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Original Research

Impact of Exercise and Cognitive Stimulation Therapy on Physical Function, Cognition and Muscle Mass in Pre-Frail Older Adults in the Primary Care Setting: A Cluster Randomized Controlled Trial

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Abstract

OBJECTIVES: Multicomponent exercise program have shown to improve function and cognition in older adults but studies on pre-frail older adults in the primary care setting are limited. This study aimed i) to evaluate impact of 6 months exercise (Ex) versus complementary effect of 3 months of cognitive stimulation therapy (CST) to 6 months of Ex (Ex+CST) on physical function, muscle mass and cognition versus control group at 3, 6 and 12 months ii) inflammatory biomarkers such as Interleukin-6 (IL-6) and Tumor Necrosis Factor Alpha (TNF-α).

DESIGN: Cluster randomised control trial.

SETTING & INTERVENTION: Pre-frail older adults ≥ 65 years attending primary care clinic. Two intervention groups i) Ex 6 months ii) CST 3 months with Ex 6 months.

MEASUREMENTS: At 0, 3, 6 and 12 months, questionnaires (on demographics, physical function, cognition, and depression) were administered and physical function assessment (gait speed, short physical performance battery (SPPB) test, handgrip strength, five times sit-to-stand (5x-STS)) was conducted. Muscle mass and its surrogates such as phase angle and body cell mass were measured using bioelectrical impedance analysis machine. Inflammatory biomarkers were measured at 0 and 3 months.

RESULTS: Data from 190 participants was analysed at 3 months (111 control, 37 Ex and 41 Ex+CST). At 3 months, significant improvement in cognition was seen only in the Ex+CST group whereas improvements in depression, gait speed, SPPB and 5x-STS were seen in both the Ex and Ex+CST groups. At 6 months, the Ex+CST group improved in cognition and depression whereas improvement in frailty and muscle mass indices were seen in both the interventions groups. At 12 months, both the interventions groups had better perceived health, gait speed and less decline in muscle mass compared with control groups. Both the Ex and Ex+CST had significant association with TNF-α at 3 months (β -2.71 (95% CI -4.80 - -0.62); p = 0.012 and β -1.74 (95% CI -3.43 – -0.06); p = 0.043 respectively).

CONCLUSION: Combined Ex+CST had significant improvement in cognition whereas the intervention groups improved in depression, physical function, muscle mass, frailty, perceived health and TNF-α levels. With growing evidence of the benefits of multicomponent interventions at primary care level, incorporating it into mainstream care with action plans on long-term sustainability and scalability should be a priority for every country.

Key words: Exercise, cognitive stimulation therapy, pre-frail, tumor necrosis factor alpha, interleukin 6, muscle mass, phase angle, body cell mass.

Introduction

The global population is ageing rapidly with Asia-Pacific being at the forefront. Older adults 60 years old and above are expected to triple between 2010 and 2050 to 1.3 billion in the Asia-Pacific (1). Despite increase in life expectancy, healthspan continues to lag behind with an average of 9 years is spent in poor health (2). Many countries are in the process of developing action plans to reduce the gap between healthspan and lifespan (3). The World Health Organisation (WHO) public health framework for Healthy Aging recommends intervening at an early stage to prevent or delay frailty and consequent disability, as detailed in the most recent publication by WHO on Integrated care for Older People (ICOPE) (4).

Frailty is a state of decline in physiological reserve predisposing older adults to adverse outcomes when exposed to stressors (5). It is a dynamic state and may be reversible before the onset of disability (6). Pre-frailty is a transition state to frailty and is increasingly being recognised as a public health target for implementation of multi-domain intervention to delay the onset of functional decline and disability (7). The prevalence of pre-frailty varies between 35% to 53% (7-9). Multi-domain interventions such as nutrition, exercise and cognitive training have been shown to prevent progression of frailty and disability (10, 11). Primary care is the foundation of healthcare systems, often being the first point of contact for older adults and a core site for preventive healthcare. Many countries have introduced frailty screening in primary care using screening tools such as the FRAIL scale and Kihon checklist with the aim of early identification, management, and prevention (5, 12).

Inflammation is common both in aging and frailty. Elevated levels of pro-inflammatory cytokines such as C-reactive protein

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(CRP), Interleukin-6 (IL-6) levels, Growth Differentiation Factor-15 (GDF-15) and Tumor Necrosis Factor Alpha (TNF-α) are found in frailty, and are associated with declining physical function and mortality (13, 14). Conversely, anti-inflammatory cytokines such as IL-10 suppresses pro-inflammatory activity in various tissues and aging is associated with declining levels of IL-10 (15). Chronic inflammation is associated with decreased muscle mass and strength, disability, dementia, increased morbidity, and mortality (16). Studies on impact of exercise on pro-inflammatory and anti-inflammatory cytokines have shown mixed results depending on the intensity and duration of exercise (17, 18). There are limited studies on association of moderate intensity exercise on inflammation in pre-frail older adults (19, 20).

Multidomain interventions incorporating cognitive training have shown to be beneficial in improving cognition in pre-frail older adults (21). Multiple studies have shown the beneficial effects of cognitive stimulation therapy (CST) in improving global cognitive function mainly in persons with dementia (22). However, there is a paucity of literature on the impact of CST and exercise in combination on functional outcomes, cognition, muscle mass and inflammatory biomarkers in pre-frail older adults. As such, our study sets out to assess the impact of 6 months exercise (Ex) versus complementary effect of 3 months of cognitive stimulation therapy (CST) to 6 months of exercise (Ex+CST) on physical function, muscle mass indices and cognition at 3, 6 and 12 months (6 months post cessation of intervention). A secondary aim was to assess the differential effects of Ex and Ex+CST on inflammatory biomarkers.

Methods

Participants and Study Design

This was a cluster randomized control trial (NCT 03797352) conducted between 2019 to 2022 involving participants from two primary care clinics 5km apart in the Western region of Singapore. Participants attending Choa Chu Kang Polyclinic were allocated to control group and participants from Bukit Batok Polyclinic were allocated to exercise only (Ex) or exercise and CST (Ex + CST) groups (Figure 1). There was no blinding and allocation to Ex or Ex+CST group was not randomised within the same site. The allocation to Ex or Ex+CST was based on which research staff recruited them. Participants ≥ 65 years old, who were ambulatory and screened to be pre-frail based on FRAIL scale by coordinators in the primary care clinic and able to consent were invited to participate. Participation was voluntary. The inclusion criteria included age ≥ 65 years old, having the ability to follow instructions and participate in the intervention as deemed suitable by a primary care physician or trained members of the study team. Participants with a pacemaker or a defibrillator, liver or gastro-intestinal disease, end stage lung disease, cardiac disease, cancer undergoing active treatment, gout, underlying psychiatric conditions and nursing home residents were excluded.

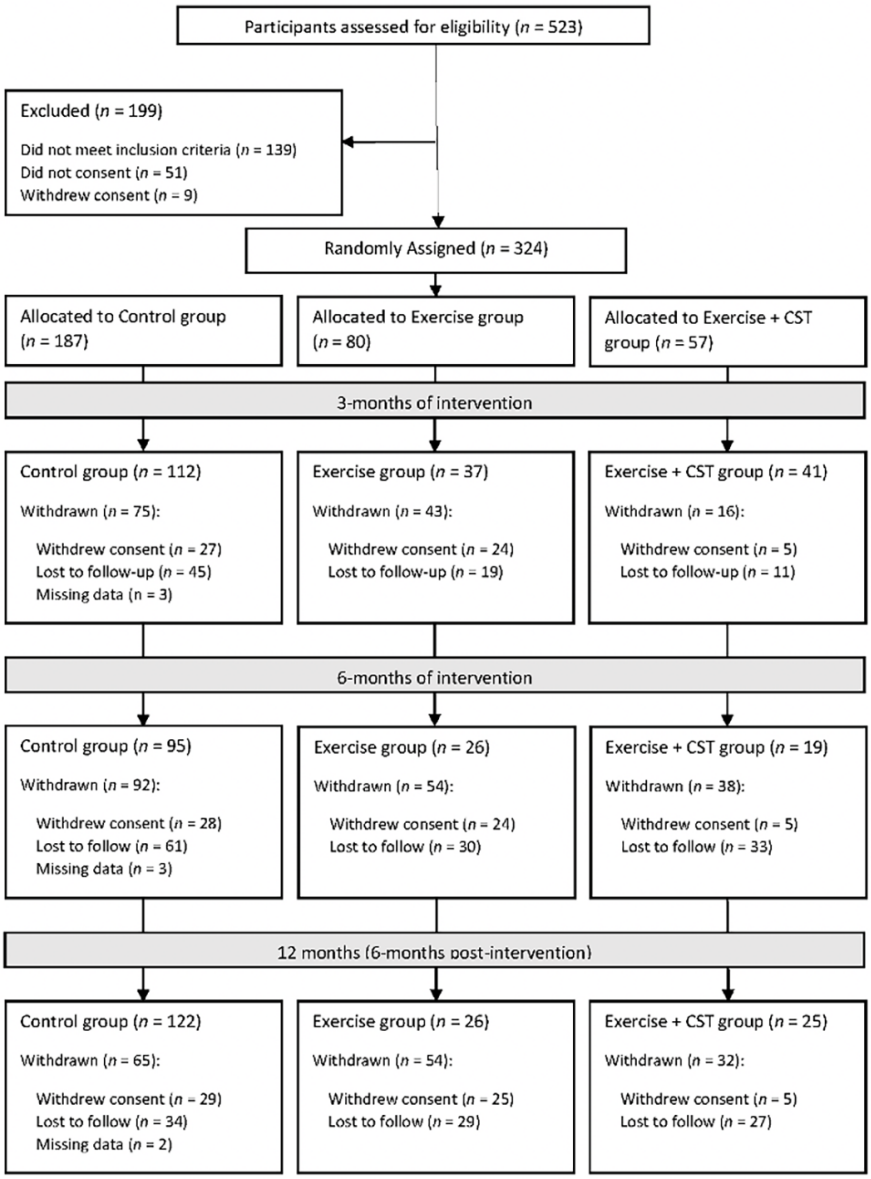
Interventions

The control group received general health education advice. The intervention groups received 60 minutes twice a week multicomponent exercise program consisting of aerobic training, resistance training, dual task, and balance training. The study team members were trained to conduct CST by qualified trainers from St Louis University, Missouri, USA. The Ex+CST group received 30 minutes of CST twice a week for a total of 3 months in addition to exercise, followed by 3 more months of exercise only. Participants were divided into English and Mandarin speaking training groups (Figure 2). CST was conducted after the 60 minutes of exercise. The training was adapted from the CST manual which included games, food, current affairs, art and word association (23). The study lasted for 12 months. Participants were assessed at 3 months, and at the end of the 6-month intervention. A 6-month washout period was observed where participants received no interventions and were then assessed at the end of this period.

Demographics and Covariates

Trained study team members collected data on demographics, chronic diseases, medications, perceived health, frailty, physical activity levels, falls, cognition, and nutrition. Frailty was assessed using the five component FRAIL scale (Fatigue, Resistance, Aerobic, Illness and Loss of Weight) (24). Participants were considered pre-frail if they scored 1-2 out of maximum score of 5. Polypharmacy was defined as taking five or more long-term medications. The 3-item UCLA Loneliness Scale (UCLA-3) was used to assess whether participants were experiencing loneliness (25). The EuroQoL-Visual Analogue Scale (EQ-VAS) was used to understand participants' perceived health (26). Physical activity level was assessed using the Rapid Physical Assessment (RAPA) tool (27). RAPA was developed to assess the quantity and intensity of physical activity in adults 50 years or older with a maximum score of 7. Score of 6-7 are considered active, 4-5 under-active regular, 3 under-active light activities, 2 under-active and 1 considered as sedentary (27). Lawton's instrumental activities of daily living (IADL) scale was used to assess IADL and Katz activity of daily living (ADL) to assess ADL (28, 29). Participants who reported at least 1 fall in the past year were considered fallers (30). Cognition was assessed using the Montreal Cognitive Assessment (MoCA) (31). The Geriatric Depression Scale (GDS) was used to identify participants with depression where those with a score ≥ 5 were considered depressed (32). Nutritional status was evaluated using the Mini-Nutritional Assessment short-form (MNA-SF) (33). The MNA-SF is a 6-item screening questionnaire which has been validated as a sensitive rapid nutrition screening instrument . Participants were classified as normal nutritional status (12 – 14 points), at risk of malnutrition (8 – 11 points) and malnourished (0 – 7 points).

Figure 1. Participant screening, group allocation, and follow-up



Physical Performance

Physical performance measures comprised of maximum handgrip strength (HGS), gait speed, and the Short Physical Performance Battery (SPPB) test. HGS was measured using Jamar hand dynamometer on the dominant hand with participant in a seated position and elbow flexed 90°. Low HGS was defined as < 28kg for males and < 18 kg for females based on the 2019 consensus by the Asian Working Group for Sarcopenia (AWGS) (34). The SPPB, with three components - balance, GS and 5 times sit-to-stand (5xSTS) timing, has a maximum score of 12 points (4 per component). Gait speed < 1.0m/s was considered slow gait.

Body Composition

Body composition was measured using the InBody S10 multi-frequency bioelectrical impedance analyser (BIA). Appendicular skeletal muscle (ASM), body cell mass and whole-body phase angle were measured as surrogate for muscle mass. Appendicular skeletal muscle index (ASMI) was derived from ASM divided by height square. Sarcopenia was diagnosed based on the 2019 AWGS criteria of gender specific cut offs for ASMI and either low HGS or poor physical performance.

Plasma Biomarkers

Non-fasting blood test was voluntary and only participants who agreed to have 15mls of blood drawn were invited. The TNF-α, IL-6, GDF-15, and IL-10 cytokines were measured by an accredited hospital-based laboratory. TNF-α cytokine was measured using Immunoenzymetric assay with a detection range between 1.0 - 498 pg./mL and IL-6 measured using the electrochemiluminescence immunoassay (ECLIA) with a detection range between 1.5 - 50 000 pg./mL. Enzyme-linked immunosorbent Assay was used to measure IL-10 with

Figure 2. Group Based Cognitive Stimulation Therapy

a detection range of 2.0 - 400.0 pg./mL and GDF-15 with a detection range of 2.0 -2400 pg./mL.

Ethics approval and informed consent

The study protocol including screening and intervention was approved by the National Healthcare Group (NHG) Domain Specific Review Board (DSRB) (Reference number: 2017/00035). Written consent was obtained from all participants.

Statistical analysis

IBM SPSS Version 28.0 was used for our data analysis. Categorical variables were presented as frequencies with percentages while continuous variables were presented as mean ± standard deviation in. $\chi 2$ test was used for significance testing of categorical variables. For continuous variables, normality assumption was tested using Sharpiro Wilk test. Significance testing for normally distributed variables with equal variances was carried out using one-way ANOVA whereas Welch test was used for those with unequal variances. The Kruskal-Wallis test was used when continuous variables were not normally distributed.

General Linear Model (GLM) was used to compare changes in continuous variables between groups adjusted for age, gender, ethnicity, education, hypertension, hyperlipidaemia, diabetes, physical activity, polypharmacy, cognition, IADL impairment and corresponding baseline values.

Mood's median test was used to compare the median levels of plasma biomarkers. Quantile regression was also performed to compare changes in plasma biomarker levels between the groups adjusted for age, gender, ethnicity, education, hypertension, hyperlipidaemia, diabetes, physical activity, polypharmacy, cognition, IADL impairment and corresponding baseline values.

Results

A total of 324 participants were initially enrolled in the study just before the Covid-19 pandemic with 187 allocated to the control group and 137 to the intervention groups (Ex = 80; Ex + CST = 57). Full data for analysis was available for 190 participants at 3 months (112 control, 37 Ex and 41 Ex + CST), 140 at 6 months (95 control, 26 Ex and 19 Ex + CST) and 173 at 12 months (122 control, 26 Ex and 25 Ex + CST) (Figure 1). The intervention study was conducted during the peak of COVID-19 pandemic with multiple lockdowns resulting in significant numbers withdrawing consent after enrolment or lost to follow-up. Some participants missed 3- and 6-month assessments due to COVID-19 measures. The median adherence was 75% for Ex+CST and 67% for Ex group. There was no significant difference between the participants who

Table 1. Baseline Characteristics

	Control n = 187 (57.7%)	Exercise n = 80 (24.7%)	Exercise + CST n = 57 (17.6%)	P-value
Demographics				
Gender				0.003
Male	96 (51.3)	33 (41.3)	15 (26.3)	
Female	91 (48.7)	47 (58.8)	42 (73.7)	
Age (years)	71.69 ± 4.99[a,b]	73.39 ± 5.20[a]	72.56 ± 5.06[b]	0.037
Ethnicity				0.253
Chinese	150 (80.2)	74 (92.5)	46 (80.7)	
Malay	18 (9.6)	3 (3.8)	4 (7.0)	
Indian	19 (10.2)	3 (3.8)	7 (7.0)	
Others	1 (0.5)	0 (0.0)	0 (0.0)	
Hypertension	141 (75.4)	55 (68.8)	40 (70.2)	0.661
Hyperlipidaemia	159 (85.0)	56 (70.0)	46 (80.7)	0.043
Diabetes	104 (55.6)	33 (41.3)	33 (57.9)	0.099
Polypharmacy	61 (32.6)	24 (30.0)	17 (29.8)	0.899
Living Alone	14 (7.5)	4 (5.0)	6 (10.5)	0.476
Loneliness (UCLA-3)	33 (17.6)	9 (11.3)	14 (24.6)	0.125
BMI (kg/m^2)	26.32 ± 4.68	25.34 ± 4.72	26.11 ± 4.58	0.291
Education (years)	7.29 ± 4.00	8.25 ± 4.22	8.39 ± 3.73	0.060
Perceived Health (EQ-VAS)	69.12 ± 15.31	70.31 ± 12.69	67.81 ± 13.79	0.604
FRAIL Total	1.24 ± 0.44	1.39 ± 0.59	1.30 ± 0.50	0.052
Physical Activity (RAPA)	3.51 ± 1.52[a]	2.69 ± 1.41[a,b]	3.39 ± 1.51[b]	<0.001
At least 1 IADL Impairment	37 (19.8)	31 (38.8)	14 (24.6)	0.004
At least 1 ADL Impairment	32 (17.0)	25 (31.3)	15 (26.3)	0.032
Sarcopenia[1]	18 (9.6)	16 (20.0)	8 (14.0)	0.057
Falls in Last One Year ≥ 1	38 (20.2)	22 (27.5)	16 (28.1)	0.322
MoCA	25.05 ± 3.42[a,b]	26.55 ± 3.21[a]	27.24 ± 2.38[b]	<0.001
Depression	56 (29.8)	19 (23.8)	12 (21.1)	0.293
Nutritional Status (MNA-SF)				0.894
Malnourished	3 (1.6)	1 (1.3)	1 (1.8)	
At risk of malnourishment	32 (17.1)	15 (18.8)	7 (12.3)	
Normal nutritional status	152 (81.3)	64 (80.0)	49 (86.0)	
Physical Performance				
Handgrip Strength (kg)	22.91 ± 7.08	21.99 ± 6.45	21.49 ± 6.78	0.363
Gait Speed (m/s)	0.94 ± 0.27	0.94 ± 0.33	0.97 ± 0.27	0.656
5x Chair Stand Time (s)	12.89 ± 4.79	13.98 ± 5.41	13.30 ± 4.46	0.251
Total SPPB Score	9.78 ± 2.07	9.55 ± 2.13	9.75 ± 2.06	0.704
Body Composition				
ASMI (kg/m^2)	6.86 ± 1.02	6.82 ± 1.50	6.71 ± 1.27	0.388
Body Cell Mass (kg)	25.82 ± 7.86	28.36 ± 7.74	26.86 ± 6.66	0.149
50khz-Trunk Phase Angle (θ)	5.67 ± 2.42	6.04 ± 3.95	5.39 ± 2.06	0.445

Values presented as n (%) or mean ± SD; Bold indicates significance ($p < 0.05$); a.b. Values with common superscript are significantly different. Abbreviations: BMI, Body Mass Index; ADL; Activities of Daily Living; MoCA; Montreal Cognitive Assessment; SPPB, Short Physical Performance Battery; ASMI, Appendicular Skeletal Muscle Index. 1. Based on Asian Working Group for Sarcopenia (AWGS) 2019's definition; 2 Adjusted for gender

dropped out before the 3 months evaluation and those who continued except for falls risk which was adjusted for in the final analysis (supplementary Table 1). There were significant differences in gender distribution where 73.7% of those in the Ex + CST group, 58.8% in the Ex group and 48.4% in the control group were females (Table 1). The mean age in the control group was the lowest (71.7 years) compared with Ex (73.4 years) and Ex + CST (72.6 years). The control group had the greatest proportion of participants with hyperlipidaemia (84.6%) versus Ex group (70.0%).

Cognition, Depression and Quality of life

MoCA scores were significantly different amongst the groups with the score lowest in the control group (25.05 ± 3.42) and highest in the Ex + CST (27.24 ± 2.38, $p < 0.001$) group.

Table 2. Mean changes in outcome variables from baseline to 3 months, 6 months, and 12 months respectively

	0 Month – 3 Months				0 Month – 6 Months				0 Month - 12 Months			
	Control n = 111 (54.6%)	**Exercise n = 37 (17.9%)**	**Exercise + CST n = 41 (27.5%)**	**p-value**	**Control n = 95 (67.4%)**	**Exercise n = 26 (18.4%)**	**Exercise + CST n = 19 (13.6%)**	**p-value**	**Control n = 122 (70.5%)**	**Exercise n = 26 (15.0%)**	**Exercise + CST n = 25 (14.5%)**	**p-value**
Cognition and Mental Health												
MoCA	0.49[a] (0.13 – 0.85)	1.67 (1.01 – 2.33)	1.83[a] (1.24 – 2.42)	<0.001	-0.03[a] (-0.52 – 0.58)	1.71 (0.70 – 2.72)	1.67[a] (0.56 – 2.78)	0.005	0.31 (-0.15 - 0.76)	0.51 (-0.40 - 1.41)	1.03 (0.12 - 1.94)	0.394
GDS	0.17[a,b] (-0.23 – 0.58)	-1.15[a] (-1.87 – 0.44)	-1.55[b] (-2.23 - -0.88)	<0.001	0.52[a] (-0.09 – 1.12)	-1.10 (-2.21 – 0.01)	-1.23[a] (-2.44 - -0.02)	0.010	0.23 (-0.20 - 0.67)	0.67 (-0.36 - 1.69)	0.32 (-0.63 - 1.26)	0.759
Perceived Health (EQ-VAS)	-3.58 (-6.40 - -0.76)	0.27 (-4.73 – 5.27)	2.32 (-2.38 – 7.03)	0.101	-1.84 (-5.14 – 1.47)	6.00 (-5.98 – 17.97)	11.16 (-0.13 – 22.44)	0.060	-1.23[a,b] (-3.43 - 0.98)	4.79[a] (-0.35 - 9.93)	6.03[b] (1.19 - 10.87)	0.012
Physical Performance												
FRAIL Total	-0.15 (-0.29 - 0.02)	-0.33 (-0.59 – 0.07)	-0.40 (-0.64 – 0.16)	0.199	0.02[a,b] (-0.24 – 0.27)	-0.56[a] (-1.04 - -0.11)	-0.57[b] (-1.08 - -0.06)	0.039	-0.28 (-0.42 - -0.15)	-0.49 (-0.82 - -0.16)	-0.44 (-0.75 - -0.13)	0.451
HGS	-0.36 (-0.97 – 0.27)	0.74 (-0.38 – 1.86)	0.17 (-0.84 – 1.18)	0.268	-0.34 (-1.08 – 0.41)	0.52 (-0.88 – 1.92)	0.88 (-0.60 – 2.36)	0.292	-0.66 (-1.25 - -0.08)	-0.41 (-1.82 - 0.99)	-0.48 (-1.76 - 0.79)	0.938
Gait Speed	-0.01[a,b] (-0.04 – 0.03)	0.17[a] (0.11 – 0.22)	0.13[b] (0.07 – 0.18)	<0.001	-0.01[a,b] (-0.06 – 0.04)	0.20[a] (0.11 – 0.30)	0.25[b] (0.14 – 0.35)	<0.001	0.02[a,b] (-0.04 - 0.05)	0.20[a] (0.10 - 0.31)	0.15[b] (0.05 - 0.24)	<0.001
5x STS Time	-0.27[a,b] (-0.88 – 0.35)	-1.87[a] (-2.93 - -0.82)	-2.24[b] (-3.22 - -1.27)	0.002	-0.25 (-1.04 – 0.54)	-1.06 (-2.46 – 0.33)	-2.23 (-3.73 - -0.74)	0.077	0.80 (-0.04 - 1.64)	0.88 (-0.99 - 2.76)	-1.03 (-2.78 - 0.72)	0.162
SPPB Total	0.13[a,b] (-0.12 – 0.38)	0.68[a] (0.25 – 1.12)	0.65[b] (0.24 – 1.05)	0.044	-0.07 (-0.47 – 0.32)	0.80 (0.08 – 1.52)	0.75 (-0.04 – 1.54)	0.059	0.07 (-0.22 - 0.36)	0.29 (-0.38 - 0.96)	0.44 (-0.19 - 1.07)	0.551
Body Composition												
ASMI	-0.04 (-0.14 – 0.07)	0.05 (-0.16 – 0.25)	0.12 (-0.04 – 0.28)	0.277	0.10[a,b] (-0.27 – 0.47)	1.73[a] (0.63 – 2.83)	1.90[b] (0.62 – 3.17)	0.002	-2.68[a,b] (-3.06 - -2.31)	-0.30[a] (-1.42 - 0.82)	-0.35[b] (-1.12 - 0.42)	<0.001
BCM	-0.23 (-0.66 – 0.20)	0.22 (-0.51 – 0.96)	0.20 (-0.36 – 0.77)	0.419	-0.03[a,b] (-1.08 – 1.02)	2.38[a] (0.68 – 4.08)	2.35[b] (0.70 – 4.00)	0.026	-0.27 (-0.70 - 0.16)	-0.91 (-1.80 - -0.16)	-0.34 (-1.07 - 0.39)	0.468
Phase Angle	-0.12 (-0.24 – 0.02)	0.02 (-0.19 – 0.24)	0.07 (-0.11 – 0.25)	0.210	-0.50[a,b] (-1.01 – 0.01)	0.65[a] (-0.23 – 1.52)	1.01[b] (0.09 – 1.93)	0.010	-0.30 (-0.41 - -0.18)	-0.17 (-0.43 - 0.09)	-0.11 (-0.33 - 0.12)	0.323
Physical Activity and Nutritional Status												
RAPA	-0.02[a,b] (-0.31 – 0.26)	1.22[a] (0.71 – 1.73)	1.06[b] (0.59 – 1.54)	<0.001	0.25[a,b] (-0.11 – 0.60)	1.18[a] (0.53 – 1.83)	1.30[b] (0.59 – 2.01)	0.009	-0.23[a,b] (-0.51 - 0.05)	1.00[a] (0.35 - 1.64)	0.53[b] (-0.09 - 1.14)	0.002
MNA	-0.14 (-0.41 – 0.14)	0.30 (-0.20 – 0.79)	0.45 (-0.01 – 0.90)	0.084	0.22 (-0.10 – 0.53)	-0.09 (-0.67 – 0.50)	0.64 (0.01 – 1.28)	0.247	0.11 (-0.14 - 0.36)	0.69 (0.11 - 1.27)	0.52 (-0.02 - 1.06)	0.146

Values present as mean (95% confidence interval); Bold indicates significance ($p < 0.05$); a.b. Values with common superscript are significantly different. MoCA, Montreal Cognitive Assessment; GDS, Geriatric Depression Scale; EQ-VAS, EuroQoL-Visual Analogue Scale; HGS, Handgrip Strength; STS, Sit-to-Stand; SPPB, Short Physical Performance Battery; ASMI, Appendicular Skeletal Muscle Index; BCM, Body Cell Mass; RAPA, Rapid Assessment of Physical Activity; MNA, Mini Nutritional Assessment. Adjusted for Age, Gender, Ethnicity, Education, Hypertension, Hyperlipidaemia, Diabetes Mellitus, Physical Activity, Polypharmacy, IADL Impairment, MoCA, Falls, Adherence and Baseline Values

Table 3. Unadjusted and Adjusted Quantile Regression Models of Median Change in Plasma Biomarkers

Biomarker	Group	Baseline Median (IQR)#	Unadjusted	Adjusted+
			Coefficient (95% CI) p-value	Coefficient (95% CI) p-value
IL6 (pg./mL)	Control	3.20 (1.50)	Reference	
	Exercise	2.65 (2.10)	-0.20 (-1.63 – 1.23) p = 0.780	0.67 (-0.79 – 2.13) p = 0.360
	Exercise + CST	3.10 (2.30)	-0.10 (-1.33 – 1.13) p = 0.871	0.32 (-0.91 – 1.54) p = 0.602
IL10 (ng/mL)	Control	2.39 (1.91)	Reference	
	Exercise	2.25 (1.48)	0.31 (-0.50 – 1.12) p = 0.446	0.24 (-0.54 – 1.02) p = 0.543
	Exercise + CST	2.61 (1.57)	0.53 (-0.17 – 1.23) p = 0.136	0.30 (-0.39 – 0.99) p = 0.385
TNF-α (pg./mL)	Control	7.80 (3.80)	Reference	
	Exercise	7.40 (2.90)	-2.70 (-4.16 - -1.24) p <0.001	-2.71 (-4.80 - -0.62) p = 0.012
	Exercise + CST	8.90 (3.80)	-0.70 (-1.93 – 0.53) p = 0.257	-1.74 (-3.43 – -0.06) p = 0.043
GDF-15 (pg./mL)	Control	943.15 (1083.90)	Reference	
	Exercise	907.60 (786.70)	333.70 (-394.09 – 1061.49) p = 0.362	129.29 (-361.58 – 620.17) p = 0.597
	Exercise + CST	943.30 (933.40)	-35.70 (-662.52 – 591.52) p = 0.909	-164.61 (-583.09 – 253.87) p = 0.431

No baseline differences were observed. + Adjusted for Age, Gender, Ethnicity, Education, Hypertension, Hyperlipidemia, Diabetes, Physical Activity, Polypharmacy, Cognition, IADL Impairment, Falls, Adherence and baseline values; IL-6, Interleukin 6; IL10, Interleukin 10E; TNF-α, Tumour Necrosis Factor-α; GDF-15, Growth Differentiation Factor-15.

Those in Ex group had the greatest proportion of participants with at least 1 IADL (38.8%) and ADL (31.3%) impairments. After 3 months of intervention, only the Ex + CST group had significant improvements in MoCA score compared to the control group (1.83, 95% CI 1.24 - 2.42, p <0.001) while both Ex (-1.15, 95% CI -1.87 - 0.44, p <0.001) and Ex + CST (-1.55, 95% CI -2.23 - -0.88, p <0.001) groups saw significant improvements in GDS scores. After 6 months of intervention, improvements in MoCA and GDS scores were sustained only in the Ex + CST groups (1.67, 95% CI 0.56 - 2.78, p = 0.005 and -1.23, 95% CI -2.44 - -0.02, p = 0.010, respectively). However, there were only significant changes in perceived health in both Ex (4.79, 95% CI -0.35 - 9.93, p = 0.012) and Ex + CST (6.03, 1.19 - 10.87, p = 0.012) groups at 12 months (Table 2).

Frailty, Sarcopenia and Physical Function

There were no significant differences in frailty score, sarcopenia, and physical function at baseline. Significant improvement in FRAIL total scores were seen in both the Ex and Ex + CST groups at 6 months (-0.56, 95% CI -1.04 - -0.11, p = 0.039 and -0.57, 95% CI -1.08 - -0.06, p = 0.039). At 3 months, participants in the Ex and Ex + CST group improved in all physical function measures except for HGS (gait speed: 0.17, 95% CI 0.11 - 0.22, p <0.001 and 0.13, 95% CI 0.07 - 0.18, p <0.01; 5x STS: -1.87, 95% CI -2.93 - -0.82, p = 0.002 and -2.24, 95% CI -3.22 - -1.27, p = 0.002; SPPB Total: 0.68, 95% CI 0.25 - 1.12, p 0.044 and 0.65, 95% CI 0.24 - 1.05, p = 0.044). Only gait speed significantly improved in both groups at 6 months (0.20, 95% CI 0.11 - 0.30 and 0.25, 95% CI 0.14 - 0.35, p <0.001) and remained significantly higher at 12 months (0.20, 95% CI 0.10 - 0.31, p <0.001 and 0.15, 95% CI 0.05 - 0.24, p <0.001) (Table 2).

Body Composition

There were no differences in muscle mass measures at baseline or at 3 months across the groups. At 6 months, both Ex and Ex + CST groups had significant improvements in ASMI (1.73, 95% CI 0.68 - 2.83, p = 0.002 and 1.90, 95% CI 0.62 - 3.17, p = 0.002), body cell mass (2.38, 95% CI -1.08 - 1.02, p = 0.026 and 2.35, 95% CI 0.70 - 4.00, p = 0.026) and phase angle (0.65, 95% CI -0.23 - 1.52, p = 0.010 and 1.01, 95% CI 0.09 - 1.93, p = 0.010). At 12 months, Ex and Ex+CST groups had significantly less decline in ASMI compared with control group.

Plasma Biomarkers

At baseline there were no significant differences in the plasma biomarker levels. After 3 months of exercise and CST interventions, only TNFα levels were significantly reduced in the Ex (B -2.71, 95% CI -4.80 - -0.62, p = 0.012) and Ex + CST (B -1.74, 95% CI -3.43 - -0.06, p = 0.043) groups as compared to the control group (Table 3).

Discussion

The aim of our study was to assess the impact of Ex and Ex + CST on physical function, muscle mass indices and cognition at 3, 6 and 12 months (6 months after cessation of intervention). Our study found that addition of CST to exercise interventions in pre-frail older adults in primary care setting had improved outcomes in cognitive and mental health domains at 3 and 6 months. Improvement in functional outcomes and muscle mass indices were evident in both intervention groups at 6 months. After discontinuation of intervention at 6 months, gait speed and perceived health were significantly higher in the intervention groups at 12 months. The findings from our study further supports the link between physical function and cognition. Both share a common pathway mediated by inflammation with common endpoint of disability and functional decline. Frailty accelerates disease expression in people with Alzheimer's disease pathology with consequent disability (35). A systematic review reported multi-domain interventions to be superior to single domain in improving frailty status, muscle mass and strength and physical function

(36). Since then, many studies have shown the benefits of multicomponent interventions in improving cognitive and physical function in community-dwelling pre-frail older adults (21, 37-39).

The Ex+CST group improved significantly in cognition, depression and physical function. To date, there are no studies on benefits of CST in pre-frail older adults. CST has largely been studied in persons with dementia (40) and has been found to be cost effective in improving QoL (41), function and cognition (42). Our study thus adds to the evidence of the impact that CST and physical exercise has on cognition in pre-frail older adults.

There are limited studies on outcomes data after discontinuation of intervention. Significant improvements were only seen in gait speed, perceived health, muscle mass and physical activity level. However, statistically significant change may not always correlate with clinically meaningful change. Using the latter, the change in SPPB would be considered significant at 6 months in the Ex and Ex+CST group and only in the Ex+CST group at 12 months (43). This adds to the imperative for sustained, long-term physical activity interventions and cognitive training programs in the primary care setting which is often the pillar for preventive population health. The intervention groups had significantly higher perceived health at 12 months. Poor self-rated health has been shown to be associated with increased mortality, frailty and 70% higher risk of slow gait over 4 years (44). Both the Ex and Ex+CST groups had significantly higher gait speed at 3, 6 and 12 months. Slow gait is recognised as the 'sixth' vital sign, a well-known harbinger of dementia and associated with adverse outcomes such as falls, fractures, social isolation, and mortality (45). It is not known if improvement in gait speed will delay or prevent poor outcomes.

The components of multi-domain interventions can be personalized based on screening tools such as the FRAIL scale which is one of the components for the Rapid Geriatric Assessment with assisted management pathway available in the EPIC electronic medical records and as a mobile application. Three-quarters of those reported fatigue had undiagnosed depression (12). People who have difficulty climbing one flight of stairs or walking 50 meters can be referred for multicomponent intervention and protein enriched diet. The ICOPE guidelines can be used to screen and manage for decline in intrinsic capacity which is a surrogate for underlying physiological reserve. It includes five key steps from screening for decline in intrinsic capacity, intervening to engaging communities and supporting caregivers (46). Various studies are in progress to determine if improvement in intrinsic capacity through implementation of multicomponent intervention can change the trajectory of frailty, one of which includes a large-scale prospective study, the INSPIRE ICOPE-CARE program in Occitania (47, 48).

Inflammation is a well-known hallmark of aging and potential mechanisms include mitochondrial dysfunction, immune senescence, microbiota composition changes, genetic susceptibility, sedentary lifestyle, obesity, and increased gut permeability (49). Inflammation is a key driver for many mental and physical health issues and non-communicable diseases (49). Exercise has shown to exert immuno-modulatory effect but studies on the effect of exercise on inflammation have shown mixed results due to varied study participants, type, duration and intensity of exercise (17). To complicate analysis, resistance training has also shown to increase IL-6, IL-10 and TNF-α levels (17). Exercise-induced reduction in visceral adipose tissue is thought to be mediated through IL-6 released during exercise (50). At 3 months, only lower TNF-α was associated with Ex and Ex+CST group. Elevated TNF-α can cause insulin resistance, beta-cell dysfunction and accelerate aging. GDF-15 is increasingly being recognised as biomarker of biological aging as well as mitochondrial dysfunction (51). It is both an anti-inflammatory and pro-inflammatory cytokine. Release of GDF-15 can be activated by various growth factors and cytokines, tissue injury, exercise, cancer, cardiovascular disease, cellular stress, exercise, and drugs like metformin (11). Very high levels are associated with mortality and poor physical function especially in diabetics, but moderately high levels may be protective possibly explained by the mitohormesis theory (51, 52). Effect of intervention on other inflammation biomarkers such as IL-6 and GDF-15 were not significant possibly due to timing of blood test as cytokines have different half-lives, short duration of intervention or varied exercise intensity (53). Nicklas et al showed elevation of IL-after 12 months of intervention (54) and Kleinert et al showed GDF-15 reached peak immediately after vigorous submaximal exercise (55).

Declining muscle mass and strength is prevalent in frailty, sarcopenia, and aging, and associated with increased mortality and morbidity (56). Muscle is considered as an endocrine organ, involved in glucose metabolism, insulin sensitivity and secretes myokines which regulates adipose, liver, brain, and muscle tissue function (57). All the muscle mass indices improved at 6 months in the intervention groups. Whole body phase angle is a well-known indicator for nutritional status, muscle size, quality and function, and predictor of mortality whereas body cell mass is a measure of metabolically active tissue and reliable indicator of muscle mass loss with aging (58-60). At 6 months, significant improvements were observed in ASMI, whole body phase angle and body cell mass but at 12 months, only differences in ASMI were significant in the intervention groups. Yamada et al recently reported that people who exercised regularly regardless of age or type of exercise had significantly higher phase angle value (61). While there are multiple studies on improvement in muscle mass with multicomponent exercise, there are no studies on improvement in phase angle or body cell mass in pre-frail older adults.

The main strengths of this study were the robust assessment measures, validation through inflammatory biomarkers and community dwelling participants from the primary care setting. There are however some limitations to mention. A large part of the study was conducted during the height of COVID-19 pandemic in 2020 which resulted in significant dropout rate which could lead to attrition bias and variable sample sizes. Despite the small sample size, significant benefits were seen in the Ex and Ex+CST groups which were not fully sustained after the discontinuation of the interventions at 12 months. Second, chronic disease, functional status and other demographic data

collected through questionnaire may be subject to recall bias. Third, the baseline cognition for participants in the Ex+CST group was significantly higher which could have resulted in a ceiling effect. However, after excluding the dropouts, there were no significant differences in the Ex and Ex+CST groups at 3, 6 and 12 months as reflected in the supplementary Table 1. Fourth, we have no information on the intensity of the exercises or maximal heart rate achieved although it was reported to be of moderate intensity. Whilst the intervention provided 120 minutes of physical exercise per week, it did not reach the minimum recommendations by the World Health Organisation of at least 150 to 300 minutes of moderate intensity aerobic physical activity or at least 75-150 minutes of vigorous-intensity aerobic physical activity; or an equivalent combination of moderate- and vigorous-intensity activity throughout the week (62). Fifth, functional and cognitive improvements could be due to multiple interacting factors e.g., hearing, nutrition and environment, and causal inferences cannot be assumed. Lastly, while this was a cluster randomised trial, allocation to Ex and Ex+CST was not randomised. In addition, participants and assessors where not blinded.

Our study adds to the growing evidence of multi-component exercises which includes CST in improving physical function and cognition of pre-frail older adults in primary care which may help change the frailty trajectory. Policymakers should consider mandating frailty screening in primary care and social prescribing incorporating multi-component interventions to change frailty trajectory at the population level. Further research on design, implementation and longer-term impact of such programs including sustainability and scalability are needed.

Conclusion

Physical exercise with or without CST in pre-frail older adults in primary care improved depression, muscle mass indices, physical function, frailty, and perceived health. Significant improvement in cognition was only evident in the exercise supplemented by CST. Both groups had significant improvement of TNF-α levels at 3 months. With growing evidence of the benefits of multicomponent interventions at primary care level, incorporating it into mainstream care with action plans on long-term sustainability and scalability should be a priority for every country.

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