, $n^2 = 0.11$). Whereas, for timed up and go, there was a significant time effect observed ($p < 0.05$, $n^2 = 0.05$).

Post hoc analysis was done to determine mean differences in change between groups from baseline to 6, 12 and 24 months (Appendix A, Table S1). Most of the physical and cognitive variables showed significant changes from baseline to 6th and 12th month ($p < 0.05$), while some outcomes were also significantly different at 24th months between intervention and control.

Secondary outcomes

The secondary measures of the AGELESS Trial included anthropometry, body composition, dietary intake, food groups, fMRI behavioral performance and psychosocial measures. Table 3 represents the effectiveness of the AGELESS trial on anthropometry and body composition.

Table 1 Sociodemographic and clinical characteristics of participants stratified by intervention and control groups (presented as n (%) or mean ± standard deviation)

Parameter	Intervention Group (*n* = 53)	Control Group(*n* = 53)	Total (*n* = 106)	*p*-value
Age	67.71 ∓5.6	68.42 ∓5.2	68.1 ± 5.5	0.52
Age Group				0.56
60–69 years	35 (66.0%)	32 (60.4%)	67(63.2%)	
70–79 years	17 (32.1%)	18 (34.0%)	35 (33.0%)	
80 + years	1 (1.9%)	3 (5.6%)	4 (3.8%)	
Gender				1
Male	22 (41.5%)	22 (41.5%)	44 (41.5%)	
Female	31 (58.5%)	31 (58.5%)	62 (58.5%)	
Ethnicity				0.69
Malay	47 (88.7%)	41 (77.4%)	88 (83%)	
Chinese	1 (1.9%)	3 (5.7%)	4 (3.8%)	
Indian	5 (9.4%)	9 (16.9%)	14 (13.2%)	
Marital Status				0.85
Unmarried/widow/divorced	27 (50.9%)	29 (54.7%)	56 (52.8%)	
Married	26 (49.1%)	24 (45.3%)	50 (47.2%)	
Living Arrangement				
Lives Alone	8 (15.1%)	7 (13.2%)	15 (14.2%)	0.87
With others	45 (84.9%)	46 (86.8%)	91 (85.8%)	
Education years	8.8 ± 2.9	7.8 ± 4.7	8.3 ± 3.9	0.20
Occupation status				0.87
Not working	47 (88.7%)	46 (86.8%)	93 (87.7%)	
Working	6 (11.3%)	7 (13.2%)	13 (12.3%)	
Monthly income (MYR)	1306.1 ± 1420.5	1106.6 ± 987.5	1205.4 ± 1219.5	0.41
Polypharmacy				
Yes	1 (1.9%)	4 (7.5%)	5 (4.7%)	
No	52 (98.1%)	49 (92.5%)	101 (95.3%)	
Multimorbidity				0.89
Yes	31 (58.5%)	32 (60.4%)	63 (59.4%)	
No	22 (41.5%)	21 (39.6%)	43 (40.6%)	
Smoking status				
Smoker	12 (22.6)	4 (7.5)	16 (15.1)	0.06
Non smoker/past smoker	41 (77.4)	49 (92.5)	90 (84.9)	
Family history of dementia				
Yes	4 (7.5%)	5 (9.4%)	9 (8.5%)	0.54
No	49 (92.5%)	48 (90.6%)	97 (91.5%)	
Hypertension				
Yes	36 (67.9%)	34 (64.2%)	70 (66%)	0.84
No	17 (32.1%)	19 (35.8%)	36 (34%)	
Hypercholesterolemia				
Yes	30 (56.6%)	30 (56.6%)	60 (56.6%)	1.00
No	23 (43.4%)	23 (43.4%)	46 (43.4%)	
Diabetes				
Yes	30 (56.6%)	30 (56.6%)	60 (56.6%)	1.00
No	23 (43.4%)	23 (43.4%)	46 (43.4%)	
Cognitive Frailty				0.40
Pre-CF	47 (88.7%)	44 (83%)	91 (85.9%)	
CF	6 (11.3%)	9 (17%)	15 (14.1%)	

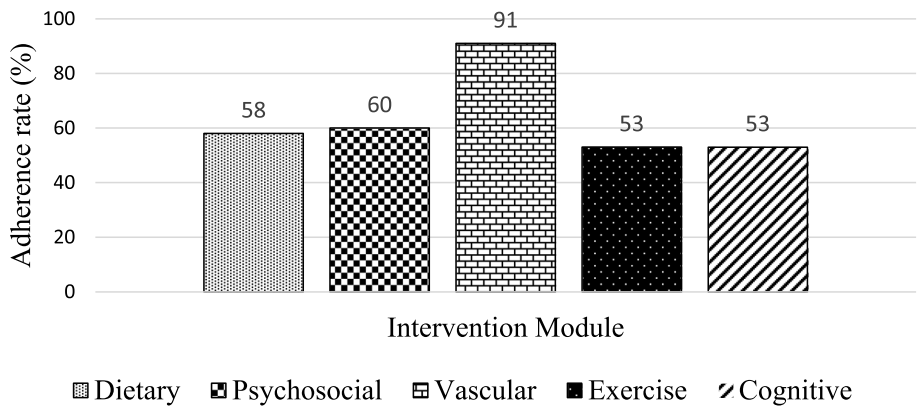


Fig. 5 Adherence rate of participants based on intervention domains

Waist circumference ($p<0.005$, $n^2=0.07$), body fat mass ($p<0.05$, $n^2=0.03$) and skeletal muscle mass ($p<0.05$, $n^2=0.03$) showed significant time*group interaction effects. No significant intervention effect was found for blood parameters assessment of vascular function (Table 3) and psychosocial parameters (data not shown).

In terms of dietary intake (Table 4), significant interaction effect was observed for energy intake ($p<0.05$, $n^2=0.03$), protein ($p<0.001$, $n^2=0.12$), niacin ($p<0.05$, $n^2=0.03$), calcium ($p<0.001$, $n^2=0.07$), vegetables intake ($p<0.001$, $n^2=0.32$), fruit intake ($p<0.001$, $n^2=0.14$), fish intake ($p<0.005$, $n^2=0.07$), legume intake ($p<0.001$, $n^2=0.15$) and milk intake ($p<0.05$, $n^2=0.04$).

The 24 months of multidomain intervention showed significant intervention effect on the behavioral performances measured through fMRI (Table 5). Left Dorsolateral Prefrontal Cortex (DLPFC) activation and Right DLPFC showed significant time*group interaction for 1 back and Stroop colour ($p<0.05$, $n^2=0.13$), and word test (SCWT) ($p<0.05$, $n^2=0.17$) respectively. No other significant group*time interactions were found for fMRI measures (data not shown).

Cognitive frailty status

Approximately 34.0% ($n=18$) were no longer (pre-) CF after 12 months of intensive intervention (transitioned to pre-physical frailty, or Mild cognitive Impairment (MCI) or robust phenotype). However, the percentage dropped to 28.3% ($n=15$) in 24 months (Fig. 6). The control group showed 39.7% (pre-)CF reversal at 12 months and 32.1% (pre-)CF reversal at 24 months. Nevertheless, there was no significant difference between the groups. Reversal rate did not differ significantly between the control and the intervention group ($p>0.05$). Also, 3.8% ($n=2$) of older adults in the control group progressed to dementia after 24 months and such an occurrence was not observed in the intervention group.

Cost effectiveness

The total cost of the AGELESS intervention for 24 months and control was RM 1592.74 (≈USD 355.05) per subject (Appendix B, Table S2) and RM 488.21 (≈USD 108.83) (Appendix C, Table S3), respectively. The ICER computation showed that 2-min step test was the most cost effective (RM149.19; ≈USD 33.26), followed by chair sit and reach (RM 280.08; ≈USD 62.40) and verbal paired associates immediate recall (RM 457.06; ≈USD 112.57) (Table 6).

Discussion

This study marks one of the initial investigations into the effects of multidomain interventions on groups experiencing cognitive frailty among aging population from a LMIC. Significant intervention effects were observed after 2 years, in both primary outcomes including verbal memory (assessed via verbal paired associates), visual memory (assessed via visual paired associates), attention and working memory (evaluated using the digit span test), lower body flexibility (chair sit and reach), walking speed (6 m walk test), cardiovascular endurance (2 min step test), as well as in secondary outcomes such as anthropometric measures, body composition, and dietary intake.

Significant trends observed during the first 12 months of assessment provide encouraging evidence of the intervention's impact within a shorter timeframe. These early improvements in cognitive and physical outcomes highlight the intervention's potential to initiate positive health changes relatively quickly. The findings suggest that the AGELESS intervention can facilitate meaningful health improvements within the first year of implementation, emphasizing the potential for short-term benefits even before completing the full 24-month period. However, most variables did not show significant maintenance of this change at 24th month, possibly due to the

Table 2 Effectiveness of the AGELESS Multidomain Intervention on Cognitive and Physical Function (Primary Outcomes) (Presented as mean ± SD)

Parameter	Timeline	Intervention ($n=53$)	Control ($n=53$)	Time effect			Group effect			Interaction		
				p-value	Partial Eta Squared	Power	*p*-value	Partial Eta Squared	Power	*p*-value	Partial eta squared	power
Cognitive function												
Categorical fluency test (score)	Baseline	10.03 ± 3.36	10.21 ± 3.41	**< 0.05***	0.12	0.85	0.88	0.01	0.13	0.33	0.03	0.16
	6th month	10.74 ± 3.37	10.70 ± 3.17									
	12th month	11.91 ± 3.27	10.58 ± 2.95									
	24th month	11.81 ± 3.16	10.95 ± 3.43									
RAVLT immediate (score)	Baseline	4.75 ± 1.68	4.85 ± 1.45	0.46	0.04	0.21	0.87	0.01	0.05	0.81	0.05	0.17
	6th month	4.77 ± 2.22	4.11 ± 2.17									
	12th month	5.35 ± 2.58	5.02 ± 2.33									
	24th month	4.92 ± 1.78	4.91 ± 1.51									
RAVLT delay recall (score)	Baseline	5.0 ± 2.99	5.42 ± 2.20	**< 0.005***	0.33	0.97	0.06	0.11	0.49	0.68	0.01	0.05
	6th month	5.4 ± 2.56	5.43 ± 2.10									
	12th month	7.05 ± 2.65	4.80 ± 2.06									
	24th month	5.48 ± 3.58	4.74 ± 2.67									
Digit Span Forward (score)	Baseline	6.28 ± 3.29	7.14 ± 3.85	**< 0.05***	0.28	0.47	**< 0.05***	0.09	0.32	**< 0.05***	0.18	0.39
	6th month	9.29 ± 2.88	7.33 ± 2.17									
	12th month	10.05 ± 2.03	8.09 ± 2.96									
	24th month	9.44 ± 2.79	8.39 ± 2.25									
Digit span backward (score)	Baseline	4.38 ± 3.11	5.24 ± 2.01	0.34	0.01	0.31	0.48	0.12	0.28	0.65	0.09	0.12
	6th month	5.16 ± 3.04	5.15 ± 2.09									
	12th month	5.21 ± 2.49	4.95 ± 3.89									
	24th month	5.01 ± 2.44	4.90 ± 2.98									
Digit span overall (score)	Baseline	8.62 ± 2.29	9.74 ± 2.79	0.15	0.03	0.29	0.66	0.01	0.07	**< 0.005***	0.16	0.86
	6th month	9.38 ± 2.69	9.32 ± 2.71									
	12th month	10.90 ± 2.93	8.89 ± 2.55									
	24th month	9.61 ± 2.60	9.25 ± 2.85									
Visual paired associates (immediate) (score)	Baseline	2.12 ± 1.21	3.11 ± 1.01	**< 0.05***	0.15	0.83	0.4	0.01	0.13	**< 0.05***	0.10	0.63
	6th month	3.98 ± 1.87	3.15 ± 1.98									
	12th month	5.08 ± 1.64	3.69 ± 1.17									
	24th month	3.36 ± 1.18	3.01 ± 1.42									

Table 2 (continued)

Parameter	Timeline	Intervention ($n=53$)	Control ($n=53$)	Time effect			Group effect			Interaction		
				p-value	Partial Eta Squared	Power	*p*-value	Partial Eta Squared	Power	*p*-value	Partial eta squared	power
Visual paired associates (delayed) (score)	Baseline	4.0 ± 1.67	4.06 ± 1.83	0.2	0.06	0.25	0.85	0.01	0.05	**< 0.05***	0.15	0.58
	6th month	4.58 ± 1.30	3.78 ± 1.70									
	12th month	5.32 ± 0.88	4.22 ± 1.31									
	24th month	4.67 ± 2.09	3.63 ± 1.15									
Verbal paired associates (immediate) (score)	Baseline	3.39 ± 1.45	3.56 ± 1.90	**< 0.05***	0.12	0.42	**< 0.005***	0.23	0.81	**< 0.001***	0.23	0.23
	6th month	4.41 ± 1.13	3.44 ± 1.55									
	12th month	5.37 ± 1.07	3.59 ± 1.42									
	24th month	4.12 ± 1.58	4.08 ± 1.34									
Verbal paired associates (delayed) (score)	Baseline	4.0 ± 1.67	4.06 ± 1.83	**< 0.05***	0.08	0.33	**< 0.05***	0.08	0.21	**< 0.05***	0.29	0.31
	6th month	4.58 ± 1.30	3.78 ± 1.70									
	12th month	5.32 ± 0.88	4.22 ± 1.31									
	24th month	4.67 ± 2.09	3.63 ± 1.15									
Physical Function												
30 s sit to stand (repetitions)	Baseline	11.81 ± 3.37	10.18 ± 2.87	0.21	0.03	0.31	**< 0.05***	0.05	0.25	0.82	0.01	0.33
	6th month	11.34 ± 3.73	11.0 ± 3.97									
	12th month	12.72 ± 3.13	10.65 ± 2.15									
	24th month	13.36 ± 3.43	11.45 ± 3.42									
Chair sit and reach (cm)	Baseline	2.50 ± 8.54	2.86 ± 7.45	0.48	0.08	0.28	**< 0.05***	0.18	0.27	**< 0.005***	0.01	0.54
	6th month	5.77 ± 8.65	3.13 ± 6.92									
	12th month	8.68 ± 6.14	3.98 ± 8.30									
	24th month	6.96 ± 5.15	3.31 ± 6.49									
Timed up and go (s)	Baseline	11.03 ± 2.65	11.74 ± 3.30	**< 0.05***	0.05	0.47	0.85	0.01	0.19	0.26	0.02	0.28
	6th month	10.89 ± 2.71	10.95 ± 2.42									
	12th month	10.55 ± 2.91	10.93 ± 2.55									
	24th month	11.76 ± 3.39	12.37 ± 3.60									
6 m walk test (s)	Baseline	4.99 ± 3.42	4.91 ± 2.32	**< 0.005***	0.12	0.52	0.07	0.05	0.32	**< 0.05***	0.01	0.55
	6th month	4.02 ± 1.05	4.76 ± 1.77									
	12th month	3.73 ± 0.88	4.21 ± 0.73									
	24th month	3.80 ± 0.80	4.51 ± 1.01									

Table 2 (continued)

Parameter	Timeline	Intervention ($n=53$)	Control ($n=53$)	Time effect			Group effect			Interaction		
				p-value	Partial Eta Squared	Power	*p*-value	Partial Eta Squared	Power	*p*-value	Partial eta squared	power
Back scratch test (cm)	Baseline	−11.84 ± 13.15	−17.27 ± 14.14	0.33	0.04	0.33	**< 0.05***	0.08	0.38	0.19	0.02	0.22
	6th month	−9.58 ± 10.19	−14.04 ± 7.92									
	12th month	−5.56 ± 10.14	−13.98 ± 9.60									
	24th month	−6.26 ± 10.13	–4.78 ± 11.20									
2 min step test (steps)	Baseline	70.81 ± 15.38	71.22 ± 13.28	**< 0.05***	0.08	0.44	0.34	0.06	0.25	**< 0.05***	0.11	0.49
	6th month	75.55 ± 11.15	74.18 ± .16.77									
	12th month	81.13 ± 10.38	74.01 ± 15.33									
	24th month	79.72 ± 10.25	72.93 ± 11.25									

Cm centimetres, *s* seconds

* $p < 0.05$, two way mixed ANOVA, adjusted for age, gender, years of education, household income, and body mass index

Table 3 Effectiveness of the AGELESS Multidomain Intervention on Secondary outcome (Anthropometry and Body Composition) (Presented as mean ± SD)

Parameter	Timeline	Intervention ($n=53$)	Control ($n=53$)	Time effect			Group effect			Interaction		
				p-value	Partial Eta Squared	Power	*p*-value	Partial Eta Squared	Power	*p*-value	Partial eta squared	Power
Body Mass Index (kg/m^2)	Baseline	28.5 ± 5.8	26.4 ± 4.6	0.62	0.01	0.17	0.06	0.03	0.48	0.91	0.00	0.09
	6th month	28.5 ± 5.6	26.3 ± 5.6									
	12th month	28.5 ± 5.7	26.2 ± 4.6									
	24th month	28.5 ± 5.7	26.0 ± 4.6									
Mid upper arm circumference (cm)	Baseline	29.3 ± 4.1	27.7 ± 3.3	0.47	0.01	0.23	**0.042***	0.04	0.53	0.31	0.01	0.32
	6th month	29.6 ± 4.2	27.7 ± 3.3									
	12th month	29.5 ± 4.1	28.8 ± 8.9									
	24th month	29.8 ± 4.1	27.6 ± 3.6									
Waist circumference (cm)	Baseline	97.6 ± 13.9	92.7 ± 10.9	**< 0.05***	0.04	0.66	0.12	0.02	0.35	**< 0.005***	0.07	0.92
	6th month	97.5 ± 13.7	92.8 ± 11.0									
	12th month	96.0 ± 13.5	91.8 ± 11.7									
	24th month	94.9 ± 12.7	93.7 ± 11.8									
Hip circumference (cm)	Baseline	102.5 ± 13.9	99.8 ± 10.7	0.40	0.01	0.27	0.17	0.03	0.27	0.12	0.02	0.50
	6th month	102.5 ± 13.9	99.9 ± 10.0									
	12th month	102.4 ± 13.9	98.2 ± 12.9									
	24th month	101.5 ± 13.3	100.3 ± 10.3									
Calf circumference (cm)	Baseline	35.2 ± 3.8	36.1 ± 10.7	0.79	0.00	0.12	0.33	0.02	0.16	0.11	0.02	0.53
	6th month	35.2 ± 3.9	36.1 ± 10.7									
	12th month	35.4 ± 3.9	34.9 ± 4.3									
	24th month	36.0 ± 3.8	34.7 ± 4.1									
Waist hip ratio	Baseline	0.96 ± 0.1	0.96 ± 0.1	0.95	0.00	0.07	0.31	0.01	0.18	0.36	0.01	0.29
	6th month	0.95 ± 0.1	0.95 ± 0.1									
	12th month	0.94 ± 0.1	0.94 ± 0.1									
	24th month	0.93 ± 0.1	0.93 ± 0.1									
Body fat mass (kg)	Baseline	27.4 ± 11.4	23.9 ± 8.1	0.28	0.01	0.27	0.06	0.03	0.46	**< 0.05***	0.03	0.61
	6th month	27.1 ± 11.0	23.2 ± 8.1									
	12th month	27.4 ± 11.0	23.3 ± 8.0									
	24th month	26.8 ± 10.9	24.1 ± 8.7									
Skeletal muscle mass (kg)	Baseline	22.2 ± 4.4	21.6 ± 4.6	0.55	0.01	0.20	0.47	0.01	0.11	**< 0.05***	0.03	0.66
	6th month	22.4 ± 4.3	21.8 ± 4.5									
	12th month	22.1 ± 4.2	21.7 ± 4.7									
	24th month	22.6 ± 4.1	21.5 ± 4.8									

Table 3 (continued)

Parameter	Timeline	Intervention ($n=53$)	Control ($n=53$)	Time effect			Group effect			Interaction		
				p-value	Partial Eta Squared	Power	*p*-value	Partial Eta Squared	Power	*p*-value	Partial eta squared	Power
Triglyceride (mmol/l)	Baseline	1.49 ± 0.69	1.35 ± 0.45	0.19	0.02	0.42	0.32	0.01	0.17	0.26	0.01	0.36
	6th month	1.54 ± 0.54	1.37 ± 0.58									
	12th month	1.46 ± 0.50	1.43 ± 0.64									
	24th month	1.49 ± 0.56	1.42 ± 0.54									
Total Cholesterol (mmol/l)	Baseline	5.23 ± 1.10	5.13 ± 1.36	0.91	0.00	0.08	0.65	0.00	0.07	0.08	0.02	0.58
	6th month	5.32 ± 1.03	5.00 ± 1.24									
	12th month	5.07 ± 1.09	5.03 ± 1.25									
	24th month	5.18 ± 1.12	5.19 ± 1.23									
HDL (mmol/l)	Baseline	1.40 ± 0.32	1.43 ± 0.53	0.40	0.01	0.27	0.92	0.00	0.05	0.76	0.00	0.13
	6th month	1.40 ± 0.32	1.43 ± 0.65									
	12th month	1.40 ± 0.33	1.36 ± 0.31									
	24th month	1.38 ± 0.31	1.37 ± 0.29									
LDL (mmol/l)	Baseline	3.09 ± 1.04	3.09 ± 1.04	0.41	0.01	0.26	0.98	0.01	0.05	0.13	0.02	0.49
	6th month	3.24 ± 0.96	3.24 ± 0.96									
	12th month	3.09 ± 1.04	3.09 ± 1.04									
	24th month	3.15 ± 1.05	3.15 ± 1.05									
FBG (mmol/l)	Baseline	6.25 ± 1.69	6.19 ± 2.45	0.55	0.01	0.20	0.29	0.11	0.19	0.28	0.13	0.34
	6th month	6.77 ± 2.73	6.08 ± 2.30									
	12th month	6.55 ± 2.43	6.14 ± 2.18									
	24th month	6.91 ± 2.86	6.17 ± 2.00									
HbA1c (%)	Baseline	6.43 ± 1.25	6.53 ± 1.63	0.68	0.01	0.15	0.90	0.01	0.05	0.15	0.02	0.47
	6th month	6.50 ± 1.43	6.49 ± 1.43									
	12th month	6.69 ± 1.64	6.54 ± 1.76									
	24th month	6.53 ± 1.59	6.30 ± 1.32									
Fasting blood sugar (mg/dL)	Baseline	7.62 ± 1.94	7.70 ± 2.58	0.65	0.01	0.16	0.73	0.00	0.06	0.22	0.01	0.39
	6th month	7.74 ± 2.25	7.54 ± 2.29									
	12th month	8.02 ± 2.59	7.72 ± 2.81									
	24th month	7.77 ± 2.51	7.35 ± 2.09									

Table 3 (continued)

Parameter	Timeline	Intervention ($n=53$)	Control ($n=53$)	Time effect			Group effect			Interaction		
				p-value	Partial Eta Squared	Power	*p*-value	Partial Eta Squared	Power	*p*-value	Partial eta squared	Power
HOMA-IR	Baseline	3.33 ± 1.47	1.87 ± 0.68	0.26	0.01	0.36	**< 0.05***	0.05	0.55	0.67	0.01	0.16
	6th month	3.19 ± 1.44	2.57 ± 1.27									
	12th month	3.27 ± 1.61	2.43 ± 1.14									
	24th month	5.36 ± 5.13	4.81 ± 6.43									

FBG Fasting Blood Glucose, *HOMA-IR* Homeostatic Module Assessment for Insulin Resistance

* $p < 0.05$, two way mixed ANOVA, adjusted for age, gender, years of education, household income, body mass index

Table 4 Effectiveness of the AGELESS Multidomain Intervention on Secondary Outcomes (Dietary intake and food group) (Presented as mean ± SD)

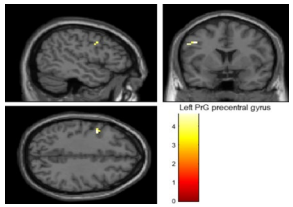
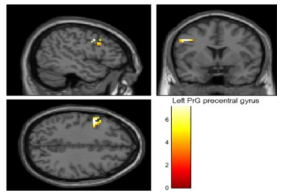
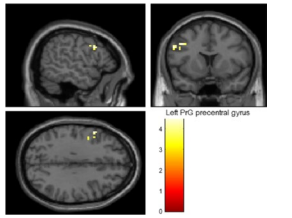
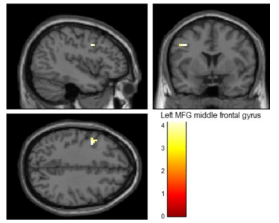
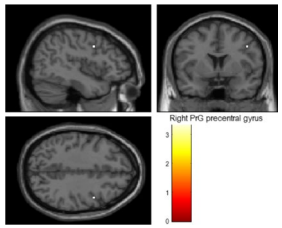
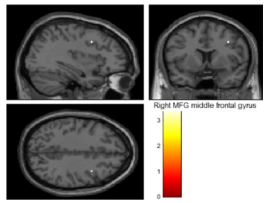
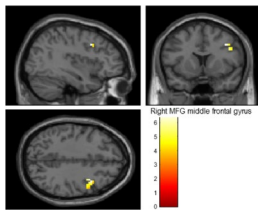
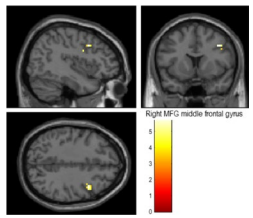
Parameter	Timeline	Intervention ($n=53$)	Control ($n=53$)	Time effect			Group effect			Interaction		
				p-value	Partial Eta Squared	Power	*p*-value	Partial Eta Squared	Power	*p*-value	Partial Eta Squared	Power
Energy (kcal/day)	Baseline	1257 ± 391	1257 ± 331	0.14	0.02	0.48	0.81	0.00	0.06	**< 0.05**	0.03	0.71
	6th month	1174 ± 354	1257 ± 283									
	12th month	1286 ± 339	1203 ± 305									
	24th month	1309 ± 327	1258 ± 267									
Protein (% of energy)	Baseline	16.2 ± 3.7	16.1 ± 2.7	**< 0.001**	0.08	1.00	0.19	0.02	0.25	**< 0.001**	0.12	1.00
	6th month	15.1 ± 3.2	15.8 ± 3.2									
	12th month	14.9 ± 2.5	15.3 ± 2.6									
	24th month	18.6 ± 5.2	15.1 ± 2.9									
Niacin (mg/day)	Baseline	6.7 ± 3.1	8.3 ± 7.1	0.46	0.01	0.24	0.64	0.00	0.08	**< 0.05**	0.03	0.74
	6th month	7.1 ± 3.6	7.4 ± 3.6									
	12th month	8.8 ± 9.2	7.3 ± 2.5									
	24th month	9.2 ± 8.9	7.2 ± 2.5									
Calcium (mg/day)	Baseline	332.0 ± 246.5	431.9 ± 294.3	0.19	0.02	0.42	0.95	0.00	0.05	**< 0.001**	0.07	0.99
	6th month	340.6 ± 232.9	423.0 ± 274.5									
	12th month	412.3 ± 362.3	369.8 ± 264.9									
	24th month	497.2 ± 358.8	367.9 ± 268.3									
Vegetables (serving/day)	Baseline	1.56 ± 0.90	1.44 ± 1.33	0.31	0.01	0.25	**< 0.001**	0.64	1.00	**< 0.001**	0.32	1.00
	6th month	2.82 ± 0.71	0.99 ± 0.64									
	12th month	3.11 ± 0.37	1.06 ± 0.67									
	24th month	3.07 ± 0.65	1.07 ± 0.73									
Fruits (serving/day)	Baseline	1.35 ± 0.64	1.02 ± 0.83	0.78	0.00	0.11	**< 0.001**	0.42	1.00	**< 0.001**	0.14	1.00
	6th month	1.84 ± 0.97	0.91 ± 0.75									
	12th month	2.16 ± 0.75	0.88 ± 0.67									
	24th month	2.00 ± 0.80	0.81 ± 0.58									
Fish (serving/day)	Baseline	1.02 ± 0.51	0.95 ± 0.69	0.11	0.02	0.49	**< 0.001**	0.15	0.99	**< 0.005**	0.07	0.95
	6th month	1.27 ± 0.71	0.82 ± 0.59									
	12th month	1.40 ± 0.60	0.85 ± 0.29									
	24th month	1.37 ± 0.67	0.83 ± 0.63									
Legume (serving/day)	Baseline	0.47 ± 0.47	0.37 ± 0.49	0.76	0.00	0.11	< 0.003	0.38	1.00	**< 0.001**	0.15	1.00
	6th month	0.72 ± 0.52	0.29 ± 0.30									
	12th month	1.05 ± 0.29	0.28 ± 0.67									
	24th month	1.04 ± 0.53	0.36 ± 0.41									

Table 4 (continued)

Parameter	Timeline	Intervention ($n=53$)	Control ($n=53$)	Time effect			Group effect			Interaction		
				p-value	Partial Eta Squared	Power	*p*-value	Partial Eta Squared	Power	*p*-value	Partial Eta Squared	Power
Milk & milk products (serving/day)	Baseline	0.50 ± 0.83	0.45 ± 0.81	0.74	0.00	0.11	0.21	0.02	0.24	**< 0.05**	0.04	0.81
	6th month	0.62 ± 0.85	0.94 ± 0.64									
	12th month	0.74 ± 0.97	0.45 ± 0.71									
	24th month	0.92 ± 0.97	0.46 ± 0.76									

* $p < 0.05$, two way mixed ANOVA, adjusted for age, gender, years of education, household income, and body mass index

Table 5 Effectiveness of multidomain intervention on fMRI behavioural performance (Presented as mean ± SD)

Parameter	Timeline	Intervention ($n=14$)	Control ($n=14$)	Time effect			Group effect			Interaction		
				p-value	Partial Eta Squared	Power	*p*-value	Partial Eta Squared	Power	*p*-value	Partial eta squared	power
1-back Left DLPFC activation	Baseline			0.63	0.03	0.16	0.22	0.08	0.22	**< 0.05***	0.13	0.66
	24th month											
	Baseline											
SCWT Congruent Right DLPFC activation	24th month			0.874	0.013	0.091	**< 0.05***	0.313	0.773	**< 0.05***	0.17	0.77

SCWT Stroop colour and word test, *DLPFC* Dorsolateral prefrontal cortex

* $p < 0.05$, two way mixed ANOVA, adjusted for age, gender, years of education, household income, and body mass index

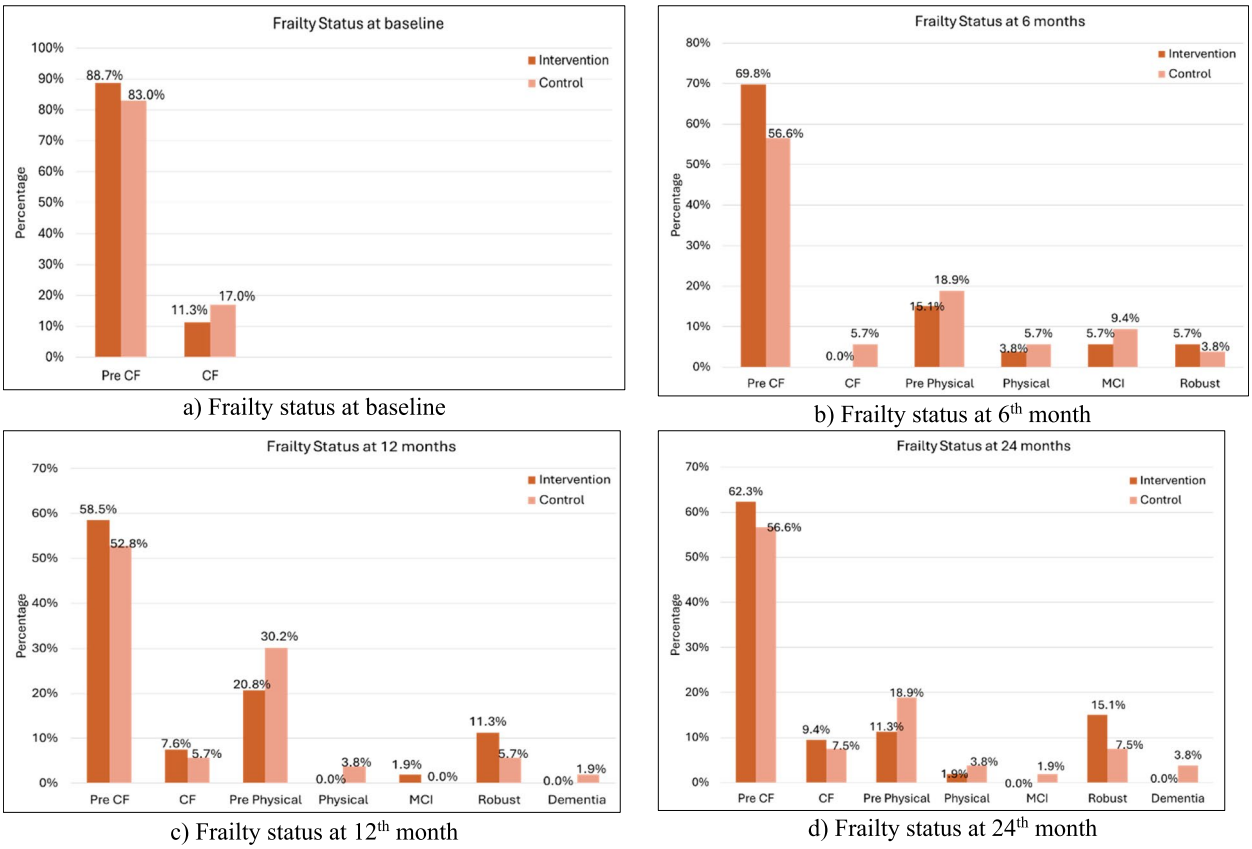


Fig. 6 Reversibility of cognitive frailty at 6th month, 12.th month and 24th month. CF: Cognitive frailty; MCI: Mild cognitive Impairment. Operationalization of definitions: Pre-CF (1–2 Fried's criteria and CDR = 0.5), CF (≥ 3 Fried's criteria and CDR = 0.5), Pre-Physical (1–2 Fried's criteria), Physical Frailty (≥ 3 Fried's criteria), MCI (CDR = 0.5), Dementia (CDR = 1), Robust (< 1 Fried's criteria and CDR = 0)

reduced intensity of the psychosocial and dietary components (once every three months) compared to the first 12 months (once every month). Also, the high drop-out rate (50%) could have limited the possibility of detecting significant changes.

Overall, the experimental group showed higher mean scores across all cognitive tests compared to the control group. Previous research has demonstrated that cognitive training, when administered alone, significantly impacts executive function, stimulates cognitive reserve, and compensates for age-related neurological damage [31–33]. Combining physical exercise with cognitive training has been suggested to enhance neurogenesis, a critical factor in maintaining cognitive function and repairing aging and neurological damage to brain cells. This combination may also increase cerebral blood flow, basal levels of brain-derived neurotrophic factor (BDNF), and insulin-like growth factor 1 (IGF-1), potentially strengthening memory [34, 35]. Additionally, improvements in physical fitness resulting from exercise training can influence brain plasticity and contribute to enhancements in memory [35].

Research indicates that multicomponent exercises, such as resistance training, balance training integrating physical and cognitive activities, and aerobic training, are associated with overall improvements in cognitive function and short-term memory [36, 37]. Previous studies have also shown that dietary choices and lifestyle factors can enhance cognitive function [38, 39]. In the current

Table 6 Incremental cost effectiveness ratio (ICER) based on statistically significant primary outcomes

Variables/ outcome measures	ICER (RM)
Chair sit and reach	280.08
6 m walk test	1660.66
2-min step test	149.19
Digit Span	1558.46
Visual paired associates (immediate)	1841.82
Verbal paired associates (immediate)	457.06
Visual paired associates (delay)	974.04
Verbal paired associates (delay)	585.29

study, there was a significant increase in the intake of vegetables, fruits, calcium, legumes, milk, fish, niacin, protein, and total energy over the 24-month intervention period. Diets rich in polyphenols found in vegetables and fruits have been demonstrated to stimulate neurogenesis in animal models [40]. Additionally, higher consumption of fish in the intervention group may have contributed to the enhancement of cognitive function, as marine omega-3 polyunsaturated fatty acids found in fish are known to have a positive impact on cognitive performance [41, 42]. The observed increase in brain activity within the intervention group may also be linked to their higher fish, fruit and vegetables consumption in the same group [43, 44].

In the present study, the fMRI data provides some insight on the possible mechanisms underlying the intervention effects on cognition. Participants in the multidomain intervention group showed increased functional activation in the DLPFC after the intervention. This is in line with previous research suggesting that multidomain interventions can increase brain activation during interference tasks in older adults at high risk of cognitive decline [45]. Although these are exploratory findings, and should thus be interpreted with caution, it is possible that the increased brain activation associated with interference tasks in cognitively high-risk older adults observed in the AGELESS study may indicate that the effects of the intervention on brain activation differ according to the participant's cognitive level and the type of cognitive task.

Multi-component exercises have shown positive outcomes in terms of strength, endurance, and flexibility among older adults with cognitive impairment [46]. However, our study did not find a significant effect on muscle strength, which could be due to the shorter duration of the strength training component (30 min per session). Research suggests that to effectively improve muscle strength, strength training sessions should ideally exceed 75 min in duration, as duration significantly impacts strength gains [47]. Nonetheless, our intervention did show an effect on skeletal muscle mass. These parameters could have been affected by factors such as the presence of comorbidities triggering age-related declines in muscle strength, and increased protein intake among participants in the active group [48, 49]. These results differ from the FINGER trial, which did not report significant effects on physical function, although there was a significant improvement on the chair rise test in the multidomain intervention compared to the control group [50]. Such discrepancy might be attributed to differences in the target population, as FINGER trial participants were on average more physically fit compared to AGELESS, with only 28.4% of the FINGER population being classified as pre-frail or frail at baseline, based on Fried´s criteria [11]. Additionally, the 2 studies had different outcome measures, as the FINGER trial used a composite score from the Short Physical Performance Battery, while the current study assessed individual scores for each physical test [11].

In the AGELESS trial, we did not observe a significant intervention effect on psychosocial measures and vascular parameters. Notably, the psychosocial module developed in this study is pioneering, given the scarcity of existing evidence on psychosocial interventions, particularly among cognitive frailty groups in LMICs. Despite the absence of a clear direct impact, it is plausible that the psychosocial intervention contributed significantly to enhancing cognitive function within the experimental group [51]. The current study's' lack of significant effects on vascular parameters mirrors the findings of the pre-DIVA study, which may be attributed to participants already receiving high-standard vascular management in primary care settings [52]. However, significant effects were observed in other vascular related parameters, including anthropometry and body composition.

In both the intervention and control group of the study, transitions across different categories of (pre)-CF were observed, based on changes related to physical and cognitive components. Following 24 months of intervention, a small percentage of participants in the experimental group transitioned to a robust state, but results were not statistically significant and must be interpreted with caution, also given the high drop-out rate. Recent data from the FINGER trial indicated a favorable trend in reversing (pre)-frailty among older men, as after the 2-year intervention pre-frail or frail men in the multidomain intervention group had higher probability of being non-frail, compared to pre-frail or frail men in the control group. No effect on frailty status was detected in women [13]. Notably, most of the FINGER study participants defined as frail were pre-frail, with a very low number of people being classified as frail. There are a few studies on the preventative role of multidomain lifestyle-based intervention in pre-frail and cognitively (pre)-frail older adults, and the current study adds to the existing literature indicating the feasibility of a multidomain approach in this target group in LMICs.

The adherence rate among participants was moderate, averaging around 50%, particularly for cognitive and exercise training sessions. We previously reported that adherence during the first year, when intervention was more intense, was not correlated with sociodemographic data, cognition (except performance in the fluency test), depressive symptoms, cardiovascular risk factors, physical fitness test, or psychosocial factors [18]. In a qualitative study among participants from the multidomain

arm, we found that caregiving responsibilities, such as caring for grandchildren, limited access to transportation, health and physical limitations, were among the factors cited as hindrances to attending weekly sessions during the 2-year period [53]. Despite these challenges with attendance, participants who did attend each session showed high compliance with the training protocol, which likely contributed to improvements in both cognitive and physical function. In line with this, in the FINGER study the greatest cognitive benefits were reported among those who participated in at least half of all proposed activities [54]. Both AGELESS and FINGER interventions were quite intensive, especially in the first 12 months, suggesting that such an intensity of intervention might be needed to achieve beneficial outcomes. Therefore, efforts should be directed towards supporting adherence.

The AGELESS Trial intervention had an estimated total cost of about RM 1592.74 (≈ USD 355.05) per participant over 24 months. In comparison, a study conducted in Singapore reported a cost of SGD 620 (≈ USD 458) per participant for a multidomain intervention aimed at older adults at risk of cognitive decline over 24 weeks [55]. Despite the longer duration of the AGELESS trial, its cost is relatively low, especially considering that it targeted dual impairments such as CF. A significant portion of the budget was allocated for transportation, as many participants lacked access to transport, which increased the logistical and operational expenses. While the cost-effectiveness of non-pharmacological interventions is less frequently reported, they are generally considered cost-effective due to their potential to reduce healthcare costs for older adults [56].

Unlike other multidomain intervention trials, the AGELESS study was specifically designed to be feasible and accessible to cater older adults from low to moderate socioeconomic backgrounds in a LMIC. Main results suggest that the AGELESS model can be cost effective and culturally appropriate to be executed among community dwelling older adults. This study follows a rigorous protocol, with blinded raters assessing comprehensive outcome measures. This trial began amid the COVID-19 pandemic, posing challenges in recruiting participants and maintaining their active involvement in the multidomain intervention [18]. The older population's heightened fear of the disease added to these difficulties [57]. This study faced several limitations that should be acknowledged. First, the limited sample size and the high dropout rate (50%) over the 24-month period may have influenced the results, preventing the possibility to detect beneficial effects. Yet, significant interventions benefits were detected in different parameters. The adherence rate of participants for exercise and cognitive training sessions was indicated as average. While there is no established gold standard for adherence rates, future studies could explore strategies to enhance consistent engagement of older adults in longitudinal studies. Second, the use of self-reported measures for certain outcomes, such as dietary intake and psychosocial variables, introduces the potential for response bias. The generalizability of the findings is limited by the specific demographic and cultural characteristics of the study population. Further research in diverse populations is necessary to confirm the broader applicability of this intervention. Future research should focus on the long-term sustainability of multidomain interventions, particularly in terms of maintaining adherence over extended periods and minimizing dropout rates.

Conclusion

Findings from the 24-month AGELESS trial indicate that this multidomain model can be an effective, feasible and cost-effective non-pharmacological approach to address cognitive and physical components of (pre)-CF, which is potentially reversible. Practitioners in geriatric health may benefit from integrating multidomain interventions that include physical activity, dietary guidance, cognitive training, and psychosocial support to address the complex needs of cognitively frail individuals. For policymakers, the cost-effectiveness of the AGELESS intervention underscores its potential as a scalable public health strategy, particularly in settings with limited healthcare resources and considering the high prevalence of modifiable risk factors for dementia in LMICs [58]. Active involvement in the AGELESS study could enhance public health literacy by spreading awareness of the ideas of "confident ageing in place" and "healthy ageing" across a larger population.

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

P.P did the main writing of the manuscript, S.S, D.K.A.S, A.A, P.S, N.I, H.H, A.I, C.AV provided supervision in proofreading and editing the manuscript. A.I, H.F, N.A.K, A.M.S, J.M.H did the data collection and analysis, J.L, F.F and M.K did the final editing.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Rigorous ethical standards were adhered by ensuring that all participants provided informed consent, fully understanding the nature of the research, potential risks, and their right to withdraw at any time.

Competing interests
The authors declare no competing interests.

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