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Nutritional, Physical, Cognitive, and Combination Interventions and Frailty Reversal Among Older Adults: A Randomized Controlled Trial

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ABSTRACT

BACKGROUND: It is important to establish whether frailty among older individuals is reversible with nutritional, physical, or cognitive interventions, singly or in combination. We compared the effects of 6-month-duration interventions with nutritional supplementation, physical training, cognitive training, and combination treatment vs control in reducing frailty among community-dwelling prefrail and frail older persons.

METHODS: We conducted a parallel group, randomized controlled trial in community-living prefrail and frail old adults in Singapore. The participants' mean age was 70.0 years, and 61.4% (n = 151) were female. Five different 6-month interventions included nutritional supplementation (n = 49), cognitive training (n = 50), physical training (n = 48), combination treatment (n = 49), and usual care control (n = 50). Frailty score, body mass index, knee extension strength, gait speed, energy/vitality, and physical activity levels and secondary outcomes (activities of daily living dependency, hospitalization, and falls) were assessed at 0 months, 3 months, 6 months, and 12 months.

RESULTS: Frailty score and status over 12 months were reduced in all groups, including control (15%), but were significantly higher (35.6% to 47.8%) in the nutritional (odds ratio [OR] 2.98), cognition (OR 2.89), and physical (OR 4.05) and combination (OR 5.00) intervention groups. Beneficial effects were observed at 3 months and 6 months, and persisted at 12 months. Improvements in physical frailty domains (associated with interventions) were most evident for knee strength (physical, cognitive, and combination treatment), physical activity (nutritional intervention), gait speed (physical intervention), and energy (combination intervention). There were no major differences with respect to the small numbers of secondary outcomes.

CONCLUSIONS: Physical, nutritional, and cognitive interventional approaches were effective in reversing frailty among community-living older persons.

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KEYWORDS: Cognitive training; Frailty; Nutritional supplementation; Physical exercise

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INTRODUCTION

Physical frailty due to multisystem declines in physiologic reserve is common among older adults, rendering them vulnerable to increased risk of hospitalization, dependency in activities of daily living, institutionalization, and dying, when exposed to stress.[1-4] A widely used clinical research definition of the frailty syndrome is the Cardiovascular Health Study (CHS) frailty phenotype, consisting of a combination of weight loss, weakness, slowness, exhaustion, and reduced physical activity.[4] There is current consensus that physical frailty is potentially reversible with appropriate interventions.

The individual effects of physical exercise, nutritional supplementation, and cognitive training have been investigated in clinical trials of older persons. Physical exercise is examined most widely, and has been shown to consistently confer favorable effects on physical outcomes such as body composition, muscle function, and functional ability (mobility and balance).[5,6] A majority of studies of nutritional interventions in older persons have failed to show convincing effects in improving physical performance and functional ability.[7-12] A limited number of preliminary studies indicate that cognitive training improved or maintained gait speed, balance,[13-16] and daily functioning of older adults.[17]

Although these interventional studies involved frail older participants, very few trials have recruited frail older individuals based on a specific definition of the frailty syndrome.[18-25] To our knowledge, no studies have evaluated concurrently the individual and combined effects of physical, cognitive, and nutritional interventions in reversing frailty or specifically evaluated frailty as a primary outcome.[20,22,23,25]

The objectives of this 12-month follow-up study were to compare the effects of 6-month interventions with physical exercise, nutritional supplementation, cognitive training, and a combination of these interventions with usual care control in reducing frailty among community-dwelling older persons. We hypothesized that physical, nutritional, cognitive, combined interventions to varying extents reduced frailty assessed with the CHS score and its physical and functional domains (body mass, muscle strength, gait speed, exhaustion, and physical activity), and the frequency of secondary outcomes including hospitalizations, falls, and dependency in activities of daily living.

CLINICAL SIGNIFICANCE

- Individual nutritional supplements, physical training, and cognitive training, and their combination, were beneficial in decreasing frailty.
- All frailty dimensions except body mass index demonstrated noticeable improvement with certain interventions over the 12 months.
- No major differences between groups were found with respect to the secondary clinical outcomes, including hospitalization, falls, and activities of daily living and instrumental activities of daily living disability.

METHODS

Study Design

The Singapore Frailty Intervention Trial was a parallel-group, randomized controlled trial. The trial was approved by the National Health Group Domain Specific Review Board in Singapore, and registered on clinicaltrial.gov with identifier NCT00973258. Eligible participants, after signed informed consent, were allocated randomly into one of 5 interventions of 24 weeks duration each: nutritional supplementation, cognitive training, physical training, combination treatment, and usual care control. Assessment of frailty and other outcomes were assessed at 0 months, 3 months, 6 months, and 12 months.

Participants and Randomization

Potential participants were identified from among community residents in the southwest region of Singapore through door-to-door open invitation from October 2009 to August 2012. Prefrail and frail older adults were identified based on 5 CHS criteria defining physical frailty[4]: unintentional weight loss, slowness, weakness, exhaustion, and low activity, which were scored 1 if present and 0 if absent. The total summed scores ranging from 0 to 5 were used to classify a participant as robust (score = 0), prefrail (score = 1 to 2), or frail (score = 3 to 5).

Prefrail or frail older adults were eligible for the trial if they were aged 65 years and above, able to ambulate without personal assistance, and living at home. Participants were excluded if they had significant cognitive impairment (Mini Mental State Examination score $\leq$23)[26]; major depression; severe audiovisual impairment; any progressive, degenerative neurologic disease; terminal illness with life expectancy $<$12 months; were participating in other interventional studies; or were unavailable to participate for the full duration of the study.

Randomization. A central computerized randomization procedure was used to randomly allocate a total of 246 participants: 49 in the nutrition supplementation group, 50 in cognitive training, 48 in physical training, 49 in combination, and 50 in the control group. The randomization sequence was generated in permuted blocks (10 per block), and treatment was allocated by a project manager not involved in the enrollment, intervention, or assessment.

Interventions

Physical Intervention. Physical exercise was of moderate, gradually increasing intensity, tailored to participants' individual abilities, of 90 minutes duration, on 2 days per week for 12 weeks in classes conducted by a qualified trainer, followed by 12 weeks of home-based exercises.

Participants performed the exercises in groups of 8 to 10, and were encouraged to continue daily individualized exercise assignments at home. The exercise program was designed to improve strength and balance for older adults, according to American College of Sports Medicine guidelines[27] for older adults, based on a single set of 8 to 15 repetition maximum (RM), or 60% to 80% of 10 RM, starting with <50% 1 RM involving 8-10 major muscle groups. They included resistance exercises integrated with functional tasks; and balance training exercises involving functional strength, sensory input, and added attentional demands were carried out at 3 levels of increasing demand (see **Appendix**, available online).[28,29]

Nutritional Intervention. Each participant was provided a commercial formula (Fortisip Multi Fibre, Nutricia, Dublin, Ireland), iron and folate supplement (Sangobion, Merck, Kenilworth, NJ), vitamin B6 and vitamin B12 supplement (Neuroforte, R.B. Pharmaceuticals, Chennai, India), and calcium and Vitamin D supplement (Caltrate, Pfizer, Singapore) taken daily for 24 weeks, which was designed to augment caloric intake by about 20% and provide about one third of the recommended daily allowances of vitamins and minerals. Given the variability in individual energy requirements, participants were encouraged to attain the maximal tolerable energy intake to gain 0.5 kg per week (see **Appendix**, available online).[28,29]

Cognitive Training. In the first 12 weeks, participants attended 2-hour weekly sessions of cognitive training where they engaged in cognitive-enhancing activities designed to stimulate short-term memory, and enhance attention and information-processing skills, and reasoning and problem-solving abilities. For the subsequent 12 weeks, participants attended fortnightly 2-hour "booster" sessions, where they reviewed the cognitive skills learned in the first 12 weeks. Activities included learning strategies used to recall verbal and visual information, tasks such as "spot the differences," categorical naming, and coding used to enhance attention and processing speed; and matrix reasoning exercises, mazes, and tangram-like games aimed at enhancing reasoning and problem-solving abilities.

Combination Intervention. Participants in this group underwent all 3 aforementioned interventions.

Control Group. Participants had access to one standard care from health and aged care services that were normally available to older people, including primary and secondary level care from government or private clinics and hospitals, and community-based social, recreational, and daycare rehabilitation services. They were given an equal volume of artificially sweetened, vanilla-flavored liquid (ingredients: nondairy creamer, liquid caramel, sugar, and water), 2 capsules and 1 tablet (ingredients: cornstarch, lactose, magnesium stearate) that were identical in appearance to the active nutritional supplements, with instructions not to replace their meals with the supplements. Both the active supplement and the control were administered by interventional nurses who had no knowledge of the participant's assignment status.

Measurements

Frailty was measured based on the CHS criteria[4] for 5 frailty components operationally defined as:

1) Unintentional weight loss: body mass index (BMI: weight/height^2 <18.5 kg/m^2 or self-reported unintentional weight loss ≥10 pounds (4.5 kg) in the last 6 months.
2) Slowness was assessed using 6-meter fast gait speed test. Participants were timed in seconds walking 6 meters as fast as possible, and the average of 2 measurements was estimated. The lowest quintile of values stratified for height and age was used to denote slowness.
3) Weakness: Muscle strength was assessed by knee extension measured isometrically in the dominant leg, with the participant seated, the angles of the hip and knee at 90° using Lord's strap and strain gauge assembly component of the Physiological Profile Assessment. The average value (in kilograms) of 3 trials was estimated. Knee extension was standardized based on sex and BMI quartile groups, and the lowest quintiles were used to denote weakness.
4) Exhaustion was measured with the composite scores on 3 questions on vitality domain in the Medical Outcomes Study SF-12 scale[30]: "Did you feel worn out?," "Did you feel tired?," "Did you have a lot of energy?," with appropriate reversed scorings. The total scores range from 3 to 15, with higher score indicating more energy. The lowest quintile of energy score (<10) derived in a population-based study in a previous study of frailty[31] was used to denote exhaustion.
5) Low activity: Physical activity was evaluated by the self-reported 31-item Longitudinal Ageing Physical Activity Questionnaire[32] measuring the frequency and duration of 6 different activities in the past 2 weeks: walking outside, bicycling, gardening, light and heavy household activities, and sports activities. The average time (in minutes) spent per day on physical activities overall was estimated and the lowest quintile used to classify participants with low activity.

Treatment adherence was measured monthly by estimating the proportion of supplements consumed or training sessions completed (averaged for 3 treatments in the combination group).

Outcome assessments were performed at baseline, 3 months, 6 months, and 12 months by assessors who were blinded to the participants' group allocation, and independently of interventional nurses who administered treatment, and monitored and recorded adverse events.

The *primary outcomes* were frailty score (continuous variable) and reduction of frailty (dichotomous variable), and measures of frailty components (BMI, fast gait speed test, knee extension, exhaustion score, and physical activity).

Reduction in frailty during follow-up was defined as a transition to a lower frailty category from baseline, such as from frail to prefrail or nonfrail) over 12 months.

The *secondary outcomes* were self-reported hospitalizations, self-reported falls, and instrumental activities of daily living (IADL) and activities of daily living (ADL) dependency.[33,34] Mortality and institutionalization were not analyzed as secondary outcomes because only 2 participants died, and only 1 was institutionalized during the study.

Sample size and power estimation were based on the assumptions of 4 Bonferroni-corrected 2-sided comparisons with an overall α of 0.05 (level of significance: 0.0125 for each comparison). A sample size of 45 participants per group is required to provide a power of 80% with $\alpha = 0.0125$ to detect 30% difference in frailty improvement rate between each treatment and control group. Assuming a 10% dropout rate, the total sample size was 248.

Data Analysis

Comparisons across treatment groups were performed by analysis of variance for continuous variables or chi-squared

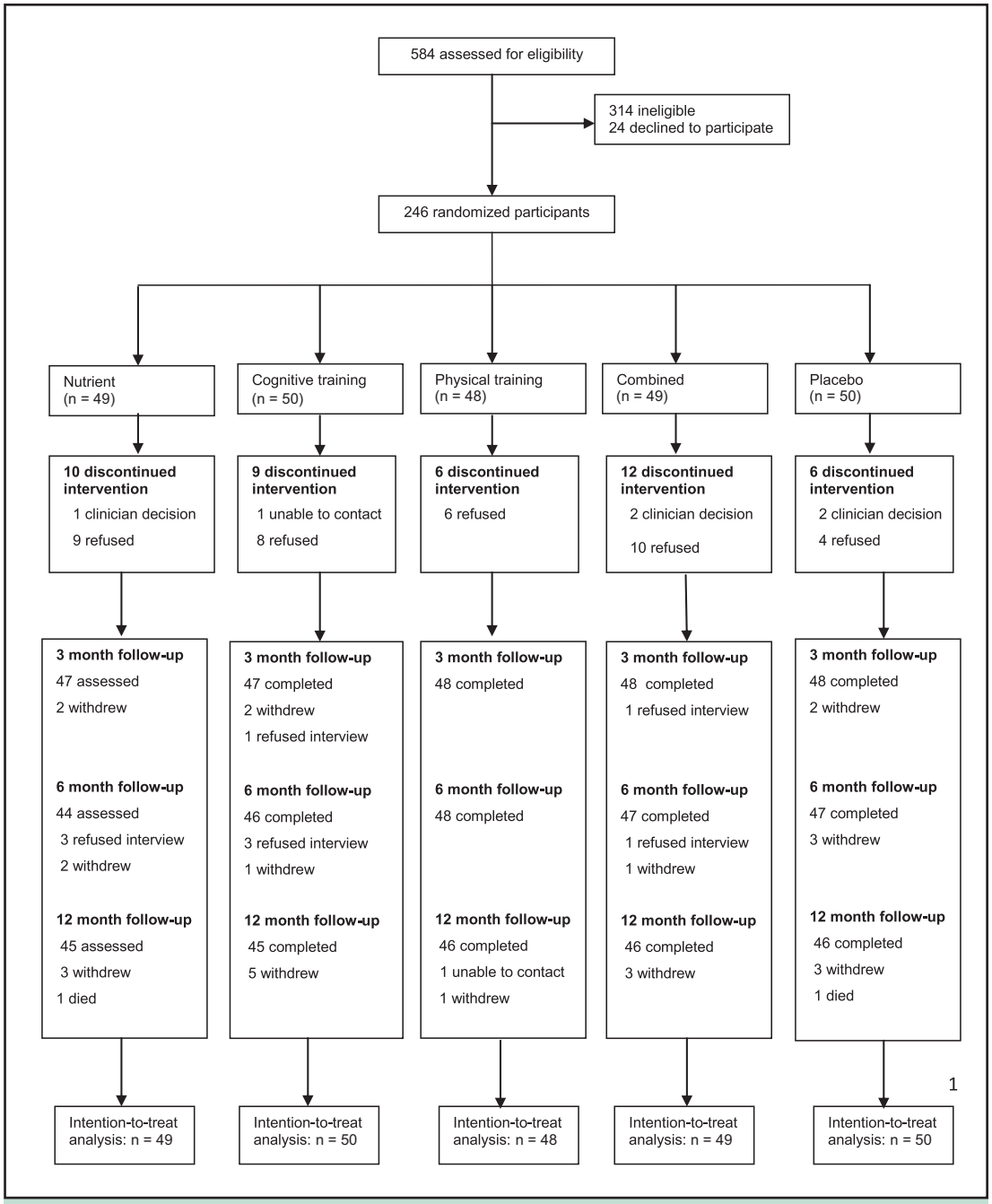

Figure 1 Flow chart of the Singapore Frailty Intervention Trial.

tests for categorical variables. The effect of intervention over time on frailty outcomes was investigated in intention-to-treat analyses. Frailty score and measures of individual frailty components were analyzed as dependent variables using linear mixed-effect modeling methods, assumed random missing values driven by variables included in the analyses, and including random intercepts to account for correlations between the repeated measures for each participant. Primary independent variables in each model included treatment group, time, and group × time interaction. Where the group × time interaction was significant, indicating changing effect over time, tests of simple main effects were performed to determine which interventional group(s) differed significantly from the control across the intervention period. Post hoc and secondary analyses were made with significance adjustment using the Bonferroni method. Logistic regression was performed for dichotomous outcome variables including improvement of frail state, functional disabilities, hospitalization, and fall. We reported mean difference between treatment groups and its 95% confidence interval (CI) for continuous outcomes and odds ratio and its 95% CI for binary outcomes. Sensitivity analysis was performed subsequently by adjusting for treatment compliance in each model. Compliance with each intervention was polychotomized using 90% (lowest tertile) and 99% (the highest value next to 100%) as cut points. There were no significant interactions between compliance and treatment in all the models, and controlling for compliance in all models did not substantially alter the results. All analyses were performed using SAS software (SAS Institute, Inc, Cary, NC).

RESULTS

Of the 584 contacted individuals, 314 (53.8%) were ineligible, and 24 (4.1%) eligible individuals declined to participate, resulting in 246 (42.1%) eligible participants in this study (**Figure 1**). The eligible participants were comparable with the eligible nonparticipants in baseline frailty status, age, sex, education, and physical function.

The dropout rate was low and comparable across the 5 intervention groups (8% for nutritional supplement; 10% cognitive training; 4% for physical training; 6% for combination, and 8% for control). The reasons for dropout included: diagnoses of tuberculosis (n = 3), lymphoma (n = 1), stomach ache or leg pain (n = 3), hearing impairment (n = 1), moved residence (n = 3), nursing home stay (n = 1), refused for no reason (n = 4), and death (n = 2).

Table 1 Participants' Characteristics at Study Inclusion (n = 246)

Characteristics	Nutritional (n = 49)	Cognitive Training (n = 50)	Physical Training (n = 48)	Combination (n = 49)	Control (n = 50)	*P* Value
Age, mean (SD)	69.7 (4.23)	69.7 (4.31)	70.3 (5.25)	70.4 (4.74)	70.1 (5.02)	.91
Male sex, n (%)	17 (34.0)	12 (24.0)	21 (43.8)	23 (46.9)	22 (44.0)	.12
Education, n (%)						.29
No formal schooling	13 (26.5)	9 (18.0)	13 (27.1)	6 (12.2)	10 (20.0)	
Primary school	20 (40.8)	27 (54.0)	22 (45.8)	22 (44.9)	29 (58.0)	
Secondary or higher	16 (32.7)	14 (28.0)	13 (27.1)	21 (42.9)	11 (22.0)	
GDS, mean (SD)	0.6 (1.38)	0.7 (0.82)	0.6 (0.89)	0.7 (1.75)	0.5 (0.86)	.96
MMSE, Mean (SD)	28.8 (1.70)	29.1 (1.29)	29.1 (1.19)	29.1 (1.06)	28.6 (1.79)	.23
≥5 medical comorbidities, n (%)	0 (0.0)	2 (4.0)	5 (10.4)	3 (6.1)	2 (4.0)	.19
BMI, kg/m^2, mean (SD)	24.0 (4.31)	23.1 (2.70)	23.5 (3.03)	24.4 (3.79)	23.6 (3.35)	.41
Fast gait speed, s, mean (SD)	5.8 (1.81)	5.4 (1.16)	6.1 (2.08)	5.4 (1.25)	5.6 (2.07)	.22
Knee extension, mean (SD)	14.0 (5.27)	12.9 (3.88)	14.1 (4.63)	14.9 (5.50)	15.5 (4.73)	.11
Energy score, Mean (SD)	10.7 (1.23)	10.5 (1.20)	10.8 (1.10)	10.7 (1.38)	10.6 (1.55)	.86
PA score (min/d), Mean (SD)	165.7 (104.7)	179.3 (113.3)	162.5 (117.2)	160.6 (116.0)	176.9 (111.0)	.89
Frailty status						
Mean (SD) score, (range: 0-5)	2.1 (0.78)	2.0 (0.91)	2.2 (0.85)	2.1 (0.81)	1.8 (0.80)	.075
Prefrail, n (%)	33 (67.4)	37 (74.0)	29 (60.4)	36 (73.5)	43 (86.0)	.067
Frail, n (%)	16 (32.7)	13 (26.0)	19 (39.6)	13 (26.5)	7 (14.0)	
Frailty components						
Weight loss, n (%)	2 (4.1)	2 (4.0)	3 (6.3)	1 (2.0)	3 (6.0)	.86
Slowness, n (%)	20 (40.8)	13 (26.0)	23 (47.9)	17 (34.7)	15 (30.0)	.17
Weakness, n (%)	26 (53.1)	28 (56.0)	26 (54.2)	25 (51.0)	20 (40.8)	.59
Exhaustion, n (%)	7 (14.3)	10 (20.0)	7 (14.6)	8 (16.3)	6 (12.0)	.85
Low physical activity, n (%)	9 (18.4)	12 (24.0)	11 (22.9)	16 (32.7)	5 (10.0)	.09
Hospitalized in past 12 mo	1 (2.0)	3 (6.0)	6 (12.5)	3 (6.1)	1 (2.0)	.21
IADL-ADL dependency, mean (SD)	1 (2.0)	1 (2.0)	0 (0.0)	1 (2.0)	4 (8.0)	.28

ADL = activities of daily living; BMI = body mass index; GDS = Geriatric Depression Scale; IADL = instrumental activities of daily living; MMSE = Mini Mental State Examination.

The mean compliance levels were 88% for combination group, 91% for nutrition supplement, 94% for control, 85% for physical training, and 79% for cognitive training. Two hundred twenty-eight participants (93%) completed 1-year follow-up assessment.

Two subjects who participated in exercise training had joint pain (hip and knee) initially that was relieved after adjusting training regimen. No other adverse events occurred during the study.

The participants' mean age was 70.0 (± 4.7 SD) years, and 61% (n = 151) were female. Approximately 28% were "frail" (n = 68), and 72% were prefrail. Frailty symptoms were predominantly exhaustion (95%) and weakness (51%), followed by slowness (36%), low physical activities (22%), and 5% weight loss. Only 3% (n = 7) were disabled on at least one IADL-ADL activity. No statistically significant differences in baseline frailty and other characteristics were observed across the treatment groups, but the proportions of frailty vs prefrailty and low physical activity was relatively lower in the control group (Table 1).

Table 2 summarizes the change in frailty scores from baseline at 3-month, 6-month, and 12-month follow-ups for the intervention and control groups. There was a significant main effect of time ($P < .001$), with the mean frailty score decreasing over the 12 months across all groups, and significant group × time interaction ($P < .044$). At 12 months, all interventions showed significant differences vs control at the pre hoc significance level of $P < .05$.

Over 12 months, 15% (7/46) of the control group participants showed reduction of frailty, but frailty reduction rates in the intervention groups were significantly higher (35.6% to 47.8%). Compared with the control group, nutritional intervention (odds ratio [OR] 2.98) and cognition intervention (OR 2.89) were almost 3 times more likely to result in frailty reduction, whereas physical intervention was associated with 4 times higher odds of frailty reduction, and combination intervention was associated with the highest odds of frailty reduction (OR 5.0).

The results for frailty domains of BMI, strength, walking speed, energy, and physical activity are displayed in Table 3 and Figure 2. For BMI, gait speed, and energy, there were significant main effects of time, but no significant main effects of group or group × time interaction. There were significant time (main) and group × time interaction effects for knee strength ($P = .009$) and physical activity ($P = .038$). No gains in knee strength were observed in the control group, but significant gains in knee strength were observed for the cognition, physical, and combination groups, but not the nutrition group at 6 months and 12 months. For physical activity, the nutrition group alone showed the largest significant increase at 6 months and 12 months. Significant gains in gait speed were observed for physical intervention at 3 months, 6 months, and 12 months, and significant gains in energy for combination intervention at 12 months.

Secondary analyses of adverse outcomes (IADL-ADL dependency, hospitalization, and falls) were based on small

Table 2 Effects of Intervention on Frailty Score and Frailty Reduction

	n	Mean (SD)				Mean Change from Baseline (95% CI)				
		Nutritional	Cognitive	Physical	Combined	Control	Nutritional	Cognitive	Physical	Combined	Control
Frailty score											
Baseline	246	2.1 (0.78)	2.0 (0.91)	2.2 (0.85)	2.1 (0.81)	1.8 (0.80)					
3 mo	238	1.5 (1.06)	1.3 (0.81)	1.2 (0.75)	1.3 (0.84)	1.3 (0.85)	−0.64 (−0.92, −0.35)	−0.67 (−0.95, −0.39)	−0.98 (−1.26, −0.70)*	−0.87 (−1.16, −0.59)*	−0.47 (−0.75, −0.19)
6 mo	232	1.4 (0.78)	1.4 (0.78)	1.3 (0.87)	1.4 (0.87)	1.4 (1.06)	−0.72 (−1.01, −0.43)	−0.60 (−0.88, −0.31)	−0.92 (−1.20, −0.63)**	−0.75 (−1.04, −0.47)*	−0.34 (−0.63, −0.06)
12 mo	228	1.5 (0.91)	1.4 (0.94)	1.4 (0.80)	1.2 (1.07)	1.6 (0.97)	−0.63 (−0.92-0.34)*	−0.62 (−0.91, −0.33)*	−0.83 (−1.12, −0.54)**	−0.92 (−1.21, −0.64)**	−0.14 (−0.43-0.14)
							OR (95% CI)				
Frailty reduction, n (%)											
12 mo		16 (35.6)	16 (35.6)	19 (41.3)	22 (47.8)	7 (15.2)	2.98 (1.10-8.07)**	2.89 (1.07-7.82)**	4.05 (1.50-10.8)**	5.00 (1.88-13.3)**	1.00 (Reference)

Linear mixed effect modeling: time, $P < .05$, group, $P = .85$ and interaction (time and group), $P < .05$.
A significant difference was found between the treatment group and control in mean change from baseline.
CI = confidence interval; OR = odds ratio.
*$P < .05$; **$P < .01$.

Table 3 Effects of Intervention on Frailty Component Outcomes

		Mean (SD)					Mean Change from Baseline (95% CI)					Significance		
	n	Nutritional	Cognitive	Physical	Combined	Control	Nutritional	Cognitive	Physical	Combined	Control	Time	Group	Time* Group
BMI, kg/m^2														
Baseline	246	24.0 (4.31)	23.1 (2.70)	23.5 (3.03)	24.4 (3.79)	23.6 (3.35)								
3 mo	238	24.3 (4.33)	23.3 (3.01)	23.5 (2.92)	24.4 (3.78)	24.1 (3.33)	0.34 (−0.02-0.70)	0.08 (−0.28-0.44)	−0.01 (−0.37-0.35)	0.01 (−0.35-0.37)	0.49 (0.13-0.85)	.001	.35	.77
6 mo	232	23.9 (4.47)	23.4 (2.97)	23.7 (3.06)	24.6 (3.64)	24.1 (3.61)	0.17 (−0.20-0.55)	0.08 (−0.29-0.44)	0.19 (−0.17-0.55)	0.16 (−0.20-0.52)	0.44 (0.08-0.80)			
12 mo	228	24.2 (4.23)	23.0 (3.52)	23.4 (3.23)	24.1 (3.83)	23.8 (3.58)	0.03 (−0.34-0.40)	−0.22 (−0.59-0.14)	−0.03 (−0.40-0.33)	−0.22 (−0.58-0.15)	0.12 (−0.25-0.48)			
Knee strength, kg														
Baseline	246	14.0 (5.27)	12.9 (3.88)	14.1 (4.63)	14.9 (5.50)	15.5 (4.73)								
3 mo	238	15.8 (5.38)	14.9 (4.41)	16.0 (4.00)	16.8 (5.82)	16.5 (4.68)	1.64 (0.54-2.74)	2.01 (0.92-3.10)	1.83 (0.74-2.92)	1.76 (0.68-2.84)	1.13 (0.03-2.22)	<.001	.18	.009
6 mo	232	15.1 (4.77)	15.2 (5.20)	16.9 (5.47)	17.5 (6.40)	15.0 (4.53)	0.97 (−0.15-2.09)	2.18 (1.08-3.27)*	2.75 (1.66-3.83)*	2.67 (1.58-3.76)*	0.02 (−1.08-1.12)			
12 mo	228	15.0 (4.34)	15.0 (4.35)	15.5 (5.19)	17.2 (6.59)	14.8 (4.47)	1.01 (−0.09-2.12)	1.98 (0.87-3.09)*	1.41 (0.31-2.51)*	2.35 (1.25-3.44)*	−0.24 (−1.34-0.87)			
Physical activity														
Baseline	246	165.7 (104.7)	179.3 (113.3)	162.5 (117.2)	160.6 (115.9)	176.9 (111.0)								
3 mo	238	201.5 (119.2)	194.8 (118.6)	185.8 (116.9)	201.6 (115.3)	183.5 (114.6)	33.9 (−3.73-71.6)	12.7 (−24.8-50.2)	23.2 (−14.3-60.78)	39.8 (2.41-77.2)	8.02 (−29.3-45.3)	<.001	.24	.038
6 mo	232	264.5 (134.9)	194.8 (115.4)	220.1 (139.7)	197.2 (139.4)	195.0 (103.0)	96.2 (57.8-134.7)†	17.1 (−20.7-54.9)	57.6 (20.1-95.1)	35.1 (−2.56-72.7)	20.5 (−17.0-58.1)			
12 mo	228	279.1 (139.0)	227.1 (98.7)	202.0 (134.6)	201.0 (138.0)	209.7 (123.3)	110.1 (71.9-148.2)†	10.2 (−43.4-63.8)	36.5 (−1.53-74.5)	40.2 (2.30-78.1)	34.8 (−2.99-72.6)			
Gait speed, s														
Baseline	246	5.8 (1.81)	5.4 (1.16)	6.1 (2.08)	5.4 (1.25)	5.6 (2.07)								
3 mo	238	4.8 (1.21)	4.7 (0.97)	4.8 (0.89)	4.7 (1.20)	5.1 (2.09)	−1.02 (−1.45, −0.58)	−0.63 (−1.06, −0.20)	−1.29 (−1.72, −0.86)‡	−0.64 (−1.07-0.21)	−0.56 (−0.99, −0.13)	<.001	.80	.072
6 mo	232	5.0 (1.02)	4.6 (0.80)	5.0 (1.04)	4.8 (1.13)	4.9 (1.47)	−0.79 (−1.23, −0.35)	−0.81 (−1.24, −0.37)	−1.10 (−1.53, −0.67)‡	−0.54 (−0.97, −0.10)	−0.70 (−1.13, −0.27)			
12 mo	228	5.2 (1.21)	5.2 (1.05)	4.9 (0.99)	5.3 (2.17)	5.2 (1.72)	−0.64 (−1.08, −0.20)	−0.16 (−0.59, 0.28)	−1.14 (−1.58, −0.70)‡	−0.01 (−0.45-0.43)	−0.41 (−0.84-0.03)			

Table 3 Continued

		Mean (SD)					Mean Change from Baseline (95% CI)					Significance		
	n	Nutritional	Cognitive	Physical	Combined	Control	Nutritional	Cognitive	Physical	Combined	Control	Time	Group	Time* Group
Energy														
Baseline	246	10.7 (1.23)	10.5 (1.20)	10.8 (1.10)	10.7 (1.38)	10.6 (1.55)								
3 mo	238	11.4 (1.79)	11.7 (1.78)	11.7 (1.68)	11.9 (1.67)	11.2 (1.99)	0.74 (0.12-1.37)	1.22 (0.60-1.84)	0.96 (0.34-1.58)	1.20 (0.58-1.82)	0.59 (−0.03-1.21)	<.001	.11	.59
6 mo	232	11.2 (1.56)	11.3 (1.71)	11.5 (1.71)	11.8 (1.71)	11.3 (1.68)	0.54 (-0.09-1.18)	0.88 (0.25-1.50)	0.77 (0.15-1.39)	1.09 (0.46-1.71)	0.89 (0.27-1.51)			
12 mo	228	11.6 (1.85)	11.5 (2.07)	11.4 (1.89)	12.0 (1.81)	10.9 (1.67)	0.94 (0.30-1.57)	1.01 (0.38-1.64)	0.65 (0.02-1.28)	1.32 (0.70-1.95)§	0.30 (−0.33-0.92)			

*Knee strength: Cognition, $P < .01$, $P < .01$; Physical, $P < .01$, $P < .05$; Combination, $P < .01$, $P < .01$ vs Control at 6 month and 12 month.
†Physical activity: Nutrition $P < .01$, $P < .01$ vs Control at 6 month and 12 month.
‡Gait speed: Physical $P < .05$, $P < .05$ vs Control at 6 month and 12 month.
§Energy: Combination, $P < .05$ vs Control at 12 month.

numbers and low frequency of occurrence (Table 4). No significant differences vs control were observed.

DISCUSSION

To our knowledge, this is the first interventional trial that evaluated concurrently the effects of nutritional, cognitive, physical, and combination interventions in reversing frailty and its physical manifestations among community-living older adults. Previous studies have evaluated either single or dual combinations of nutritional, cognitive, or physical interventions,[7,8,10-17] or evaluated an integrated multidomains intervention without differentiating their individual effects.[24] Furthermore, most trials typically have recruited older adults with reduced physical functioning, labeled as "frail," without a specific definition of frailty based on validated criteria.[7,8,10-17] As such, trials conducted in heterogeneous groups of so-called frail populations have yielded mixed results based on diverse outcomes, making it difficult to assess their relative individual and combined effects.

The effects of physical intervention on physical functioning have been evaluated in over 47 trials of older adults with poor physical functioning, 16 of them among community-dwelling older adults. Only 3 trials have identified frail older adults specifically[18,19,35]; however, none of them used frailty as an outcome measure; one involved posthospitalized patients,[18] and another involved tai chi intervention.[19] This study shows the effect of physical exercise in specifically reversing the degree of frailty. The intervention used multicomponent physical training, and the observed improvements in muscle strength and gait speed are consistent with those reported elsewhere. These physical interventions have in common similarly high rates of compliance (more than 85%) and use similarly long duration (≥5 months), performed 3 times per week, for 30-45 minutes per session.[5]

Nutritional intervention is proposed widely to be an important component of frailty management. However, a large majority of studies in heterogeneous groups of older persons at risk of malnutrition have failed to demonstrate convincingly positive effects on physical performance and functional outcomes.[7-11] Only one study of protein-energy supplementation administered to undernourished Korean older adults with slow gait showed benefit of reduced physical functional decline.[12] In agreement with that study, we showed that, independently of physical exercise, nutritional supplementation reduced frailty, and in particular, increased the level of physical activity. The nutritional supplementation in this study was designed to increase protein-calorie and micronutrients intakes; further studies are needed to elucidate the effects attributable to individual components of dietary intake and micronutrients.

An emerging number of preliminary studies show that among sedentary older persons, cognitive training targeting attention and executive function had the remarkable effect

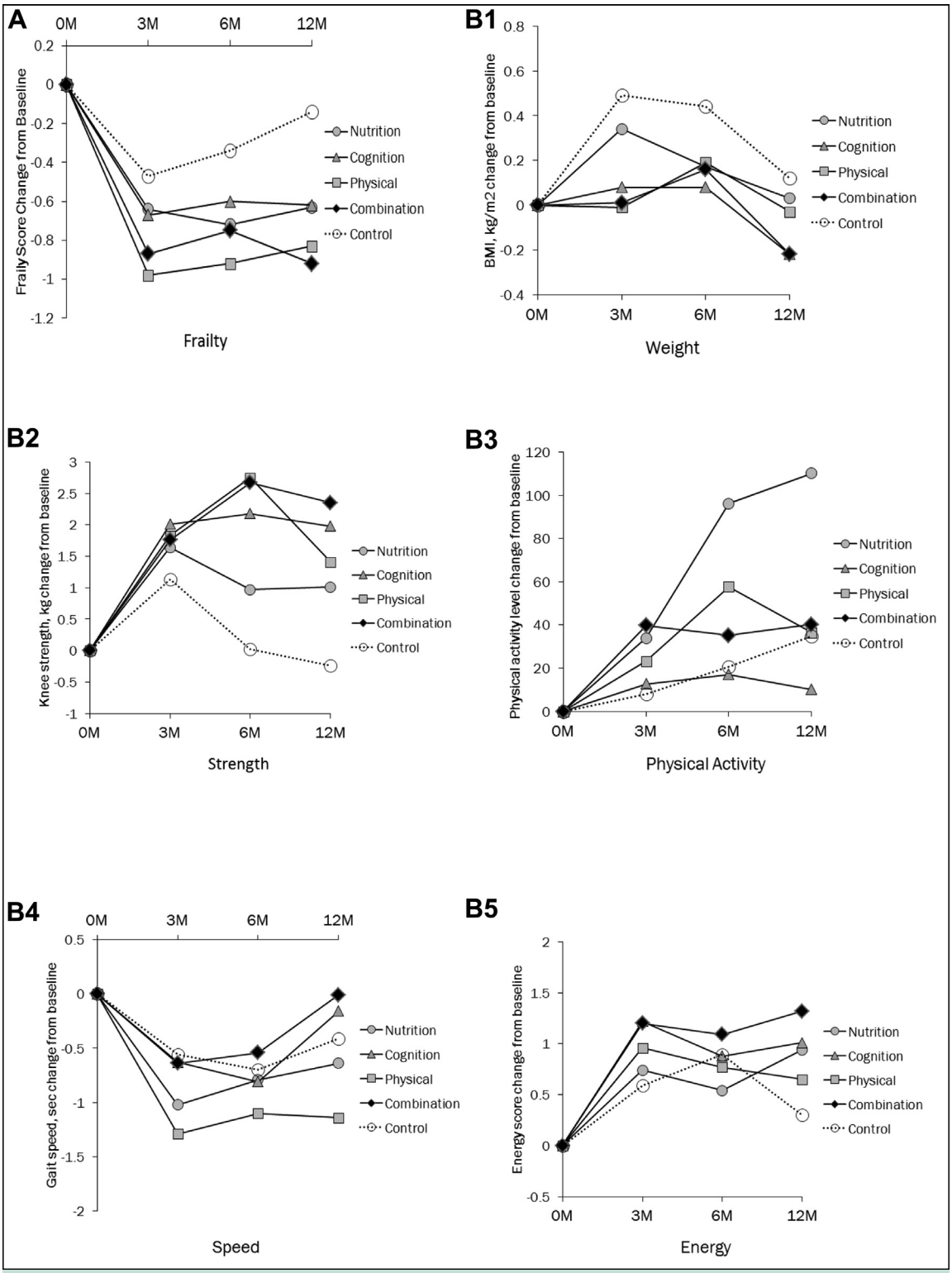

Figure 2 Frailty score (**A**) and components weights (**B1**), strength (**B2**), physical activity (**B3**), speed (**B4**), and energy (**B5**): change from baseline at 3 months, 6 months, and 12 months by Intervention and Control groups.

of being transferred to improved motor balance and gait speed.[13-16] Our study showed that a cognitive training program designed to stimulate short-term memory and enhance attention and information processing as well as reasoning and problem-solving abilities, was effective in reducing frailty and, particularly, in improving lower limb strength. Due to the large amount of significance testing, some beneficial effects of cognitive training possibly may be

Table 4 Secondary Analyses of Adverse Outcomes by Intervention Groups

Outcomes		Nutritional (n = 49)	Cognitive Training (n = 50)	Physical Training (n = 48)	Combination (n = 49)	Control (n = 50)	Overall *P*-Value
IADL-ADL dependency, n (%)							
3 mo	238	1 (2.1)	1 (2.1)	1 (2.1)	2 (4.2)	5 (10.4)	.34
6 mo	232	2 (4.6)	1 (2.2)	4 (8.3)	2 (4.3)	2 (4.3)	.76
12 mo	228	3 (6.7)	2 (4.4)	4 (8.7)	2 (4.4)	3 (6.5)	.95
Hospitalization, n (%)							
3 mo	238	1 (2.1)	3 (6.4)	1 (2.1)	0 (0.0)	1 (2.1)	.42
6 mo	239	1 (2.1)	3 (6.3)	1 (2.1)	4 (8.3)	2 (4.2)	.64
12 mo	242	1 (2.1)	5 (10.2)	3 (6.3)	6 (12.2)	2 (4.2)	.27
Any fall, n (%)							
3 mo	238	1 (2.1)	1 (2.1)	2 (4.2)	1 (2.1)	5 (10.4)	.34
6 mo	239	2 (4.3)	1 (2.1)	3 (6.3)	1 (2.1)	5 (10.4)	.38
12 mo	242	4 (8.3)	2 (4.1)	3 (6.3)	2 (4.1)	5 (10.4)	.67

Figures for IADL-ADL dependency at each follow-up visit are point-prevalent frequencies.
Figures for hospitalization and falls at each follow-up visit are cumulated frequencies.
No post hoc pairwise comparisons were insignificant at $P < .012$.
ADL = activities of daily living; IADL = instrumental activities of daily living.

chance findings, but the results are largely consistent with previous studies and thus, lend support to the strategy of cognitive remediation to improve mobility. A large randomized controlled trial involving 4 treatment groups showed that (inductive) reasoning training resulted in significantly less functional decline in IADL than control intervention, whereas neither speed of processing (visual search and identification) training nor memory (verbal episodic memory) training had a significant effect on IADL.[17] Further analyses should explore specific dimension of cognitive training that were instrumental in this transfer of effect.

As expected, the combined intervention showed a significant effect in reducing frailty, and particularly in improving muscle strength and energy. Two prior studies also have shown that the combinational approach among older persons characterized as frail using a specific frailty definition were effective in reversing frailty, but neither study was able to estimate the specific effects of individual interventions. One study of prefrail and frail older adults based on the CHS frailty criteria reported that a 3-month combination of nutritional consultation and exercise training had a short-term beneficial effect on frailty status, evident at 3 months, but not at 6 or 12 months.[23] The second study[25] conducted in Sydney, Australia employed an individualized intervention that included appropriate nutritional evaluation and supplementation, psychological treatment, social activities, and physical exercise. Given the differences in the design and implementation setting of the combination intervention, we observed a doubly greater effect of multidomain treatment for frailty in this study. In the Australian study, the benefit of multidomain intervention was not evident at 3-month follow-up and was apparent only at 12 months (given that there was no assessment at 6 months). Our results indicated that the benefit of 6 months duration of combined intervention was evident at 3 months and 6 months, and sustained at 12 months, indicating persisting benefit for at least 6 months.

We found no major differences between groups with respect to secondary outcomes (IADL-ADL dependency, hospitalization, and falls). Our study has limited power to detect differences in these low-frequency outcomes for these prefrail and frail participants who were selected from among older persons in the community. They had relatively good cognitive and physical functioning, and only a few (n = 11, 5%) reported weight loss or had a BMI of <18.5. Furthermore, very few (only 5%) of our participants were hospitalized in the 12 months before their study participation. Hence, the benefits of the interventions could not possibly be attributed to the effect of recovery from illness, especially in the first 3 months. The presence of a ceiling effect on physical, cognitive, and nutritional status at baseline may limit the potential to show significant improvement. It is possible that frail participants who are more compromised on their nutritional and cognitive status may possibly benefit more from nutritional supplementation or cognitive training. In this connection, the proportion of frailty vs prefrailty and low physical activity at baseline was relatively lower in controls than in other groups. The control group may therefore have limited range of reduction in frailty, leading to an overestimation of the observed improvement.

It was not possible to blind participants to interventions except perhaps nutritional supplement, and even the use of the control is expected to only partially control for the effect of attention and socializing stemming from contacts with the staff and from group training. It is unlikely that such contacts could affect frailty and physical performance specifically, but could have had an effect on mood and the reporting of energy and vitality.

The occurrences of clinical adverse events (hospitalization, functional disability, and mortality) were rare in our study participants. We were thus unable to directly evaluate

whether the statistically significant improvement in frailty status translates to a substantial clinical difference in these functional and health service outcomes. The improvement in frailty status in terms of their transition at least from frailty to prefrail or prefrail to robust, were, however, clinically significant. Published data indicate that both frailty and prefrailty compared with robust are predictive (over 3 years) of 1.3- to 2.6-fold increase in incident falls, worsening mobility, ADL disability, hospitalization, and death.[1]

There are several unique features of this study that limit the generalizability of our results. Firstly, the high compliance rate for all intervention groups achieved through the excellent rapport with participants is exceptional even among rigorously conducted clinical trials. The sample characteristics of Chinese older adults with relatively younger age, good physical and cognitive performance, and less frequent hospitalizations should be noted.

In conclusion, our findings indicate that physical, nutritional, cognitive, and combination interventional approaches are effective in reducing frailty. This study thus shows that it is feasible to identify prefrail and frail older persons in the community and primary care setting and intervene effectively to reduce their level of frailty and possibly prevent future risks of hospitalization, functional dependency, institutionalization, and deaths.

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Authorship: TPN had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. He formulated the hypothesis, performed literature review, designed the study, reviewed the data, and drafted and reviewed the manuscript. Liang Feng reviewed the literature, analyzed the data and drafted and reviewed the manuscript. MN, MSZN, Lei Feng, GC, SAK, SMC, PY and KBY participated in the review of the literature, study design, and data collection, and the review of the data and manuscript drafts.

APPENDIX

Supplementary materials accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.amjmed.2015.06.017.

APPENDIX

Physical Exercise

Resistance exercises using dumbbells and ankle weights were performed in both the seated and kinetic chair positions (weight bearing), integrated in functional tasks such as standing up from a chair, reaching and stepping forward, and heel and toe stands. Balance training exercise[27,28] involving functional strength, sensory input, and added attentional demands were carried out at 3 levels: level 1 (stable surface and within base) involving side by side stance, semi-tandem stance, tandem stance, single-limb stance, alternate heel stand and tiptoe, with progressively decreasing arm support and reducing visual input (eyes open/eyes closed); level 2 (uneven/mobile surfaces, out of base) involving varying surfaces (foam, rocker board), stepping up and down without hand hold, forward/backward walking, sideways walking, progressively decreasing arm and base of support, and increasing movement complexity (head turns, reaching in different directions); level 3 (functional/multi-tasking) involving change of directions while walking, dual-task activities while standing and walking (cognitive and motor tasks such as holding/carrying objects of different weights or sizes, picking up objects from low surfaces/floor, talking about a particular topic, counting backwards, simple mathematical calculations), crossing obstacles, treadmill walking (with increasing speeds and decreasing hand hold).

Nutritional intervention

Fortisip Multi Fibre (Nutricia, Dublin, Ireland) is a 200-mL liquid formula, supplying 300 kcal in the form of carbohydrate (49%), fat (35%), protein (35%), and dietary fiber (4.6 g per 200 mL). One capsule of Sangobion (Merck, Kenilworth, NJ) contains 1 mg folate and 29 mg iron; one tablet of Neuroforte (R.B. Pharmaceuticals, Chennai, India) contains 200 μg B12 and 200 mg vit B6; and one tablet of Caltrate (Pfizer, Singapore) with vitamin D contains 200 IU vitamin D and 600 mg of calcium.