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Original Study

Results of High-Protein, High-Calorie Oral Nutritional Supplementation in Malnourished Older People in Nursing Homes: An Observational, Multicenter, Prospective, Pragmatic Study (PROT-e-GER)

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A B S T R A C T

Keywords:
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Objectives: To assess if the impact of oral nutritional supplements (ONS) on nutritional and functional status in malnourished older persons living in nursing homes shown by clinical trials are also found outside a trial setting.

Design: Observational, multicenter, prospective, pragmatic study.

Setting and Participants: This study was carried out in 38 nursing homes throughout Spain. Nursing home physicians recruited consecutive residents, older than 65 years, with a diagnosis of malnutrition, when a clinical decision to start ONS had been taken after unsuccessful initial management with dietary interventions.

Intervention: The participants received daily 2 bottles of an energy-rich, high-protein commercial ONS for 3 months.

Measures: Primary outcomes were changes in nutritional status (body weight, body mass index [BMI], and Mini Nutritional Assessment-Short Form [MNA-SF]); secondary outcomes were functional changes (Functional Ambulation Classification, Barthel index, handgrip strength, and Short Physical Performance Battery [SPPB]), as well as safety and adherence after 12 weeks of follow-up.

Results: A total of 282 residents (median age 86 years, 67% women) were included, and 244 (86.5%) completed the follow-up. At baseline, 77.3% of the participants were malnourished (BMI 19.7 kg/m², interquartile range 18.3–21.8). After 12 weeks of follow-up, participants experienced significant increases in body weight (2.6 ± 3.1 kg, 5.2 ± 5.9%), BMI (1.0 ± 1.2 kg/m²) and MNA-SF (4.0 ± 2.5 points). There were also significant improvements in functional status measured by the Barthel index, handgrip strength, SPPB, and gait speed. Good adherence was registered in 94.6% of the participants. No relevant side effects were found.

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Conclusions and Implications: Improvements in nutritional and functional status can be found when using a high-protein, high-calorie ONS in older undernourished people living in nursing homes.

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Malnutrition in nursing home residents is associated to a large number of comorbidities, and an increased likelihood of mortality.¹ Depending on the methodology used to assess nutritional status and the population studied, the prevalence of malnutrition in older people living in nursing homes ranges between 6.5% and 85.0%.^{2–5} Maintaining a good nutritional status of long-term care residents is an important and demanding challenge for health care providers working in these facilities.⁶ Early detection of residents at risk of malnutrition or already malnourished, followed by an adequate nutritional intervention, could contribute to the preservation or resaturation of nutritional status, muscle function, functional independence, and quality of life and could potentially prolong survival.^{1,7,8}

Oral nutritional supplements (ONS) are an option for the treatment and prevention of malnutrition in older people who are malnourished or at risk of malnutrition, especially when other interventions (education, food fortification) have failed to improve nutritional status.^{9,10} However, although there are some studies that show the positive effects of ONS on nutritional status and weight, there are very few data about their ability to improve functional status. Moreover, it is unclear if clinical trial findings translate to usual clinical practice settings, including nursing homes.^{11–13} This is especially true for older people with dementia or limited mobility, because they are often excluded from intervention research studies.¹⁴

In this pragmatic study, our aim was to find if the effects of nutritional supplementation found in randomized clinical trials are also evident when supplements are used in clinical practice to treat malnutrition in nursing homes.

Methods

The full protocol of this study and a baseline description of the sample has been published elsewhere.¹⁵ The protocol was approved by the local Ethics Committee for Clinical Research (September 28, 2015), and was registered at www.clinicaltrials.gov (NCT03083912, October 25, 2016).

Briefly, this is a multicenter, prospective, observational, pragmatic study carried out in skilled nursing homes throughout Spain from 2016 to 2018. Nursing home physicians recruited residents who had been diagnosed with malnutrition after a decision to start treatment with an ONS had been taken. The diagnosis of malnutrition had been made by the participants' physician using usual diagnostic criteria and was checked at study entry by the following criteria: (1) body mass index (BMI) <20 kg/m² or BMI <22 kg/m² if older than 70 years, (2) weight loss ≥10% in 6 months or ≥5% in 1 month, (3) no intake in ≥3 days or intake reduction ≥7 days in the presence of BMI between 18.5 and 24 kg/m² or between 24 and 29 if the resident was older than 85 years. Inclusion and exclusion criteria are shown in [Supplementary Table 1](#). Residents with a prescription of two 200-mL bottles a day (1 in the morning, and 1 in the afternoon) of an energy-rich (1.3 kcal/mL), high-protein (6.2 g/100 mL; 20% of caloric content) nutritional commercial supplement (Fortimel Complete; Nutricia, Zoetermeer, The Netherlands) for at least 3 months were included. The decision to study a single brand of ONS was intended to reduce the complexity of adding the variable of the type of supplement. The nutritional characteristics of the oral supplement used in the study (Fortimel Complete) are the following: (1) energy/100 mL: 560 kJ (134 kcal); (2) fat: 4.3 g (saturated 0.5 g, monounsaturated 2.6 g, polyunsaturated 1.2 g);

(3) carbohydrates: 16.6 g (sugars 5.1 g, lactose 0.04 g); (4) fiber 2.0 g (soluble 1.2 g, insoluble 0.8 g); (5) proteins 6.2 g; (6) sodium chloride (NaCl): 0.16 g. Dietary counseling and food fortification had been tried for at least 3 months, following individual nursing home protocols, before the supplement was prescribed.

The baseline nutritional assessment included weight and height (using available measurement devices in each center), BMI, Mini Nutritional Assessment-Short Form (MNA-SF),¹⁶ residents' types of diet and their calorie content (calorie content of the diet offered was assumed as calorie intake, as the amount of food ingested was not controlled), presence of dysphagia (defined as the need of adapted food texture or documentation in medical records), and autonomy when eating (in 4 levels: no help; little help, less than 10 minutes; moderate help, 10 to 20 minutes; and dependent, help for 20 or more minutes). Functional status assessment included the Functional Ambulation Classification (FAC),¹⁷ the Barthel index (BI),¹⁸ handgrip strength,¹⁹ and the Short Physical Performance Battery (SPPB).²⁰ The Cumulative Illness Rating Scale (CIRS-G) was used for the assessment of multimorbidity.²¹ The number of drugs consumed by participants at the time of inclusion was also recorded. A Spanish validated version of the Mini Mental State Examination (MMSE) was used to assess cognitive function,²² and the Global Deterioration Scale was used for the assessment of the stage of dementia.²³ The FRAIL questionnaire (an acronym for Fatigue, Resistance, Ambulation, Illnesses, Loss of weight)²⁴ was used to assess frailty status. All assessments were performed by the local nursing home physician, nurse, or nutritionist, as available, in care of the participant, who are already trained in the use of geriatric assessment instruments.

Nursing home staff were also encouraged to promote adherence to the supplement by reminding participants and caregivers of the importance of this intervention and answering any questions about its use. Local nurses recorded adherence daily by measuring the amount of supplement remaining in each bottle. Adherence was considered good if residents consumed 50% or more of the product for more than 75% of the study duration. Safety was assessed by prospective registration of intolerance, gastrointestinal symptoms, uncontrolled diabetes mellitus, and emergency department visits.

Primary outcomes were the changes in nutritional status (body weight, BMI, MNA-SF) and secondary outcomes were changes in functional status (FAC, Barthel index, handgrip strength, and SPPB), as well as safety and adherence after 12 weeks of follow-up.

Statistical Analysis

As described in the protocol,¹⁵ we calculated the sample size based on the estimated difference in weight before and after treatment, the number of variables used, and an estimated dropout rate of 30%, and projected that we needed 285 participants. Continuous data are presented as mean ± SD or median and interquartile range (IQR), depending on the results of the normality test (the Shapiro-Wilks test was used to test normality). Some data are presented with mean and median to better illustrate changes after follow-up. Qualitative variables are presented as percentages. Comparisons between different variables are 2-tailed, using parametric tests or no parametric tests as appropriate. Binary logistic regression models were used to determine baseline variables independently related to changes in weight. Variables already included in other variables were excluded. We

considered the following as dependent variables: weight gain after 12 weeks of follow-up (yes vs no) and weight gain after 12 weeks higher than 3 kg after 12 weeks of follow-up (yes vs no).

The sample was divided into quartiles according to baseline BMI to determine if there were differences in body weight gain, defined as any increase in weight from baseline to end of study (as a relevant nutritional parameter) or in Barthel index and handgrip strength (as measures of disability and muscle function) at the end of the follow-up among baseline quartiles. Data analysis was performed using IBM SPSS Statistics software, version 24 for Mac (IBM Corp, Armonk, NY).

Results

Characteristics of the Nursing Homes

Fifty-three skilled nursing homes from 8 regions of Spain agreed to participate in this study, 38 of 53 included at least 1 participant. Only 8 of the active nursing homes had more than 200 beds, and the rest were smaller.¹⁵

Baseline Characteristics of the Population

A total of 320 participants were screened, of whom 282 were included in the study.¹⁵ As participants had already received the ONS prescription and the study, with a pragmatic design, only added some additional assessments, there were few exclusions, mostly related to end-of-life situations. Most of the participants complied with each of the inclusion criteria: 263 (93.9%) had a low BMI, 260 (92.2%) reported significant weight loss, and 262 (92.9%) had reduced food intake. Of those included, 244 (86.5%) completed the 12-week follow-up and had data available for analysis. The flow of participants through the study is shown in [Supplementary Figure 1](#).

A total of 38 participants withdrew from the study (13.4%); none of these withdrawals was attributed to side effects. Reasons for dropout were death unrelated to the intervention (18), change of nursing home (3), protocol violation (3), and other not specified by the investigator (14). Participants who did not complete the study had a baseline higher median age (90 vs 86 years; $P = .009$) and some significantly worse functional parameters at baseline in comparison with those that completed the study, such as median Barthel index score: 25.0 vs 45.0 ($P = .001$); median handgrip strength: 6.7 vs 12.7 kg ($P < .001$) and median Global Deterioration Scale (GDS) score: 4.5 vs 4.0; ($P = .032$). However, there were no significant differences in weight, BMI, MNA-SF scores or categories, calorie intake, or frailty assessment.

The median age of the participants was 86 years (IQR 80.0–91.9), 67.0% were women. Baseline characteristics are shown in [Table 1](#). Physical and mental disability were prevalent, with 69.9% having a Barthel index <70 ; 93% an SPPB ≤ 7 ; 71.3% carrying a diagnosis of dementia, and 73.6% with an MMSE <20 . Median body weight of the residents was 50.6 kg (45.0–58.0) and median BMI was 19.7 kg/m² (18.3–21.8). All participants met the inclusion criteria for the diagnosis of malnutrition, but according to MNA-SF categories, 77.3% of residents were malnourished, 20.9% were at risk of malnutrition, and 1.8% had a normal nutritional status (yet they were included in the study because they met the malnutrition criteria according to the inclusion criteria).

Changes in Nutritional Status After 12 Weeks of Follow-up

After 12 weeks of follow-up, participants experienced significant increases in weight (mean increment: 2.6 ± 3.1 kg), BMI (mean increment: 1.0 ± 1.2 kg/m²), and MNA-SF (mean increment: 4.0 ± 2.5) compared with their baseline values. Mean body weight percentage gain was $5.2\% \pm 5.9\%$ ($5.3\% \pm 7.3\%$ in men and $5.1\% \pm 5.1\%$ in women),

median weight gain was close to 5% ([Table 2](#)). Globally, 220 of 244 participants gained some weight (90.2%), of which 107 (37.9%) gained 3 kg or more.

Median increases in weight were significantly higher in participants in the lower baseline BMI quartile (BMI ≤ 18.3 kg/m²) than in those in the highest quartile (BMI ≥ 24.4 kg/m²): 3.0 kg (1.6 to 4.4) vs 1.5 kg (–1.3 to 2.8). Similarly, median increases in BMI were significantly higher in participants in the lowest baseline BMI quartile compared with those in the highest quartile: 1.1 kg/m² (0.6–1.8) vs 0.6 kg/m² (–0.5 to 1.2).

Univariate analysis showed that weight gain at the end of the intervention was associated with a low baseline BMI, low calorie intake, and male gender. In multivariate analysis, only low BMI at baseline remained significantly associated to any weight gain after 12 weeks of follow-up ([Table 3](#)). Low BMI and low Barthel index at baseline were associated with weight gain higher than 3 kg after 12 weeks of follow-up in univariate and multivariate analysis ([Supplementary Table 2](#)).

Table 1
Baseline Characteristics of Participants

	n = 282
Age, y	86 (80–91)
Women, n (%)	189 (67)
Height, cm	160 (152–167)
Weight, kg	50.6 (45.0–58.0)
BMI, kg/m ²	19.7 (18.3–21.8)
Categories for BMI, n (%)	
BMI ≤ 18.3 kg/m ²	71 (25.2)
BMI: 18.4 – 19.7 kg/m ²	70 (24.8)
BMI: 19.8 – 21.8 kg/m ²	71 (25.2)
BMI ≥ 21.8 kg/m ²	70 (24.8)
MNA-SF	6.0 (4.0–7.0)
Categories for MNA-SF, n (%)	
Malnourished (0–7)	218 (77.3)
At risk of malnutrition (8–11)	59 (20.9)
Normal nutritional status (12–14)	5 (1.8)
Calorie intake/day, kcal	1800 (1500–1800)
Dysphagia, n (%)	56 (19.9)
Eating autonomy	
Independent	120 (42.6)
Need help	98 (34.8)
Dependent	64 (34.8)
CIRS-G	11 (8–15)
Drugs, n	6 (4–8)
Barthel index	45 (15–70)
FAC, n (%)	
0	75 (26.5)
1	50 (17.7)
2	32 (11.3)
3	44 (15.6)
4	60 (21.2)
5	21 (7.4)
Maximum handgrip strength, kg	12.0 (6.7–16.5)
Total SPPB*	4.0 (0.0–6.0)
Gait speed, m/s [†]	0.5 (0.4–0.7)
Frailty assessment, n (%)	
FRAIL ≥ 3 criteria	182 (64.5)
FRAIL < 3 criteria	95 (33.6)
Missing	5 (1.7)
MMSE [‡]	12 (5–20)
GDS Reisberg [§]	4 (3–6)

Data shown as median (interquartile range) or as otherwise indicated.

*Data from tests assessed properly (30 men and 70 women).

†Data from residents who could perform the gait speed test (21 men and 33 women).

‡Data available from 280 participants.

§Data available from 201 participants.

Table 2
Nutritional and Functional Status at Baseline and After 12 Weeks of Follow-up

	Week 0	Week 12	n	P Value
Weight (kg)	50.9 (45.0–57.7)	53.0 (47.7–60.9)	244	<.001
Weight gain (median)	–	4.7% (2.8–7.6)	244	
BMI (kg/m ²)	19.7 (18.3–21.7)	20.7 (19.3–22.4)	244	<.001
MNA-SF	6.0 (4.0–7.0)	10.0 (9.0–11.0)	242	<.001
Barthel index	45.0 (20.0–75.0)	50.0 (20.0–78.7)	244	.008
Handgrip strength (kg)	13.0 (8.0–17.1)	15.0 (10.0–19.0)	234	<.001
SPPB	4.0 (0.0–6.0)	4.5 (2.0–7.0)	100	<.001
Gait speed (m/s)	0.5 (0.4–0.7)	0.6 (0.4–0.8)	55	.006

Data shown as median (interquartile range).

Changes in Functional Status After 12 Weeks of Follow-up

After the intervention, there were improvements in Barthel index (mean increment: 1.7 ± 12.8), handgrip strength (mean increment: 1.3 ± 4.0 kg), SPPB (mean increment: 1.0 ± 2.4), and gait speed (mean increment: 0.05 ± 0.25 m/s) but not in FAC (Table 2, Supplementary Figures 2–7) with no significant differences between men and women in any of these changes. Mean handgrip strength gain in percentage was $+16.5\% \pm 46.2\%$ from baseline.

The elements of the Barthel index that changed the most were those related to ambulation, stair climbing, and bladder control. Mean ambulation domain scores increased from 8.9 ± 6.1 to 9.5 ± 5.9 ($P = .014$). The proportion of participants considered independent for mobility increased from 38.5% to 43.0% ($P < .001$). Mean stair climbing domain scores changed from 3.2 ± 3.3 to 3.4 ± 3.6 ($P = .13$). The proportion of participants independent for stair climbing increased from 11.5% to 16.0% ($P < .001$). Similarly, mean bladder control domain scores increased from 3.8 ± 3.7 to 4.1 ± 3.9 ($P = .13$).

Regarding relationships between functional improvements and baseline characteristics, changes in Barthel index were inversely related to baseline BMI ($r = -0.175$; $P = .006$). Accordingly, changes in Barthel index were statistically significant in participants with lower BMI at baseline but not in those with higher BMI at baseline (Figure 1). Median increases in Barthel index were significantly higher in participants in the lowest baseline BMI quartile compared with the highest quartile: 2.5 (0.0 to 5.0) vs 0.0 (–5.0 to 5.0) ($P < .043$). However, handgrip strength significantly increased regardless of BMI categories (Figure 2).

Correlation Between Changes in Nutritional and Functional Status After 12 Weeks of Follow-up

Body weight gain percentage was directly related with improvements in Barthel index, handgrip strength, total SPPB, and gait speed, with weak but significant correlations between 0.130 and 0.311

($P < .05$ in all cases). Accordingly, weight gain percentage was related to improvements in gait speed ($r = 0.311$; $P = .03$) (Supplementary Table 3). Increases in BMI were directly related to improvements in handgrip strength and total SPPB and changes in MNA-SF were directly related to changes in Barthel index ($r = 0.129$; $P = .044$) but not with other functional status parameters (Supplementary Table 3).

Adherence, Safety, and Dropouts

Good adherence was registered in 231 of the 244 residents who completed the 12-week follow-up (94.6%). The intervention was well tolerated in most participants with no major complications related to the intervention. There were no reported cases of gastrointestinal intolerance, uncontrolled diabetes mellitus, or emergency department visits related to the intervention. No withdrawals were attributed to side effects.

Discussion

This multicenter, prospective, observational pragmatic study in 38 skilled nursing homes in Spain included a large sample of residents, with high degree of disability and high prevalence of cognitive impairment, who had received a prescription of an ONS to treat malnutrition. This study suggests that in usual clinical practice the use of an ONS may achieve a consistent body weight gain and improvements in nutritional status in most of the participants. Body weight gain was directly and significantly related to improvements in functional parameters such as the Barthel index, SPPB, and handgrip strength. This intervention was well tolerated and was associated with a good adherence.

This research may be considered as a pragmatic trial: participants are similar to those who receive the intervention in usual care, all efforts have been made to recruit complex patients, the setting where the trial is performed is a usual care setting, using local resources (ie, carried out by the same nursing home staff in care of the participants), organization and flexibility of care delivery allow for a good adherence, and the primary outcome seems to be relevant to participants.²⁵ The inclusion of very old, disabled, nursing home patients in clinical research may help understanding if interventions that have proved to be useful in clinical trials and in other health care settings can have an effect in this particular population.^{10,26}

Poor nutritional status is a usual cause for concern in older people and their caregivers, particularly those who are hospitalized or institutionalized, because it is strongly associated to increased morbidity and mortality.^{27,28} Impaired nutritional status has also been associated with worse muscle strength and functional limitations.²⁸ In the present study, all participants were malnourished at baseline, and most had poor functional status. At the time of the study, no international

Table 3
Relationship Between Weight Gain After 12 Weeks of Follow-up (Yes vs No) and Baseline Characteristics

	Univariate Analysis				Binary Logistic Regression			
	β	OR	95% CI	P	β	OR	95% CI	P
Age	–0.04	0.96	0.90–1.02	.191				
Sex (male)	0.19	1.21	0.48–3.04	.038				
BMI	–0.24	0.79	0.69–0.89	<.0001	–0.25	0.78	0.67–0.89	<.0001
Calorie intake/d (per 100 kcal increase)	0.00	1.00	1.00–1.00	.004				
Dysphagia (yes/no)	0.64	1.90	0.54–6.65	.314				
Autonomy when eating (4 categories)	0.14	1.15	0.77–1.72	.494				
Barthel index	–0.01	0.99	0.98–1.07	.340				
Handgrip strength	0.06	1.06	0.99–1.13	.083				
CIRS-G	0.07	1.07	0.99–1.16	.074	0.08	1.09	1.00–1.18	.060
Use of ≥ 5 drugs	–0.60	0.55	0.23–1.33	.184				
MMSE	–0.03	0.97	0.93–1.02	.258				
FRAIL index	–0.13	0.87	0.59–1.30	.506				

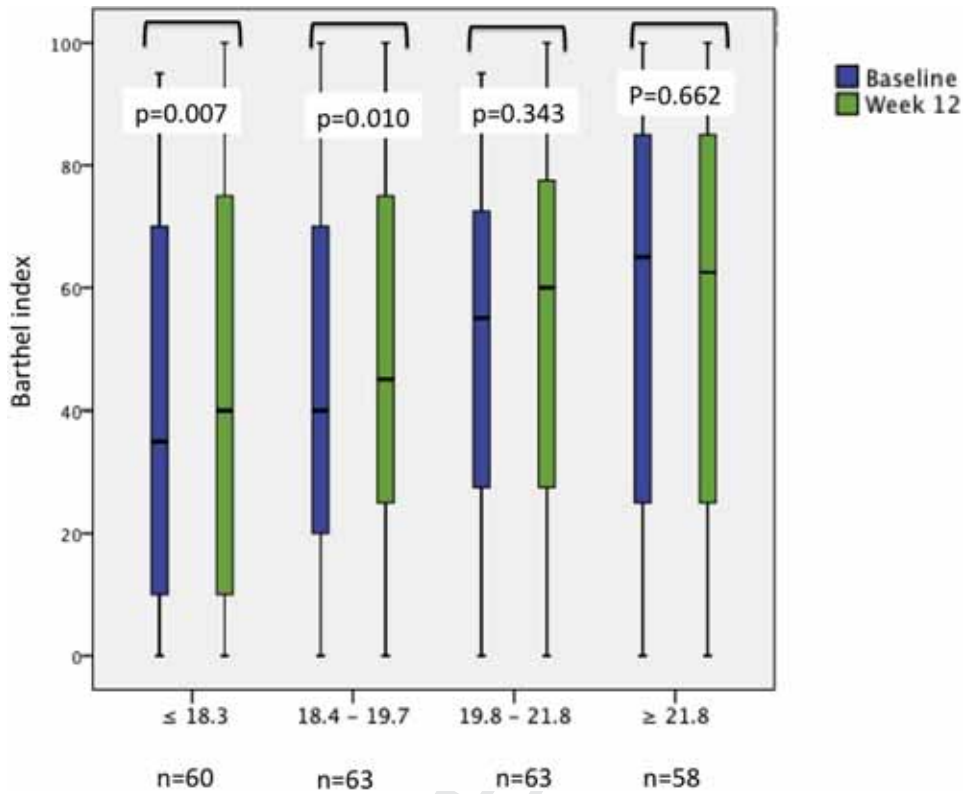


Fig. 1. Barthel index at baseline and after 12 weeks of follow-up according to BMI quartiles.

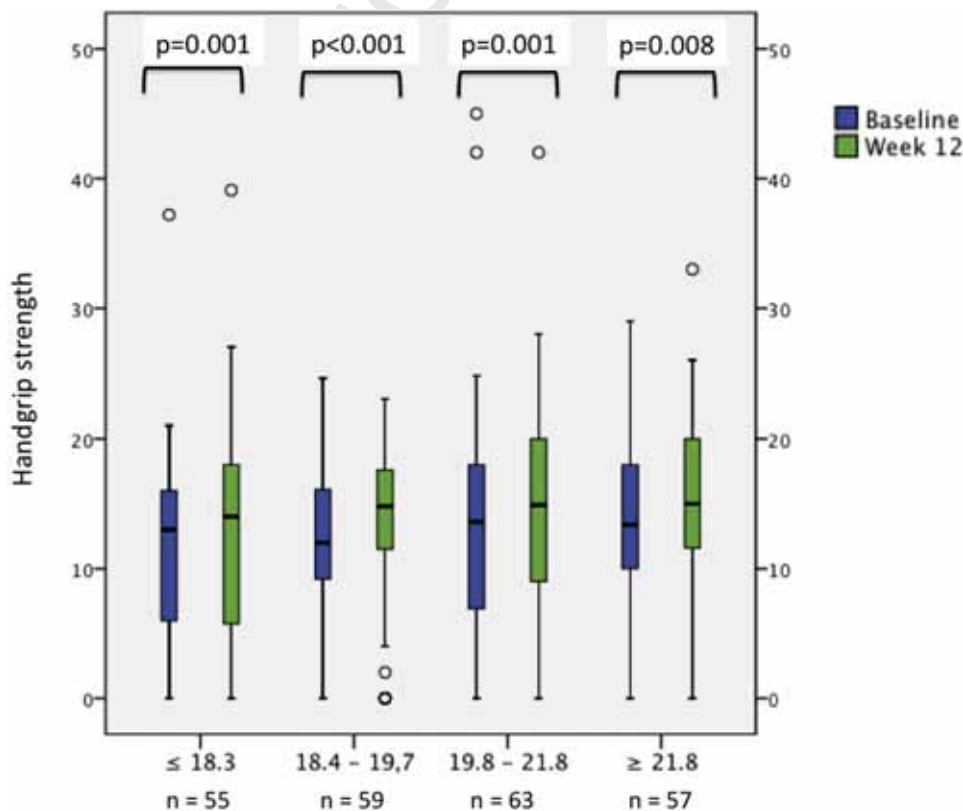


Fig. 2. Handgrip strength at baseline and after 12 weeks of follow-up according to BMI quartiles.

consensus criteria were available,²⁹ so the diagnosis of malnutrition was performed by each participant's physician using different methods, as done in clinical practice.³⁰ We confirmed that most participants had a low MNA-SF on inclusion. Also, as recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines and by the MaNuEL Knowledge Hub,^{10,31} dietary counseling and food fortification had been tried before the supplement was added. After the intervention, increases in body weight were associated with improvements in functional status as measured by Barthel index, handgrip strength, total SPPB, and gait speed. The change in SPPB found in our participants is considered as clinically relevant (1 point), but the increase in gait speed is below the usual 0.1 m/s considered as a clinically relevant difference. Although this association does not establish causality, we think that it provides some hint that improvements in nutritional status are to some extent the cause of improvement in function, particularly related to greater muscle strength.

A Cochrane review published in 2009 examined randomized and quasi-randomized controlled trials focused on protein and energy supplementation in older people at risk from malnutrition.³² It concluded that supplementation produces a small but consistent weight gain in this population and a possible effect on mortality, with no evidence found on the effect on functionality. More recent systematic reviews have shown conflicting evidence on the effect of oral supplementation on function.^{33–36} The largest multicenter randomized controlled trial (RCT) on nutritional supplementation in malnourished hospitalized older people to date did find an improvement in handgrip strength with oral supplements,³⁷ and 2 large RCTs on sarcopenia also found improvements in function.^{38,39} None of these studies was performed in nursing homes.

The evidence of long-term efficacy and suitability of supplements in frail older institutionalized individuals is scarce. In a 9-month RCT, Bonnefoy et al.⁴⁰ studied the effects of protein–energy supplements plus exercise on body composition and muscle function in 57 frail older individuals. In participants with dietary supplements, muscular power of the quadriceps increased by 57% at 3 months ($P = .03$) but showed only a tendency at 9 months.⁴⁰ Most of the residents were not malnourished at baseline, so these data cannot be extrapolated to malnourished residents. Fiatarone et al.⁴¹ conducted a randomized, placebo-controlled trial comparing exercise training plus multi-nutrient supplementation, both interventions, and neither in 100 frail nursing home residents over a 10-week period. They found that multinutrient supplementation without concomitant exercise did not reduce muscle weakness or physical frailty. However, mean BMI of the participants was approximately 25 at baseline, suggesting a good nutritional status.⁴¹ Similarly, Smoliner et al.⁴² studied the effects of food fortification on nutritional and functional status in frail older nursing home residents: 62 at risk of malnutrition and 3 severely malnourished according to MNA. They did not observe convincing improvements in muscle function. Nevertheless, the present study included a much higher proportion of malnourished patients (77.3% vs 4.6% in the study of Smoliner et al.⁴²) so the results are not directly comparable. Price et al.⁴³ performed an RCT to evaluate the effect of nutritional supplementation in 136 undernourished older persons (≥ 75 years) admitted to hospital. Mean BMI of the population at baseline was very low ($19.9 \pm 2.4 \text{ kg/m}^2$), as in our study. Mean handgrip strength increased more in the intervention group (13.9%) than in the control group (7.2%) ($P = .055$),⁴³ what is in line with our results. In addition, Tsuboi et al.⁴⁴ performed a systematic review evaluating the effects of nutritional supplementation on activities of daily living and functional ability of older people in residential facilities. Eight clinical trials comprising 698 participants were included. They found significant improvements in handgrip strength (mean difference 1.65 kg, $P = .04$), but no difference in activities of daily living, gait velocity, or preventing death.⁴⁴

In our study, the benefits of ONS was higher in those participants with lower BMI. The subgroup with highest BMI showed little benefit from the intervention. In addition, multimorbid patients and those with higher baseline caloric intake obtained more benefits from the intervention. Thus, this study may help in defining which nursing home subjects may benefit from adding a nutritional supplement when the aim is to improve nutritional status and function.

We did not measure the direct or indirect cost of the intervention. Malnutrition is associated with a considerable burden of health care costs in long-term care facilities.⁴⁵ Nutrition interventions, such as ONS, have the potential to improve patient well-being and reduce health care costs. Limited data exist on the economics and impact of these interventions in very frail older people with malnutrition in long-term care facilities.⁴⁶ Nevertheless, some evidence suggests that use of ONS in care homes may be cost-effective relative to dietary advice.⁴⁷ However, ONS should not be the only intervention, but part of a broader strategy that should include screening of malnutrition, adequate food intake, education, and exercise training, and involve not only medical and nonmedical health care workers but also the residents and their relatives.⁷

To achieve beneficial effects, adherence is crucial. Adherence with ONS is usually reported to be good in clinical trials. In 46 clinical trials in mostly older participants across health care settings (mean age 74 years), overall adherence was 78%, better in the community (81%) than in the hospital (67%).¹⁰ We found a high adherence rate (94.6%), and this finding is in line with our previous multicenter study that showed adherence up to 96% to the administration of an oral high-protein, energy-rich supplement for 12 weeks⁴⁸ and in line with high adherence in community settings in our country.⁴⁹

The main limitation of this study is the lack of control group of residents who did not receive the intervention. However, nutrition intervention has been shown to work in RCTs³²; the intention of a pragmatic trial is to confirm that the effects found in trials are also observed in usual clinical practice. Also, not using supplements or using a placebo in older patients with established malnutrition raises serious ethical concerns, especially when other less intensive interventions had already been unsuccessful. A second issue is that the fact that knowing that their patients were included in a study may have prompted nursing home physicians and nurses to improve general care of participants, so this improved care may be responsible for the study findings. This is supported by the fact that functional results seem to be better than those found in RCTs. However, improvements in nutritional (intermediate) outcomes seems to give at least some role to nutritional supplementation in improving functional outcomes. Losses to follow-up might be another limitation of the study. However, the number of dropouts was low (13.4% of the population), so their impact on the results is probably limited. The limited number of participants able to perform physical performance tests also limits generalization and casts doubts about the role of such tests in nursing home settings. Finally, weight gain can be due to increased hydration, fat mass, or muscle mass. We did not explore body composition to assess differential effects of the intervention in each body compartment.

On the other hand, the main strength of the study may be the fact that its design is close to real clinical practice so it may accurately reflect the situation of malnourished residents in nursing homes, because only end-of-life situations were excluded. This aspect, together with the large size of the sample and the multicenter design, might allow the generalization of the results to the overall nursing home resident population.

Conclusions and Implications

Although more long-term studies are required, we provide evidence that ONS can improve nutritional and functional status of

malnourished older people living in nursing homes in real clinical practice. The benefit is higher in those with poorer BMI, higher calorie intake from diet, and more morbidity at baseline.

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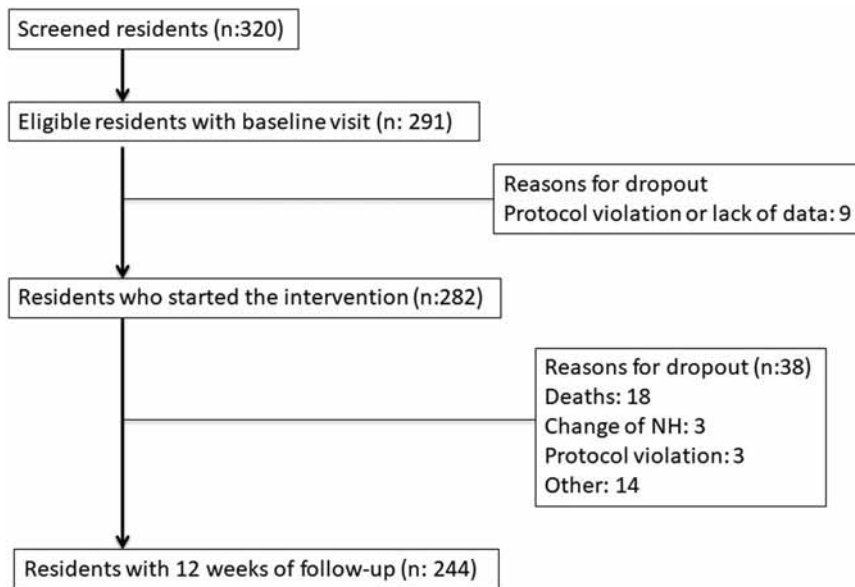
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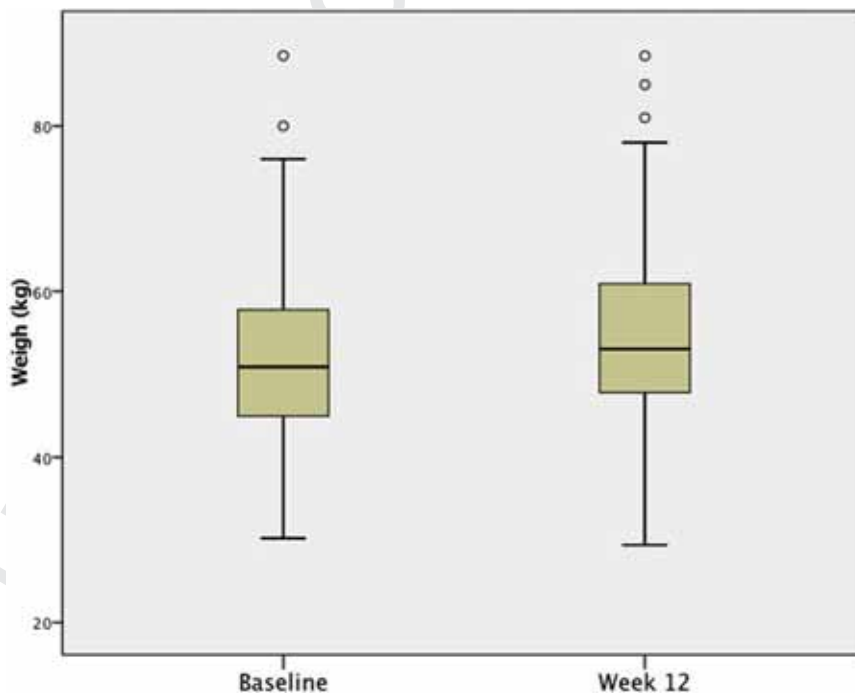
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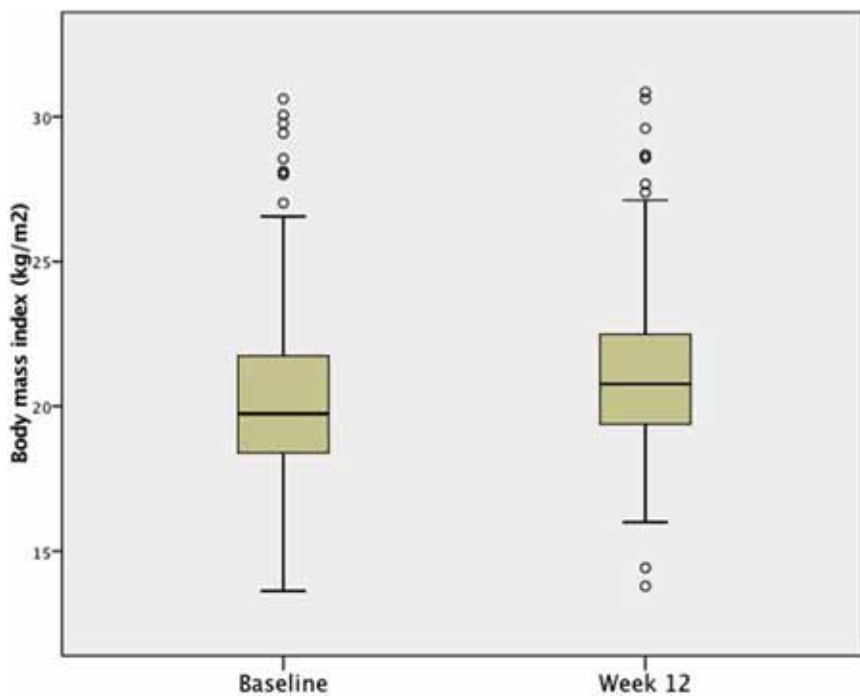
Appendix



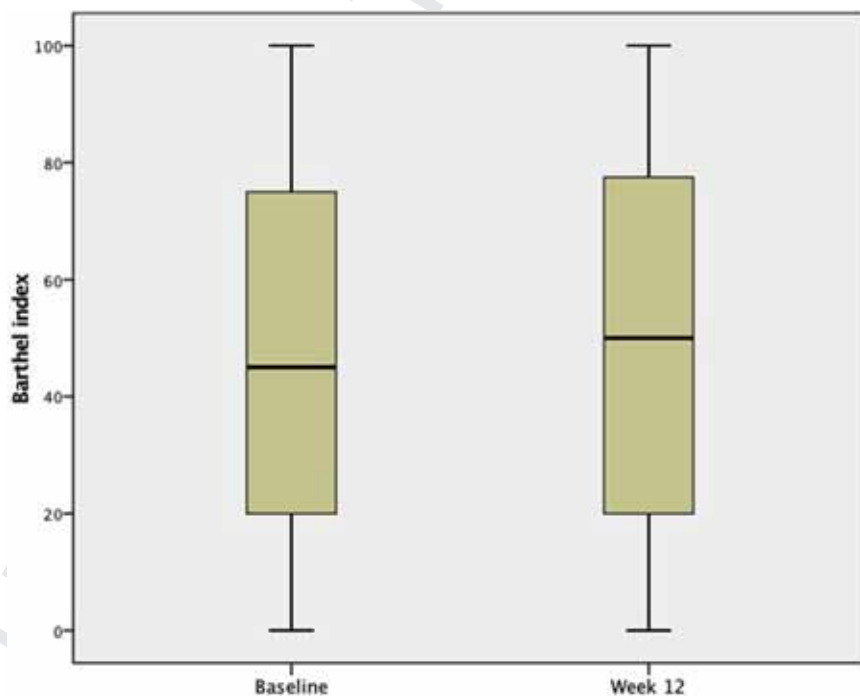
Supplementary Fig. 1. Flowchart of participants.



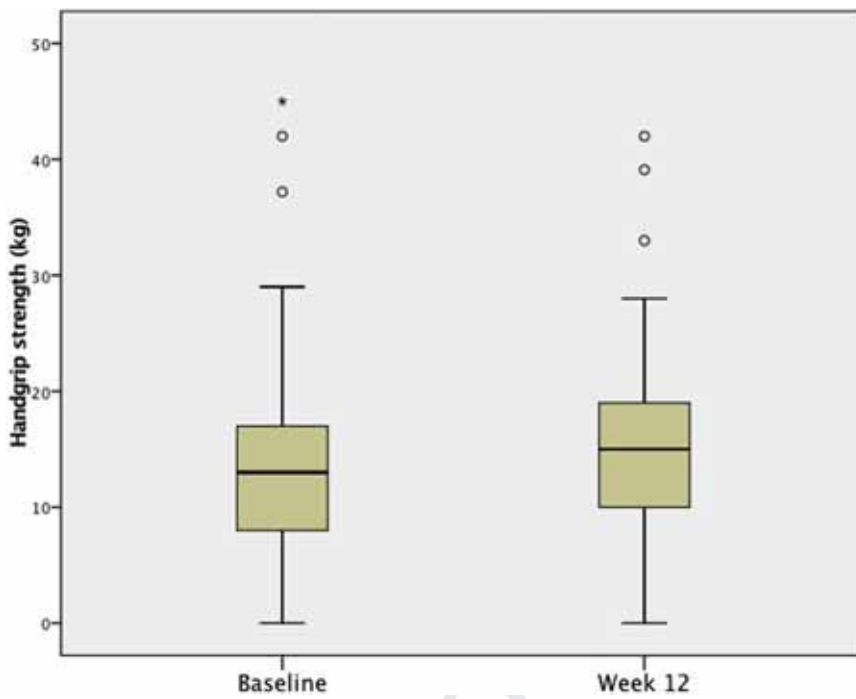
Supplementary Fig. 2. Weight at baseline and after 12 weeks of follow-up.



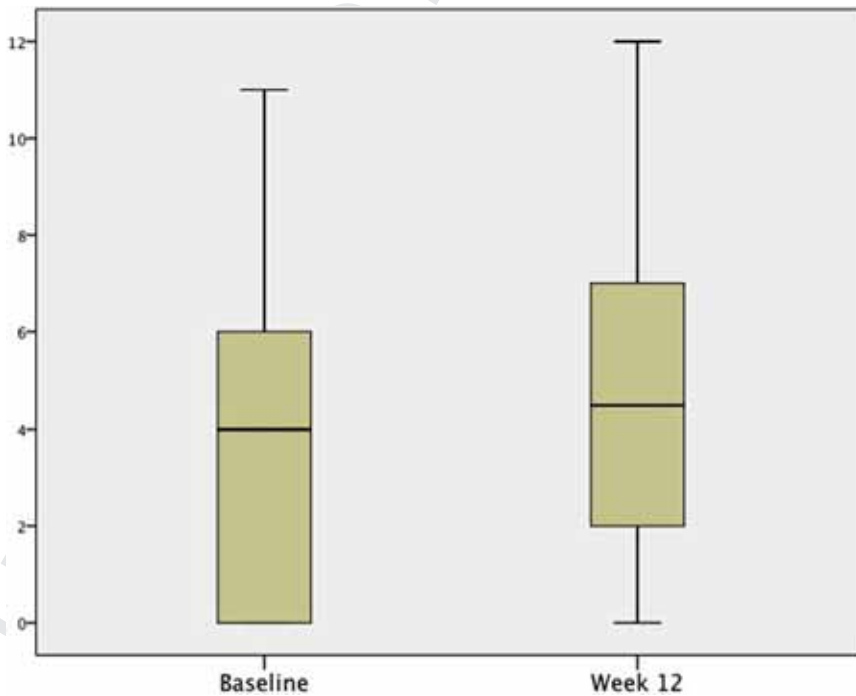
Supplementary Fig. 3. BMI at baseline and after 12 weeks of follow-up.



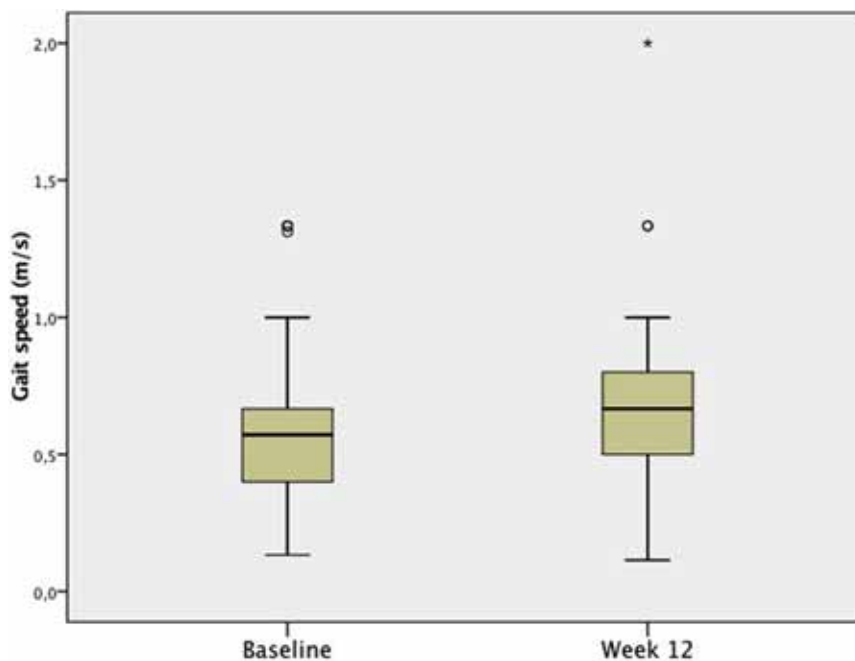
Supplementary Fig. 4. Barthel index at baseline and after 12 weeks of follow-up.



Supplementary Fig. 5. Handgrip strength at baseline and after 12 weeks of follow-up.



Supplementary Fig. 6. SPPB at baseline and after 12 weeks of follow-up.



Supplementary Fig. 7. Gait speed at baseline and after 12 weeks of follow-up.

Supplementary Table 1

Inclusion and Exclusion Criteria

Inclusion	Exclusion
<ul style="list-style-type: none"> • Age ≥ 65 y • Both sex • Subjects living in nursing homes • With a diagnosis malnutrition or at risk of malnutrition* 	<ul style="list-style-type: none"> • Residents receiving nutrition through a tube (nasogastric or due to gastrostomy) • Terminal condition or receiving palliative care • Life expectancy less than 6 months • Special nutritional requirements, such as malabsorption, short bowel syndrome, or residents with specific nutrition for renal insufficiency
<ul style="list-style-type: none"> • Prescription before inclusion by attending physician of 2 bottles a day of a high calories (1.3 kcal/mL) and high proteins (protein: 20% of caloric content) nutritional supplement (Fortimel Complete) • Supplement intended to be used for at least 3 months 	

*For the diagnosis of malnutrition, the following criteria were used: (1) BMI < 20 kg/m² or BMI < 22 kg/m² if older than 70 years, (2) weight loss $\geq 10\%$ in 6 months or $\geq 5\%$ in 1 month, (3) no intake in ≥ 3 days or intake reduction ≥ 7 days in the presence of BMI between 18.5 and 24.0 kg/m² or between 24 and 29 if the resident was older than 85 years.

Supplementary Table 2

Relationship Between Weight Gain Higher than 3 kg After 12 Weeks of Follow-up (Yes vs No) and Baseline Characteristics

	Univariate Analysis				Binary Logistic Regression			
	β	OR	95% CI	P	β	OR	95% CI	P
Age	-0.02	0.97	0.94–1.00	.12				
Sex (male)	0.25	1.29	0.77–2.14	.33				
BMI	-0.12	0.89	0.81–0.97	.007	-0.16	0.85	0.79–0.94	.001
Calorie intake/d (per 100 kcal increase)	0.00	1.00	1.00–1.00	.320				
Dysphagia (yes/no)	-0.02	0.98	0.53–1.79	.939				
Autonomy when eating (4 categories)	-0.14	0.87	0.70–1.09	.222				
Barthel index	-0.01	1.01	1.00–1.02	.023	0.01	1.01	1.00–1.02	.003
Handgrip strength	0.03	1.03	1.00–1.07	.061				
CIRS-G	0.03	1.03	0.99–1.07	.107				
Use of ≥ 5 drugs	-0.11	0.90	0.55–1.45	.655				
MMSE	0.02	1.02	0.99–1.04	.248				
FRAIL index	-0.11	0.89	0.71–1.12	.325				

Supplementary Table 3

Correlations Between Weight Gain Percentages, Increases in BMI and MNA-SF Score With Changes in Functional Parameters After 12 Months of Follow-up

Changes in Functional Parameters	Weight Gain Percentages			Increases in BMI			Increases in MNA-SF		
	Correlation (r^*)	<i>P</i>	n	Correlation (r^*)	<i>P</i>	n	Correlation (r^*)	<i>P</i>	n
Δ Barthel index	0.130	.043	244	0.094	.141	244	0.129	.044	242
Δ Maximum handgrip strength (kg)	0.196	.003	234	0.220	.001	234	−0.054	.413	233
Δ FAC	0.089	.165	244	0.73	.254	244	0.119	.064	242
Δ Total SPPB	0.217	.030	100	0.199	.047	100	0.156	.121	100
Δ Gait Speed (m/s)	0.311	.030	49	0.281	.05	49	0.191	.189	49

**r*: Spearman's correlation coefficient.