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Effect of protein supplementation on physical performance in older sarcopenic people– randomized controlled trial

Abstract

Objectives: To test the long-term effects of whey-enriched protein supplementation on muscle and physical performance.

Design: A 12-month randomized controlled double blind trial with a 43-month of post-trial follow-up.

Setting: Community dwelling people.

Participants: A total of 218 older (>74 years) people with sarcopenia.

Intervention: 1) control with no supplementation, 2) isocaloric placebo and 3) 20g x 2 whey-enriched protein supplementation. All participants were given instructions on home based exercise, dietary protein and vitamin D supplementation of 20µg/d.

Measurements: Physical performance was assessed by short physical performance battery (SPPB) and continuous summary physical performance scores (CSPPS). Hand grip strength and calf intracellular resistance based skeletal muscle index (CRi-SMI) were measured by bioimpedance spectroscopy (BIS). The measurements were performed at 0, 6, and 12 months. The post-trial follow-up was performed by a postal questionnaire and national census record data.

Results: The subjects were old (75-96 years) and mostly women (68%). The test supplements had no significant effects on physical performance, the 12-month changes for SPPB being -0.55, -0.05 and 0.03 points in control, isocaloric and protein groups (p=0.17), respectively. The changes in CSPPS were similar between the intervention groups (p=0.76). The hand grip strength decreased significantly in all intervention groups and the 12-month changes in CRi-SMI were minor and there were no differences between the intervention groups. Half of the patients (56%) in both supplement groups reported mild gastrointestinal adverse effects. Differences were found neither in the all-cause mortality nor physical functioning in the post-trial follow-up.

Conclusions and implications: The whey-enriched protein supplementation in combination with low intensity home based physical exercise did not attenuate the deterioration of muscle and physical performance in community dwelling older sarcopenic people.

Introduction

According to the European Working Group on Sarcopenia in Older People consensus sarcopenia is defined as low muscle strength, low muscle quantity or quality and low physical performance[1]. Low muscle strength identifies probable sarcopenia, low muscle quality confirms the diagnosis and if all the three criteria are met, sarcopenia is considered severe[1]. Age-related muscle loss is closely related to malnutrition, physical inactivity, inflammation, and cachexia[2,3], which also are hallmarks of frailty[4]. Multifaceted mechanisms underlying age-related muscle loss and weakness range from complex aging phenomena to life style changes and consequences of clinical diseases. Sarcopenia and frailty are associated with a risk of adverse outcomes, physical disability, poor quality of life, and increased risk of morbidity and mortality[1-4].

Many of studies have recently explored to what extent sarcopenia is preventable, and special attention has been called to physical activity and nutrition[1,5]. The effectiveness of nutritional supplements containing protein and energy has been gathered into a Cochrane review that consisted of 62 randomized or quasi-randomized controlled trials[5]. Most trials had poor study quality. Supplementation produced a small but consistent weight gain in older people. Mortality may be reduced in older people who are undernourished. However, this review found no evidence of improvement in functional benefit or reduction in the length of hospital stay with supplements. Yanai et al. has reviewed 19 clinical trials to study effects of protein, amino acids, leucine, vitamin D and beta-hydroxy-beta-methylbutyrate[6]. The endpoints varied from the muscle synthesis rate and muscle mass indicators to different muscle functions. Some observational studies suggested a daily dietary protein intake of 1.0-1.2 g/kg for prevention of sarcopenia. Optimal repartition over each daily meal or 25-30 g of high quality protein

per meal was also recommended. However, further studies with larger number of older subjects were warranted.

A comprehensive review summarized the current knowledge about effectiveness of combined exercise and nutrition interventions to improve muscle outcomes in older people[7]. The number of participants (>65 years) ranged from 17 to 217 and the duration of interventions varied from eight weeks to nine months. Enhanced benefits were shown in some trials indicating potential for further larger intervention trials. The oldest people at highest risk were under presented in these trials.

In order to fill this lack of knowledge we enrolled older (>74 years) sarcopenic and community dwelling people to a 12-month double blind randomized controlled trial (RCT) with a 43-month post-trial follow-up. Potential benefits of whey protein have raised special interest[8,9] and prompted us to enrich the test supplement with whey protein. All participants were also given instructions on simple low intensity home based physical exercise and vitamin D supplementation of 20 µg/d[10,11]. We hypothesized that the whey protein supplementation would maintain or improve the physical performance of the participants over the isocaloric placebo and no supplementation.

Methods

General design and interventions

The detailed methods of this 12-month double blind RCT have been published elsewhere[12]. Briefly, a postal screening of the older population (>74 years, n=3275) and further clinical examination of 773 community dwelling older people living in the Porvoo city were performed (appendix figure). The

participants had to be able to walk indoors independently although canes and walkers were allowed. They also had low hand grip strength (men ≤30.0 kg, women ≤20.0 kg) or slow habitual gait speed (≤0.80 m/s), low CRi-SMI (2 standard deviations below young adults, 2.06 cm^2/Ω for men and 1.50 cm^2/Ω for women) measured by segmental calf BIS (bioimpedance spectroscopy). Other inclusion criteria stated that participants' plasma creatinine was <150 μmol/l, they had no terminal illness (estimated prognosis >6 months), no pacemaker, no bilateral replacement arthroplasty of the knee and finally, and no severe skin lesions in BIS electrode placement sites (dorsal foot, dorsal ankle, lateral knee, dorsal wrist, and dorsal palm.

After baseline assessment total of 218 sarcopenic persons were randomly allocated into three arms: 1) control with no supplementation, 3) isocaloric placebo, and 3) 20g x 2 protein supplementation. At baseline, all the participants received written instructions and a short oral counselling on simple low intensity home based physical exercise such as stationary walking and getting up form a chair, importance of dietary protein showing common protein sources without exact target intakes, and the use of vitamin D supplementation with the dose of 20 μg/d. During follow-ups all patients were also orally reminded of these instructions, but the information was not updated. In groups 2 and 3 the participants were instructed to take twice daily a 250 ml beverage as a snack between meals immediately after an exercise session, whereas in group 1 the participants took regular protein-rich foods in a similar fashion. In the protein supplementation group the participants received a maximum of 40 grams (20 grams x 2, 48% whey) of extra milk derived proteins daily compared with 7.5 grams (3.75 grams x 2, 20% whey) in the isocaloric placebo group. After each exercise session and ingestion of supplement the participants recorded the level of exercise and the amount of ingested supplement. The energy content of the test supplements was 70kcal/100ml. The compliance to the home-based exercise, nutritional supplements and vitamin D supplement were assessed by interviewing the patients

during each study visit. All supplements were manufactured and provided free of charge by Valio Ltd, Helsinki, Finland. Randomization was performed by computer-generated (Microsoft Excel 2010, Redmont, WA, USA) random list including 100 sets of numbers 1, 2, and 3 to indicate each treatment group. The group treatments were randomized off-site at the start of recruitment and the content of the supplement (isocaloric vs. protein) was kept sealed outside the research group until data collection and analysis of endpoints was complete. All the supplements were packed in blank 250 ml tetras and flavored identically with strawberry.

The study was approved by the local Ethics Committee. Informed consent was obtained from each patient or if necessary from their closest proxy (Mini Mental Examination (MMSE) <19 points) before any study procedures which were performed according to good clinical practice. The CONSORT checklist was not available in the preparation of the study protocol, but the results of this randomized controlled trial were reported according to the CONSORT statement within the limits of our data. Recruitment of patients was started during May 2012 and all intervention were completed by the end of year 2014.

Measurements and outcomes

The primary outcome measures included 6- and 12-month changes in physical performance according to the short physical performance battery (SPPB, 0-12)[13] and continuous summary physical performance scores (CSPPS, 0-100), [14,15] and changes in muscle functions (hand grip strength). The questionnaires also included the physical component of the RAND-36 scale[16]. Two consecutive measures of handgrip strength (kg) from both hands were measured to the nearest 1.0 kg with subjects sitting in an upward position and the arm in a 90-degree angle (JAMAR dynamometer, Saehan Corp. Masan, Korea)[17]. The mean of the best result from both hands was recorded. Habitual gait speed was

measured over a 4-meter course without a walking aid when possible and the best time of two attempts was recorded to calculate the gait speed = distance (m)/time (s)[18]. The patients were instructed to walk down a hallway through a 1-meter zone for acceleration, a central 4- meter "testing" zone, and a 1-meter zone for deceleration. Chairs used for the SPPB chair stand test had a back rest without arm rests, with a sitting height of 42-44cm and a sitting depth of 42-45cm. Same chairs were used during follow-up measurements. Height and weight were measured, and body mass index calculated accordingly. Skeletal muscle indices (SMI) were measured with a single channel, tetra polar BIS device (SFB7, ImpediMed Ltd., Eight Miles Plains, Queensland, Australia) that scans 256 frequencies between 4 kHz and 1000 kHz. Raw data were analyzed with the supporting software (version 5.3.1.1, SFB7, ImpediMed Ltd., Eight Miles Plains, Queensland, Australia) supplied by the manufacture to obtain values for calculation of CRi-SMI = electrode distance^2/calf intracellular resistance[19,20]. Single frequency (50 kHz) resistance data were obtained and Janssen equation used to calculate the skeletal muscle mass in order to determine the single frequency skeletal muscle mass index (SF-SMI) = skeletal muscle mass/height^2. The measurements were performed according to the instructions of the manufacturer and under standardized conditions (at the same time of day, empty bladder etc,). Nutritional status was assessed by the Mini Nutritional Assessment (MNA)[21] and a three-day dietary record[22,]. Cognition was assessed by the MMSE[23]. All measurements were performed at baseline, at 6, and 12 months.

Post-trial follow-up

The census status of the participants in the Porvoo Trial was obtained from the bureau of Official Statistics of Finland (SVT) in April 2016. Thereafter a postal questionnaire was sent to the survivors. The questionnaire contained questions about housing, need for help, functioning, and activities of daily living as well as the physical component of RAND-36 scale.

Statistics

Sample size calculation has been presented in our previous article.[12] Statistical comparison between the groups at baseline was performed using analysis of variance or the chi-square test when appropriate. All participants assessed at baseline, 6-month, and 12-month examinations were included in the data analyses of changes in SPPB and CSPPS (modified intention to treat). Repeated measures were analyzed using generalized estimating equation (GEE) models with the unstructured correlation structure. GEEs were developed as an extension of the general linear model (e.g., ordinary least squares regression analysis) to analyze longitudinal and other correlated data. GEE models take into account the correlation between repeated measurements in the same subject; models do not require complete data and can be fitted even when individuals do not have observations at all time-points. The 95% confidence intervals (CIs) and statistical models were obtained using bootstrapping in cases of violation of assumptions. Stata version 13.1 (Stata Corp., LP, College Station, TX) was used for the analyses.

Results

The subjects were old (75-96 years) and women (68%) outnumbered men (Table 1). The baseline MMSE scores ranged from 15 to 30 the mean score being 26 and the mean number of daily prescribed drugs was 5.7. The baseline characteristics of subjects did not differ after randomization (Table 1). A total of 40 (18%) subjects (22 controls, 8 in protein group, 10 isocaloric group, p=0.005) dropped out during the intervention period, the majority of them (n= 23) within the first six months (Supplemental figure S1). The drop-outs in the control group were more frequent in men (57% vs. 20%, p=0.002),

they had lower MMSE (24.8 vs 26.3, p=0.027) and lower MNA (21.3±2.8 vs 23.2±2.7, p=0.010) at baseline than those who completed the study. According to the dietary records there were no differences among the three groups in the compliance to the nutritional supplement or in the physical activity. The mean daily dietary protein intake (supplements excluded) ranged from 0.97 g/kg to 1.15 g/kg in the three groups at six- and 12-month examinations and no significant changes or differences between the groups were observed during follow-up (data not shown). Subjects reported taking on average 58% of the daily supplement volume in the protein group, the respective figure being 64% in the isocaloric group. The mean time spent in different physical activities (house hold work, home exercise, walking, etc.) was estimated at 4.0, 3.5 and 3.9 h/week (p = 0.66) in the control, protein and isocaloric groups, respectively. One in two (n=98, 45 %) of the subjects was estimated to have a good compliance (≥50% of the supplement and ≥2h/week of physical activity) throughout the 12-month intervention.

The two test supplements had no significant effects on indicators of physical performance. Thus, the changes the short physical performance battery (SPPB) and continuous summary physical performance scores (CSPPS) did not differ between the groups during the 12-month intervention period (Figure 1). The same held true for the physical component of RAND-36 scores (data not shown). On the contrary, physical performance tended to deteriorate during the trial period, the mean (95%CIs) 12-month changes for SPPB being -0.55 (-1.02, -0.07), -0.05 (-0.47, 0.38) and 0.03 (-0.39, 0.46) points in the control, isocaloric and protein groups, respectively. The respective CSPPS values were -1.9 (-4.4, 0.62), -1.1 (-3.4, 1.2) and -2.3 (-4.5, -0.01).

There was a slight but significant weight gain during the first six months in both supplement groups that leveled off at 12-months, but again no significant differences were found between the three intervention groups (Figure 2). The hand grip strength decreased significantly and similarly in all three

groups (Figure 2). The mean (95%CIis) 12-month changes were -1.9 kg (-2.7, 1.1), -1.7 kg (-2.5, -0.99) and -1.9 kg (-2.6, -1.1) in the control, isocaloric and protein groups, respectively. The muscle mass estimated by means of CRi-SMI decreased slightly in both supplemented groups, but no statistically significant differences were observed among the three groups (Figure 3A). The mean (95%Cis) 12-month changes in CRi-SMI were -0.01 (-0.05, 0.04), -0.05 (-0.09, -0.01) and -0.05 (-0.10, -0.01) in control, isocaloric and protein groups, respectively. The second muscle index, SF-SMI remained practically unchanged (Figure 3B). Secondary analyses showed that differences of the changes in SPPB and CSPPS were insignificant also in those with good compliance (data not shown).

The test supplements caused a significant increase in gastrointestinal complaints. Up to 56% in both test groups reported some adverse effects, whilst the respective figure was 9 % in the control group. The taste of supplements caused concern in some cases (n=13), but the gastrointestinal symptoms included also feelings of early satiety, nausea, diarrhea and constipation similarly in both supplement groups. The complaints in the control group were limited to the required documentation of dietary records and physical activity.

Of the 218 participants 46 died within the 43-month follow-up. No differences were found in the all-cause mortality among the test groups (Table 2). A total of 137 survivors responded to the post-trial follow-up postal questionnaire. The majority was still living at home without help and no differences were found in the physical component of RAND-36 scores among the intervention groups.

Discussion

Our study showed that the whey enriched protein supplementation in combination with low intensity home based physical exercise did not attenuate the deterioration of muscle and physical performance in community dwelling older sarcopenic people, but caused a temporary weight gain and lead to mild gastrointestinal complaints in half of the participants. The results of the present study do not rule out possible positive effects of protein supplementation in some groups, but strongly suggests that its impact is not decisive in real life home-dwelling older people who already have significant manifestations of muscle loss and weakness.

The results are in accordance with numerous smaller studies on various target groups[5-7]. They are also in line with the results of our trial on nursing home residents, in which the six-month supplementation with whey protein fractions resulted in an increase in body weight, tended to increase whole body fat free mass but did not improve functioning[24].

Plausible explanations for the lacking effectiveness is the relatively good nutritional status and adequate protein intake of these sarcopenic subjects. In fact, the baseline energy intake was within the ranges of recommendations and the BMI of participants was not low. Furthermore, the baseline daily protein intake was 1.0 g/kg, and in line with the recommendations, although the optimum amount of dietary protein has been debated intensively[5,6,25]. Despite the fact that protein depletion is a significant risk for the development of sarcopenia in epidemiologic studies, several studies have failed to demonstrate positive effects of excess protein intake on muscle mass and physical performance[5,6,7,9]. That holds true for different protein extractions including whey protein fractions and essential amino acids[5,6,7].

Recent reviews and meta-analyses published after termination of our trial illustrate that the protein supplementation hardly solves the sarcopenia problem of older adults. The meta-analysis of Tieland et al. suggested that according to eight studies protein or amino acid supplementations had no positive effects on lean body mass or muscle strength in predominantly healthy elderly people[26]. Hou et al. summarized the results of 21 trials and found that the protein supplementation combined with resistance training effective in the enhancing muscle mass and strength but did not improve other muscle functions[27]. On the contrary, Ten Haaf et al. included 36 studies in their meta-analysis and concluded that that the protein supplementation does not lead to increases in lean body mass, muscle strength or physical performance in non-frail community older adults[28]. They recommend further studies to clarify, whether specific protein supplementations are beneficial for older people with low habitual protein intake. Of the newest trials that of Bo et al. is closest to ours[29]. They found that in a 6-month study of 60 sarcopenic older patients that the combined supplementation of whey protein. vitamin D and E improved muscle mass and strength as well as anabolic markers in older adults with sarcopenia.

Of the life-style factors physical activity and muscle training have been proved to be the most important in the prevention and restoration of muscle loss in all age groups[7]. The importance of progressive resistance exercise in improving physical performance has been particularly emphasized, during which the nutritional requirements may also be increased. In order to avoid deteriorating effects of the sedentary life style, all participants were advised to physical activity, importance of dietary protein and to use vitamin D according to recommendations. It is likely that the level of physical activity was not high enough to prevent the decline in muscle functions. In this respect, this study conveys an important message: physical activation of older home-dwelling sarcopenic people is not an easy task.

The negative result of the present study should be viewed in light of the fact that this trial is one of the largest and the most long-lasting RCT published on this area. It was also complemented by a long-term post-trial follow-up. The focus of study and the real-life approach to the problem are other indisputable strengths. The exclusion criteria were kept as few as possible. It is worth noting that the participants were older than in most previous studies and therefore at the highest risk of both deteriorating sarcopenia and its multiple consequences. The use of bioimpedance spectroscopy (BIS) to measure changes in muscle has enabled us to include geriatric patients requiring home visits for the examinations.

Some weaknesses are difficult to be avoided in real life experiments. The drop-out rate, 18% within one year, may be tolerable in the older population. Interestingly, the drop-outs were most common in the control group conceivably due to the lower incentives and motivation compared with participants receiving nutritional supplements free of charge. The fact that the drop-outs also had lower MMSE and lower MNA at baseline may have also falsely improved the observed results in the control group possibly masking the age-related decrease in the skeletal muscle index (Figure 3).

The relatively low compliance and adherence to the test supplements is a certain cause for concern because it could dilute possible positive effects of supplements. However, even with the average of 58% ingested volume the protein supplementation dose was 23.2 g/d, which is comparable to most previous studies[5,6,7]. Furthermore, the significant differences in adverse effects indicate active use of the test supplements and obstacles for the wide-scale usage of long term nutritional supplementation in prevention of sarcopenia in older populations.

Despite conflicting clinical trial results the theoretical knowledge has kept continuous interest in the role of whey protein supplementation in the prevention and even treatment of sarcopenia. A recent RCT PROVIDE showed improvements in muscle mass and lower-extremity function among

sarcopenic older adults with a 13-week vitamin D and leucine-enriched whey protein oral nutritional supplementation[30]. A post-hoc analysis of the trial also suggested that sufficient baseline levels of 25-hydroxyvitamin D and protein intake may be required to increase muscle mass as a result of intervention with a vitamin D and protein supplement in sarcopenic older adults[31]. A 12-week RCT on supplementation with whey protein, essential amino acids, and vitamin D, in conjunction with age-appropriate exercise boosted fat-free mass and strength and contributed to well-being in sarcopenic elderly[32]. In addition, a new trials have been registered, in which the effects of light training and nutrients including whey protein will be tested in older people on wide array of variables[33,34]. Furthermore, on-going PROMISS trial investigates inclusion of protein rich foods alone or with advice to use them in conjunction with normal daily physical activity on physical performance in community-dwelling older adults[35].

Conclusion and implications

in this study the whey enriched protein supplementation in combination with low intensity home based physical exercise did not attenuate the deterioration of muscle and physical performance in community dwelling older sarcopenic people, but caused a temporary weight gain and led to mild gastrointestinal complaints in more than half of the participants.

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Figure legends

Figure 1. Changes in short physical performance battery (SPPB) and continuous summary physical performance scores (CSPPS) by the intervention group. N=218, p-values and estimates calculated by generalized estimating equation models with the unstructured correlation structure, p-values < 0.050 are considered statistically significant.

Figure 2. Changes in body weight and hand grip strength by the intervention group. N=218, p-values and estimates calculated by generalized estimating equation models with the unstructured correlation structure, p-values < 0.050 were considered statistically significant.

Figure 3. Changes in calf intracellular resistance skeletal muscle index (Cri-SMI) and single frequency skeletal muscle index (SF-SMI) by the intervention group. N=218, p-values and estimates calculated by generalized estimating equation models with the unstructured correlation structure, p-values < 0.050 were considered statistically significant.

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Table 1. Characteristics of participants

Variable	Control	Isocaloric	Protein	P-value
Number	72	73	73	
Age, years	83.7±5.1	84.0±3.9	83.6±4.7	.881
Women, %	70.8	62.5	69.9	.504
Number of Daily Drugs	5.7±3.1	5.3±2.7	6.1±2.8	.281
Mini Mental State Examination	25.8±2.5	25.6±3.5	26.2±2.7	.420
SF-SMI[a], kg/m^2	7.6±1.7	7.7±1.7	7.3±1.6	.356
CRi-SMI[b], cm^2/Ω	1.29±0.34	1.27±0.35	1.28±0.34	.959
Short Physical Performance Battery	7.9±2.8	7.7±2.7	7.8±3.0	.940
Gait Speed, m/s	0.85±0.31	0.84±0.28	0.88±0.34	.748
Hand Grip Strength, kg	19.4±5.9	20.5±6.7	18.5±6.5	.171
Mini Nutritional Assessment	22.7±2.8	22.9±2.6	22.3±3.0	.445
Body Mass Index	26.3±3.8	26.8±4.0	25.3±4.0	.064
Energy intake, kcal/d	1644±419	1698±469	1641±517	.770
Protein intake, g/kg/d	1.0±0.3	1.0±0.4	1.1±0.5	.720

Comparison performed using analysis of variance or the chi-square test when appropriate.

[a]Single Frequency Skeletal Muscle Index

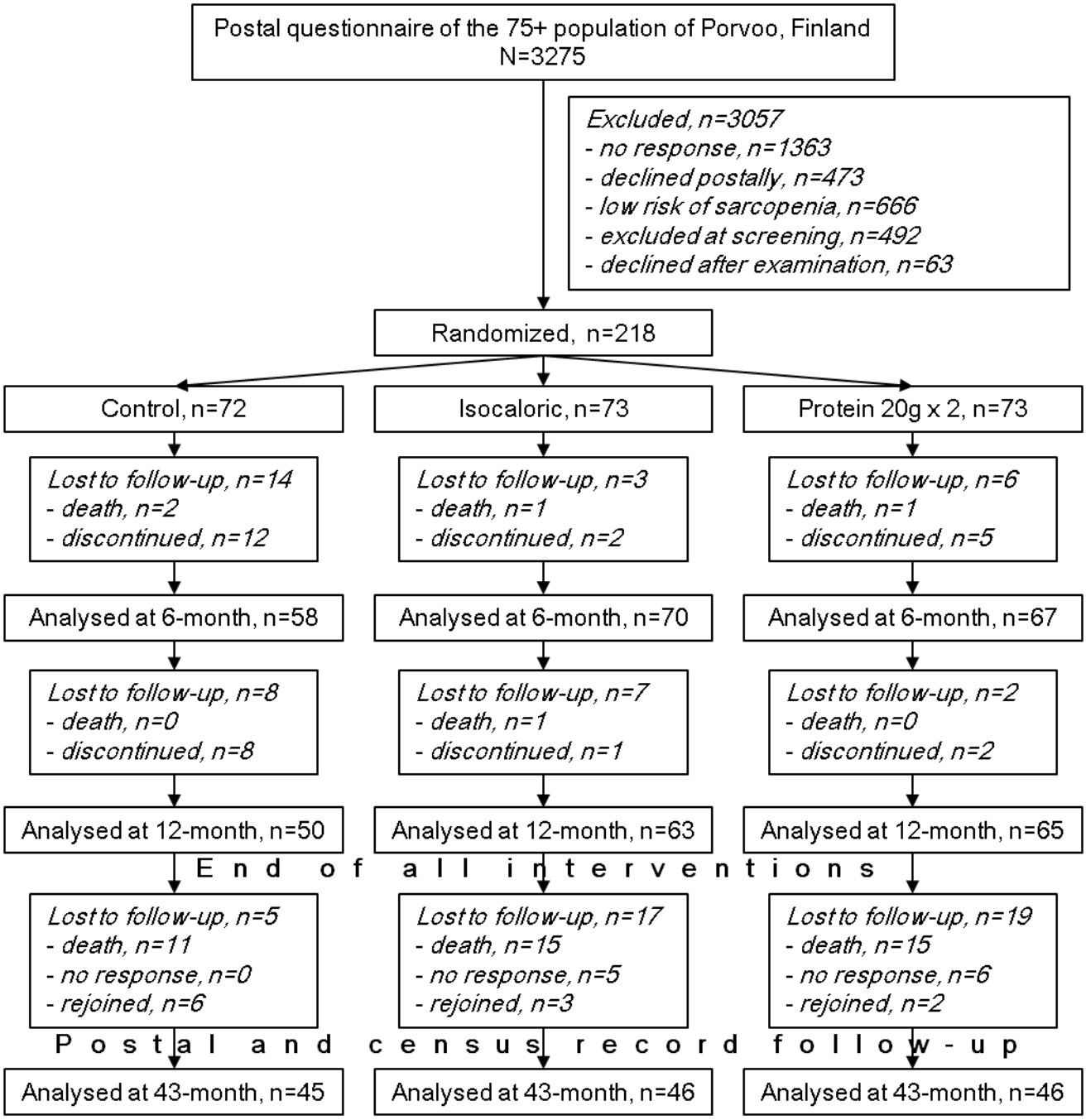
[b]Calf Intracellular Resistance Skeletal Muscle Index

400

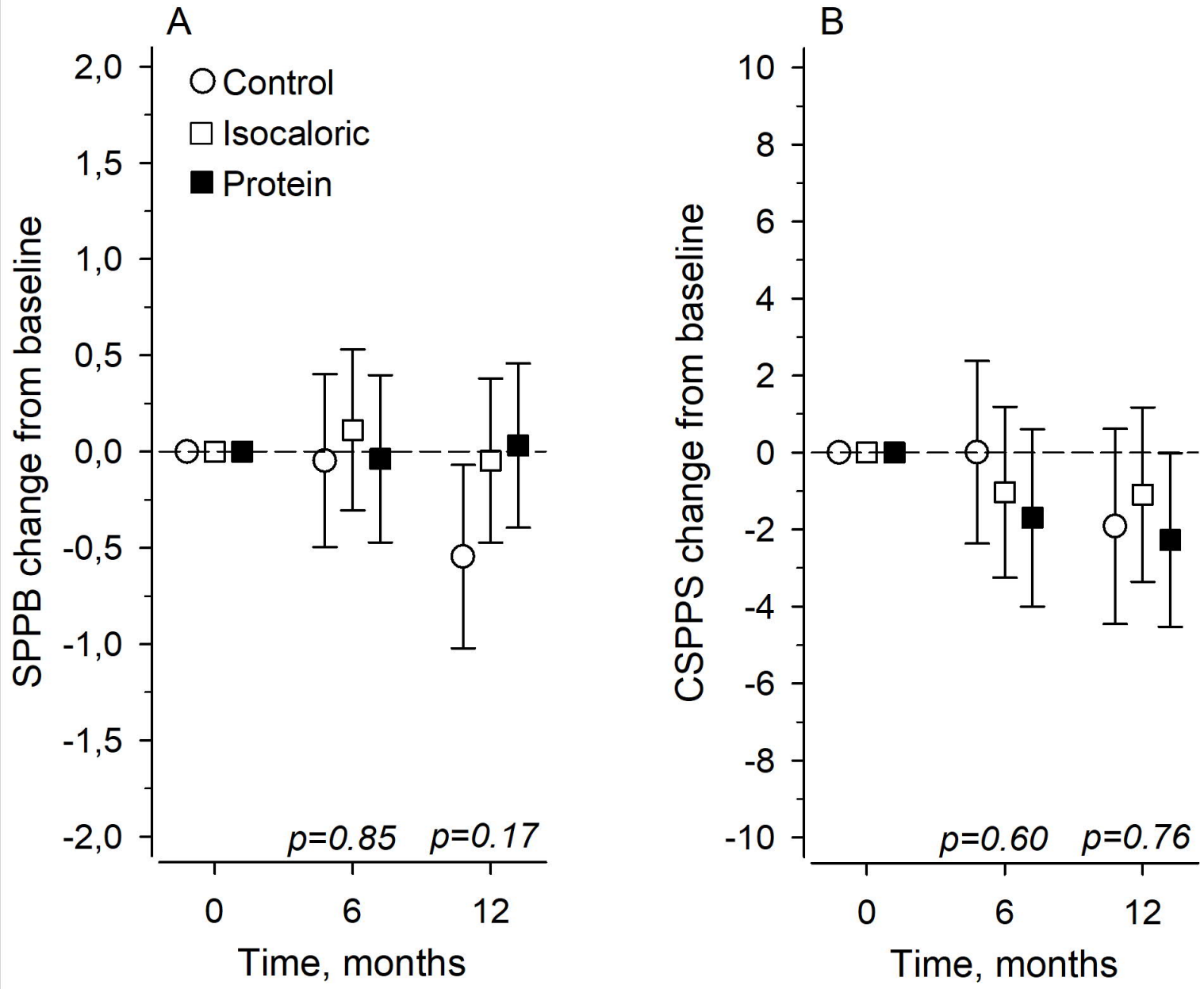
Table 2. Physical functioning and need for help at four-year follow-up

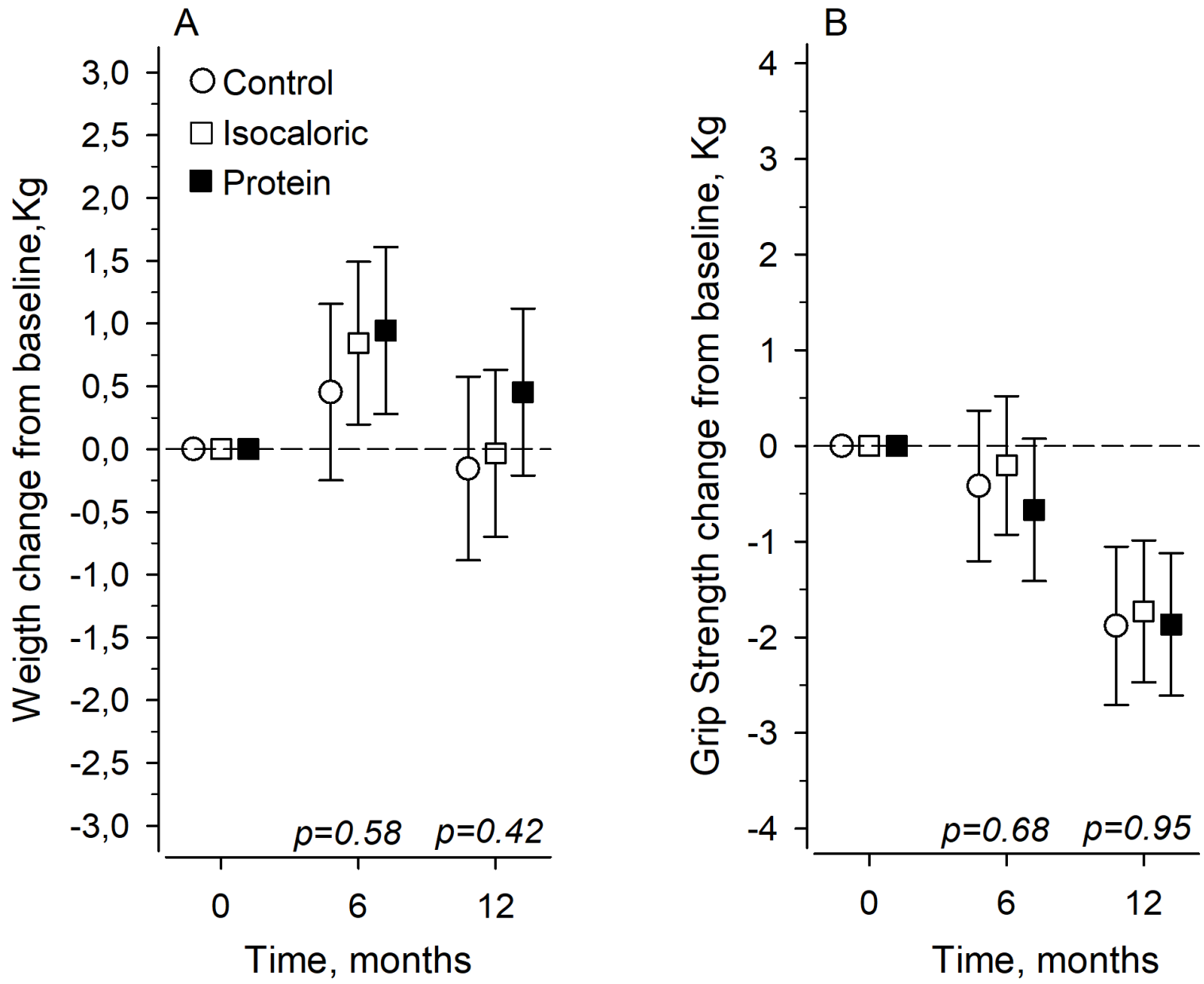
Variable	Control N = 45	Isocaloric N = 46	Protein N = 46	P-value
At home, %	97.8	97.8	95.6	.803
At home, without help, %	56.5	66.7	68.9	.714
Physical RAND-36 (SD)	39.9 (32.1)	45.2 (25.1)	43.8 (28.8)	.393
No difficulties outdoors, %	42.2	41.3	45.6	.915
No difficulties indoors, %	57.8	68.4	67.4	.545

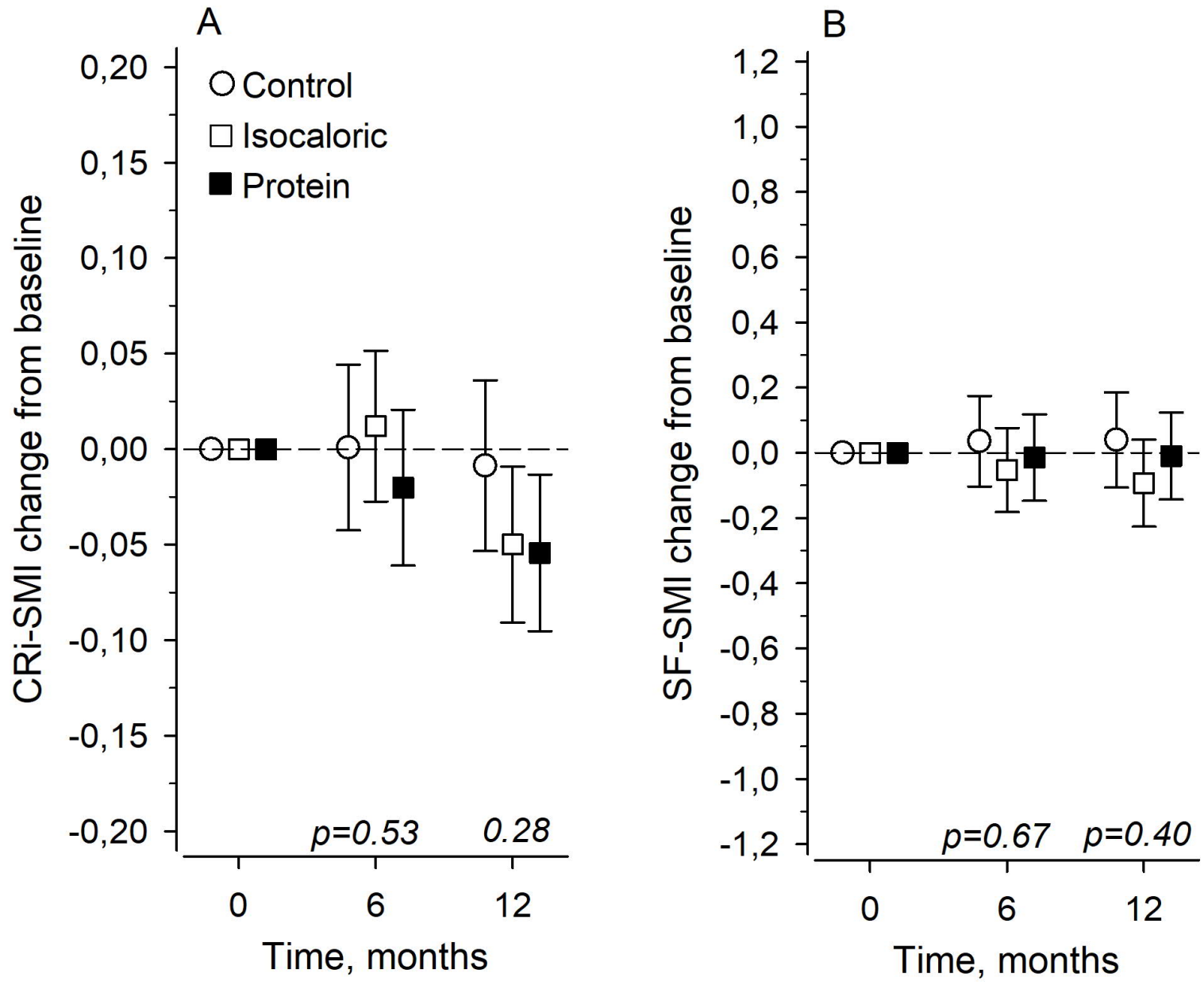
401 Comparison performed using chi-square test.



Appendix Figure. Flowchart of participants


A
Control
Isocaloric
Protein
SPPB change from baseline
2,0
1,5
1,0
0,5
0,0
-0,5
-1,0
-1,5
-2,0
p=0.85
p=0.17
0
6
12
Time, months
B
CSPPS change from baseline
10
8
6
4
2
0
-2
-4
-6
-8
-10
p=0.60
p=0.76
0
6
12
Time, months


A
Control
Isocaloric
Protein
3,0
2,5
2,0
1,5
1,0
0,5
0,0
-0,5
-1,0
-1,5
-2,0
-2,5
-3,0
Weigth change from baseline,Kg
p=0.58
p=0.42
0
6
12
Time, months
B
4
3
2
1
0
-1
-2
-3
-4
Grip Strength change from baseline, Kg
p=0.68
p=0.95
0
6
12
Time, months


A
B
Control
Isocaloric
Protein
CRi-SMI change from baseline
SF-SMI change from baseline
0,20
0,15
0,10
0,05
0,00
-0,05
-0,10
-0,15
-0,20
1,2
1,0
0,8
0,6
0,4
0,2
0,0
-0,2
-0,4
-0,6
-0,8
-1,0
-1,2
p=0.53
0.28
p=0.67
p=0.40
0
6
12
Time, months