A Randomized, Controlled Trial of Quadriceps Resistance Exercise and Vitamin D in Frail Older People: The Frailty Interventions Trial in Elderly Subjects (FITNESS)

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OBJECTIVES: To determine the effectiveness of vitamin D and home-based quadriceps resistance exercise on reducing falls and improving the physical health of frail older people after hospital discharge.

DESIGN: Multicenter, randomized, controlled trial with a factorial design.

SETTING: Five hospitals in Auckland, New Zealand, and Sydney, Australia.

PARTICIPANTS: Two hundred forty-three frail older people.

INTERVENTIONS: Patients were randomized to receive a single dose of vitamin D (calciferol, 300,000 IU) or placebo tablets and 10 weeks of high-intensity home-based quadriceps resistance exercise or frequency-matched visits.

MEASUREMENTS: The primary endpoints were physical health according to the short-form health survey at 3 months and falls over 6 months. Physical performance and self-rated function were secondary endpoints. Assessments took place in the participants' homes at 3 and 6 months after randomization and were performed by blinded assessors.

RESULTS: There was no effect of either intervention on physical health or falls, but patients in the exercise group were at increased risk of musculoskeletal injury (risk ratio = 3.6, 95% confidence interval = 1.5–8.0). Vitamin D supplementation did not improve physical performance, even in those who were vitamin D deficient (<12 ng/mL) at baseline.

CONCLUSION: Neither vitamin D supplementation nor a home-based program of high-intensity quadriceps resistance exercise improved rehabilitation outcomes in frail older people after hospitalization. There was no effect of vitamin D on physical performance, and the exercises increased the risk of musculoskeletal injury. These findings do not support the routine use of these interventions at these dosages in the rehabilitation of frail older people. **J Am Geriatr Soc 51:291–299, 2003.**

Key words: randomized controlled trial; exercise; vitamin D; aged; rehabilitation

Advancing age is associated with declines in physiological reserve and physical functioning and an increased risk of disability and dependency. Sarcopenia (age-associated reduction in muscle mass and strength), particularly of the lower limbs, is common in older people[1] and has important health consequences that include reduced mobility and an increased risk of injurious falls and subsequent disability.[2,3] Two promising and widely applicable interventions to improve muscle strength and modify the risks of sarcopenia are progressive resistance strength training exercises (resistance exercise) and vitamin D supplementation.

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Complex or multifaceted exercise programs can improve muscle strength and balance and reduce the incidence of falls in community-dwelling older people,[4–6] but it is uncertain which therapeutic elements of such programs are most likely to benefit patients, and thus there is difficulty in translating the evidence into the delivery of efficient, appropriate, and cost-effective rehabilitation.

One specific intervention that has been strongly advocated as a standard component of exercise and rehabilitation programs for older people is resistance exercise,[7] which involves patients exercising against a load that is progressively increased as their strength improves. Many

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trials have shown that supervised resistance exercise can dramatically increase strength in medically stable older adults, particularly when this exercise is performed at a high intensity.[8,9] However, trials to date have provided only limited data on the effects of resistance exercise on substantive clinical outcomes such as falls and health-related quality of life (HRQoL). Moreover, most trials have involved relatively fit older people who have undertaken resistance exercise under highly supervised sessions using specialized equipment. It is unclear whether resistance exercise is safe and effective in clinical practice such as in the rehabilitation of frail older people recently discharged from the hospital. This would appear to be an appropriate group to target for such an intervention, because many older people experience deconditioning and functional decline while in the hospital.[10,11]

Vitamin D deficiency is common in frail and institutionalized older people[12] and is associated with an increased risk of osteoporosis and hip fracture.[13] Vitamin D is a low-cost intervention that is often used in the prevention of osteoporosis and fractures, although the effectiveness of vitamin D alone on fracture prevention is still unclear.[14] Vitamin D receptors are present in muscle,[15] and the association between vitamin D deficiency and weakness, abnormal gait, and falls[12] suggests that vitamin D has a direct effect on muscle function. However, the small number of trials that have examined the effect of vitamin D supplementation on muscle strength, physical performance, and falls has produced mixed results.[16–18]

The Frailty Interventions Trial in Elderly Subjects (FITNESS) study was undertaken to provide a reliable assessment of the effects of resistance exercise and vitamin D supplementation. The primary aim of the trial was to determine, in a 2 by 2 factorial design, whether a simple home-based program of resistance exercise to the quadriceps muscles or a single high dose of vitamin D (calciferol) could improve self-reported physical health and reduce the risk of falls in frail older people who had recently been discharged from hospital.

METHODS

Design

FITNESS was a multicenter, randomized, controlled trial with a factorial design to compare (1) the effects of a 10-week program of resistance exercise to the quadriceps muscles with frequency-matched social home visits and (2) a single high dose of vitamin D (calciferol) with placebo on self-reported physical health and falls in frail older people after hospitalization. Secondary outcomes were measures of physical performance and self-reported measures of physical function, social activities, and mental health. A factorial design provided an efficient way to evaluate the effects of two separate interventions.

Recruitment took place in three large public metropolitan acute care and rehabilitation teaching hospitals in Auckland, New Zealand, and two such hospitals in Sydney, Australia, from February 1999 to December 2000. The Clinical Trials Research Unit of the University of Auckland performed central computerized randomization, data management, and statistical analyses. An independent data safety monitor reviewed unblinded safety data every 6 months, with instructions to stop the trial if there was clear evidence, beyond reasonable doubt, of benefit or harm (defined as a difference of 3 standard deviations between treatment groups).

The relevant research ethics committees in Auckland and Sydney approved the study, and all study patients gave written informed consent to participate.

Patients

Research officers identified potentially eligible patients by screening all patients admitted to geriatric rehabilitation units (inpatient or day ward) in each of the study centers. Inclusion criteria were aged 65 and older, considered frail according to simple clinical measures of frailty as described by Winograd et al.,[19] and no clear indication or contraindication to either of the study treatments (i.e., the clinician had substantial uncertainty about the benefits of the treatments for a specific patient). The research officers prospectively screened the medical records of all patients admitted to the hospital wards and, using simple clinical criteria, classified the patients into one of three groups: independent, frail, or fully dependent. Frail patients were those who had one or more health problems or functional limitations from a list of indicators that included dependency in an activity of daily living (ADL), prolonged bed rest, impaired mobility, or a recent fall. Patients were excluded if they were considered not frail (i.e., fit and independent or fully dependent in ADL) or if, in the opinion of the responsible clinician, that treatment was considered to be potentially hazardous or definitely indicated for a patient. Because this was a pragmatic trial that screened a large number of patients admitted to hospital wards, no specific test or cutoff score was used to exclude participants, with the exception of the frailty assessment. Patients were excluded if they had a poor prognosis and were unlikely to survive 6 months, severe cognitive impairment that would compromise adherence to the exercise program (generally people with scores <20 on a 30-point Mini-Mental State Examination (MMSE)), physical limitations that could limit adherence to the exercise program (e.g., poor upper limb function that limited application of the weights), unstable cardiac status, or large ulcers about the ankles that would preclude safe application of the ankle weights. In addition, because of difficulties that would arise with their follow-up assessments, people who lived outside the hospitals' normal geographical zones and patients who were not fluent in English were excluded.

Randomization

Once the research officer had obtained informed consent and completed the baseline assessments, patients were allocated to one of the four treatment arms using a computerized central randomization scheme. The study biostatistician generated the randomization sequence. A stratified block randomization technique (six patients per block) was used to ensure that the number of patients in the four treatment arms was balanced within each center. During the trial, only the study biostatistician knew the size of the block.

Trial Interventions

The aim of this trial was to investigate interventions that, if proven effective, could be easily and inexpensively incor-

porated into current healthcare services. The resistance exercise intervention consisted of a quadriceps exercise program using adjustable ankle cuff weights undertaken three times per week for 10 weeks. The aim was for patients to exercise at a high intensity by midway through the program. This was defined as exercising at 60% to 80% of the patient's one repetition maximum (1RM) (the maximum weight that can be lifted once while maintaining good form). The 1RM was evaluated using the ankle weights. Each session began with individualized warm-up stretches (e.g., hamstring and quadriceps stretches), followed by three sets of eight repetitions of knee extensions. Patients performed the exercises in a seated position, with adjustments to their position and posture made by the therapist when appropriate. Most of the patients performed their first two exercise sessions in the hospital and continued the rest of their sessions at home. An experienced physical therapist monitored progress weekly, alternating telephone calls with home visits. During the home visits, the research physical therapist ensured that the exercises were performed correctly, retested the patients' muscle strength, and increased the training weight accordingly. The therapist encouraged the patient to use correct body posture during the exercise sessions and modified the task and home equipment where necessary to encourage safe performance. Compliance was monitored through a patient diary.

The exercise control group received frequency-matched telephone calls and home visits from the research physical therapist. During these contacts, the research physical therapist inquired about the patients' recovery, gave general advice on any problems encountered, and supported appropriate actions taken toward recovery.

The vitamin D intervention was given in a single oral dose. Patients received either six 1.25-mg calciferol (300,000 IU) or matching placebo tablets. A study nurse administered the tablets, which were stored in a sealed opaque envelope.

Measurements and Procedures

Research nurses who were blinded to the assigned treatments conducted follow-up visits at 3 and 6 months post-randomization in the patients' place of residence. For the vitamin D intervention, the patients and those administering the interventions were also blinded to the treatment allocation. The resistance exercise interventions were single blind, but attention control visits were used to minimize bias. To determine the effectiveness of outcome assessor blinding for the resistance exercise intervention, the study nurses were asked at the 6-month visit to guess which patients were in the exercise group.

The primary outcomes were self-rated physical health at 3 months and falls over the 6-month period. Self-rated physical health was assessed at 3 and 6 months using the physical component score (PCS) of the Medical Outcomes Study 36-item short form questionnaire (SF-36), a standard measure of HRQoL. The PCS score is a weighted average of all eight domains of the SF-36, with particular emphasis on the four physical domains: physical functioning, role-physical, bodily pain, and general health.[20] Patients recorded falls in a fall diary, a customized calendar with magnets on the back. For the first 10 weeks of the trial, participants received weekly reminders from the physical therapists to complete the fall diary. The research nurses examined the fall diaries and sought further details about each fall at their 3- and 6-month home visits. In addition, participants received a reminder phone call between these visits to encourage them to continue to record their falls. A person who was blinded to treatment assignment coded the fall data.

Assessments of physical performance and self-reported activities were recorded at baseline and at the 3- and 6-month visits. The performance measures were isometric knee extensor strength measured using a hand-held dynamometer with the knee flexed to 90°;[21] the Berg Balance Test,[22] a measure of functional balance in which balance is rated from 0 (low) to 4 (high) across 14 tasks; timed up-and-go, a timed mobility task that involves rising from a chair, walking 3 meters, turning around, and returning to sitting in the chair;[23] and the time taken to walk 4 meters. The research nurses used portable equipment to measure and mark the distances for the timed mobility assessments at each site. A single maximal isometric knee extensor strength score was created by determining the maximum of three measurements for each leg, then calculating the mean of the two scores (right and left leg). Research staff administered the MMSE[24] and assessments of self-reported basic ADL (the Barthel Index),[25] fear of falling (the modified falls self-efficacy scale),[26] and participation in higher "non-ADL" levels of activities (the Adelaide Activities Profile).[27] Blood samples were taken to determine 25-hydroxyvitamin-D (25-OH-D) levels at baseline and at 3 and 6 months (acetonitrile radioimmunoassay). Assays were undertaken in accredited laboratories in Auckland and Sydney.

The field research staff recorded all adverse events, and a blinded assessor coded them. A significant injury or medical event was defined as an event that caused the participant to seek attention from a health professional or limited their ADLs for at least 2 days. Patients were also asked to rate their degree of pain and fatigue each week during the 10-week intervention period using a 4-point Likert scale.

Statistical Analysis

The primary objectives of the trial were to compare self-reported physical health and fall rate between the resistance exercise and control groups and between vitamin D and placebo. A total sample size of 240 patients was projected to provide a power of 80% with $\alpha = 0.05$ to detect a 10% difference in the PCS of the SF-36 between groups, assuming a 10% dropout rate. This sample size also provided 80% power with $\alpha = 0.05$ to detect a reduction in the proportion of people who fall per year from 0.5 to 0.3, assuming a 10% dropout rate. The power calculations assumed an additive scale of measurement between the two groups.[28]

Analysis was on an intention-to-treat basis. Adjustments to the analyses would be performed if imbalances in important baseline characteristics were observed. Means and 95% confidence intervals (CIs) were calculated for normally distributed data. For skewed data, medians and 95% CIs were used.[29] Fall rates were calculated by dividing the number of people who fell by the total person years of follow-up. For continuous data, the Wilcoxon

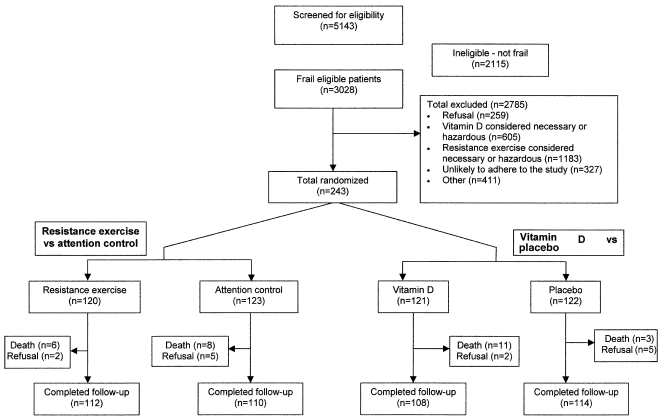

Figure 1. Flow of patients through the study.

signed rank test was used to compare changes in the active and control groups. To determine whether the interventions affected the time to first fall after entering the study, Kaplan-Meier survival curves were constructed and hazard ratios and 95% CI were calculated for each treatment group. The relative risk ratio (RR) for adverse events was calculated using a standard 2 by 2 table of the number of people who experienced adverse events compared with the number who did not.

RESULTS

Five thousand one hundred forty-three older patients were entered onto the screening register of all admissions to geriatric and rehabilitation wards across the five centers. As shown in Figure 1, 3,028 patients met the criteria for frailty. The main reason for exclusion of these potentially eligible patients was that resistance exercise was considered hazardous because of extreme frailty or dependency. Two hundred forty-three frail older patients were recruited into the trial.

The characteristics of patients at entry to the trial are outlined in Table 1. Because the primary aim of this study was not to investigate the interactive effects of these interventions, all results are reported for the active and placebo (control) groups for each intervention. The mean ± standard deviation age of patients was 79.1 ± 6.9; 53% were women. The median 25-OH-D level at entry was 17 ng/mL (95% CI = 16–19). Sixty-one percent of patients had suboptimal 25-OH-D levels (<20 ng/mL), and 30% were vitamin D deficient (<12 ng/mL). Patients had impairment in physical performance, as indicated by the slow times recorded for the timed up-and-go and walking tests, and low scores for balance. Baseline characteristics were well balanced across the groups, and thus all analyses were unadjusted.

No patient was lost to follow-up. Fourteen patients died, with cardiovascular events being the most common cause of death. All deaths occurred at least 1 week after

Table 1. Baseline Demographic and Clinical Characteristics of Patients by (Two by Two) Factorial Treatment Group

Characteristic	Resistance Exercise (n = 120)	Attention Control (n = 123)	Vitamin D (n = 121)	Placebo (n = 122)
Age, mean (95% CI)	80 (79–81)	78 (77–80)	79 (77–80)	80 (78–81)
Female, n (%)	66 (55)	63 (51)	64 (53)	65 (53)
Living at home, n (%)	108 (90)	108 (88)	108 (89)	108 (89)
25 hydroxy vitamin D, ng/mL, median (95% CI)	18 (15–21)	16 (15–18)	15 (14–18)	19 (16–21)
Body mass index, mean (95% CI)*	25 (24–26)	24 (24–25)	24 (23–25)	25 (24–26)
Medical history, n (%)				
Ischemic heart disease†	27 (23)	29 (24)	30 (25)	26 (21)
Stroke†	52 (43)	57 (46)	59 (49)	50 (41)
Any fracture†	48 (40)	58 (47)	53 (44)	53 (43)
Fall in previous year	68 (57)	68 (55)	66 (55)	70 (57)
Self-report measures, median (95% CI)				
Falls self efficacy scale, (range 0–140)§	101 (93–105)	108 (99–114)	102 (96–110)	104 (98–110)
Barthel index, (range 0–20)§	19 (18–19)	19 (18–19)	19 (18–19)	19 (18–19)
Mini-Mental State Examination, (range 0–30)§	27 (27–28)	27 (27–28)	27 (26–28)	28 (27–28)
Physical performance, median (95% CI)				
Quadriceps strength, kg‡§	10 (9–12)	11 (9–11)	11 (9–12)	10 (9–11)
Timed walking test, sec‖	9 (7–9)	8 (7–9)	8 (8–9)	8 (7–9)
Timed up and go, sec‖	24 (21–27)	23 (20–26)	24 (21–27)	24 (19–26)
Berg balance test, (range 0–56)§	40 (37–42)	40 (38–42)	38 (37–42)	40 (38–42)

* Weight in kilograms divided by square of height in meters.
† Most of these events took place at least 1 year before this hospital admission.
‡ Data presented as the mean of both legs.
§ A higher score indicates better performance.
‖ A lower score indicates better performance.
CI = confidence interval.

Table 2. Comparison of Primary Outcome Measures Between Treatment Groups (N = 222)

Primary Measure	Resistance Exercise (n = 112)	Attention Control (n = 110)	Vitamin D (n = 108)	Placebo (n = 114)
Physical component score of 36-item short form questionnaire at 3 months, mean (95% CI)*	34 (32–36)	35 (33–37)	35 (33–37)	35 (33–36)
Difference, mean (95% CI)	−1 (−4–1)		0 (−2–3)	
Falls over 6 months				
Total number of falls	164	149	157	156
Number of people who fell	60	64	64	60
Fall rate, person-years	1.02	1.07	1.11	0.99
Relative risk of a fall (95% CI)	0.96 (0.67–1.36)		1.12 (0.79–1.59)	
Hazard ratio—time to first fall (95% CI)	0.97 (0.68–1.37)		1.14 (0.80–1.62)	

Note: There were no significant treatment differences (i.e., $P < .05$) for any of these variables.
* A higher score indicates better function.
CI = confidence interval.

patients were randomized, and most occurred more than 1 month postrandomization. Seven patients refused home assessments at 6 months. Thus, 6-month outcome measurements were obtained for 222 patients (91%).

Compliance with the single high dose of calciferol or placebo was 100%. Patients in the exercise group adhered to 82% of prescribed sessions (mean 24.6 of 30 sessions). Although the therapists tried to achieve a high intensity of resistance exercise in all patients, this was limited by the common complaint of muscle soreness, particularly in the first weeks of the program, and because patients had difficulty applying heavy ankle weights in the final weeks of the program. To reduce muscle soreness and back pain that occurred in the first few participants, the protocol was modified so that patients trained at an intensity of 30% to 40% of their 1RM for the first 2 weeks of the program. The mean exercise intensity at the end of training, expressed as a percentage of the patients' 1RM, was 51 ± 13%. Only 25% of the patients were able to reach a high intensity of exercise (greater than 60% of their 1RM). The participants succeeded in undertaking a progressive resistance training program, with the average training weight increasing from 5.8 ± 2.9 lb to 11.2 ± 5.5 lb during the 10-week program.

The efficacy of blinding was confirmed at the end of follow-up by asking the blinded assessors to guess each patient's treatment allocation. Correct guesses were less than chance (38%), indicating adequate blinding.

Resistance Exercise

There was no significant effect of resistance exercise on the primary measures of falls or HRQoL (Table 2) or on any of the secondary outcome measures (Table 3). The effects of resistance exercise on the change in scores from baseline to 3 months of the physical performance assessments are shown in Figure 2. In both groups, physical performance improved across all measures in the first 3 months of follow-up. However, the control group had greater improvement in mobility (timed up-and-go) than the exercise group (Wilcoxon *P*-value = .045).

Fall-related injuries did not differ between the two groups, but a difference existed for the endpoint of injuries and medical problems not related to falls. The resistance exercise group had an increased risk of musculoskeletal injury that required medical attention or resulted in limitation in ADLs for at least 2 days. (Eighteen people had musculoskeletal injuries in the exercise group, compared with five in the control group; RR = 3.6, 95% CI = 1.5–8.0.) Most of these events were episodes of back or knee pain that were directly attributable to the exercises. In addition, the resistance exercise group experienced a significant increase in self-reported fatigue, compared with controls, according to the Likert rating scale ($P = .002$), and the resistance exercise group had lower scores in the vitality domain (VT) of the SF-36. The mean VT score at 6-month follow-up was 48 (95% CI = 44–51) in the resistance exercise group, compared with 53 (95% CI = 49–57) in the control group.

In an exploratory subgroup analysis, no effect of resistance exercise was found in those patients who had high adherence (>80% of prescribed sessions completed) to the resistance exercise program.

Vitamin D

The dose of vitamin D was effective in increasing mean 25-OH-D levels at 3 and 6 months compared with placebo (active vs placebo, median change from baseline to 3 months = 9 ng/mL (95% CI = 7–11) vs 0 ng/mL (95% CI = −2–1)). Of the 43 patients in the active treatment group who had low 25-OH-D levels at baseline (<12 ng/mL), 95% had normal levels at 3 months. Nevertheless, despite this correction of vitamin D deficiency, there was a consistent lack of effect across all primary (Table 2) and secondary outcomes (Table 3 and Figure 2). Even in the subgroup of people with low baseline 25-OH-D levels (<12 ng/mL), vitamin D did not alter any of the physical performance measures, including maximum strength at 3 months (active vs placebo, median = 12.5 kg (95% CI = 10.5–13.9) vs 11.5 kg (95% CI = 9.0–13.9)).

DISCUSSION

Frailty is a condition or syndrome resulting from a multisystem reduction in physiological capacity not necessarily related to a specific single disease process that leads to a decline in physical performance.[30] Therefore, frailty indicates vulnerability and risk of disability and dependency.

Table 3. Comparison of Secondary Outcome Measures at 6-Month Follow-Up (N = 222)

Secondary Measures	Resistance Exercise (n = 112)	Attention Control (n = 110)	Between-Group Difference (95% CI)	Vitamin D (n = 108)	Placebo (n = 114)	Between-Group Difference Mean (95% CI)
36-item short form questionnaire, mean (95% CI)§						
Physical component score	35 (33–37)	37 (35–39)	−2 (−6–1)	35 (32–37)	37 (35–39)	−3 (−5–0)
Mental component score	49 (47–52)	51 (49–53)	−2 (−5–1)	50 (48–52)	51(48–53)	−1 (−4–2)
Physical function	36 (31–42)	42 (37–47)	−6 (−13–2)	36 (31–42)	42 (37–47)	−6 (−13–2)
Role-physical	51 (43–59)	59 (51–66)	−7 (−18–4)	50 (42–58)	60(52–67)	−10 (−20–1)
Bodily pain	64 (58–69)	69 (64–75)	−5 (−13–2)	65 (59–70)	68 (63–74)	−3 (−1–4)
General health	58 (53–62)	64 (59–68)	−6 (−12–0)*	60 (56–64)	61 (57–66)	−1 (−8–5)
Vitality	48 (44–51)	53 (49–57)	−5 (−11–0)*	48 (45–52)	52 (48–56)	−4 (−9–1)
Social function	74 (68–80)	76 (70–82)	−2 (−10–6)	73 (67–79)	77 (71–83)	4 (−12–5)
Role-emotional	78 (72–85)	84 (78–90)	−6 (−15–3)	81 (75–88)	81 (75–88)	0 (−9–9)
Mental health	74 (70–78)	78 (75–81)	−4 (−9–1)	75 (72–79)	77 (73–80)	−2 (−6–4)
Barthel index (range 0–20), median (95% CI)†§	19 (19–20)	20 (19–20)	0 (0–0)	20 (19–20)	20 (19–20)	0 (0–0)
Falls self efficacy scale (range 0–140), median (95% CI)†§	110 (105–116)	120 (110–127)	−5 (−13–0)	111 (106–119)	118 (109–126)	−3 (−10–3)
Adelaide activities profile), median (95% CI)†						
Domestic chores, (range 0–24)§	11 (6–14)	12 (9–13)	0 (−2–2)	11 (7–13)	12 (10–14)	−1 (−3–1)
Household maintenance, (range 0–21)§	6 (3–7)	6 (5–6)	0 (−2–1)	6 (3–6)	6 (5–7)	0 (−2–0)
Service to others, (range 0–15)§	3 (3–4)	3 (3–4)	0 (−1–1)	3 (3–4)	4 (3–4)	0 (−1–0)
Social activities, (range 0–12)§	3 (3–4)	4 (3–4)	0 (−1–1)	3 (3–4)	3 (3–4)	0 (0–1)
Quadriceps strength, kg, median (95% CI)†‡§	12 (11–14)	12 (11–14)	0 (−2–1)	13 (11–15)	12 (11–14)	1 (−1–2)
Timed walking test, seconds, median (95% CI)†‖	6.0 (5.7–6.6)	5.7 (5.0–6.4)	−0.4 (−1–0.3)	5.9 (5.5–6.8)	5.9 (5.2–6.4)	−0.3 (−0.9–0.4)
Timed up and go, seconds, median (95% CI)†‖	18 (17–22)	16 (14–19)	−2 (−4–1)	18 (15–20)	18 (15–19)	0 (−3–2)
Berg balance test (range 0–56), median (95% CI)†§	43 (39–45)	45 (41–46)	−1 (−4–2)	43 (40–46)	45 (40–46)	−1 (−3–2)

* Wilcoxon rank-sum test significant at the 5% level.
† Median differences and 95% confidence interval (CI) calculated using method of Campbell and Gardner.[26]
‡ Data presented as the mean of both legs.
§ A higher score indicates better performance.
‖ A lower score indicates better performance.

Given that frailty is a common and potentially modifiable condition in older people, it is an appropriate focus for prevention, rehabilitation, and public health strategies.

This study was designed with the expectation that two practicable interventions targeted at a key component of frailty—muscle weakness—could improve the physical function and health of recently hospitalized frail older patients. Unfortunately, neither the home-based quadriceps resistance exercise program nor the single high dose of vitamin D reduced the risk of falls or led to an improvement in physical health or performance over natural recovery from illness. Moreover, the results suggest that this form of resistance exercise was harmful to patients, as evidenced by the higher incidence of musculoskeletal injuries in this group than in controls.

This is one of the largest randomized trials for either of these interventions, and it had adequate power to detect modest effects on key outcomes. The design of this study is also more rigorous than most previous trials for either intervention. The use of concealed randomization allocation, intention-to-treat analysis, blinded outcome assessors, and well-validated measures all reduced the likelihood that bias affected the results for either intervention. Unlike many previous studies of resistance exercise, adverse events

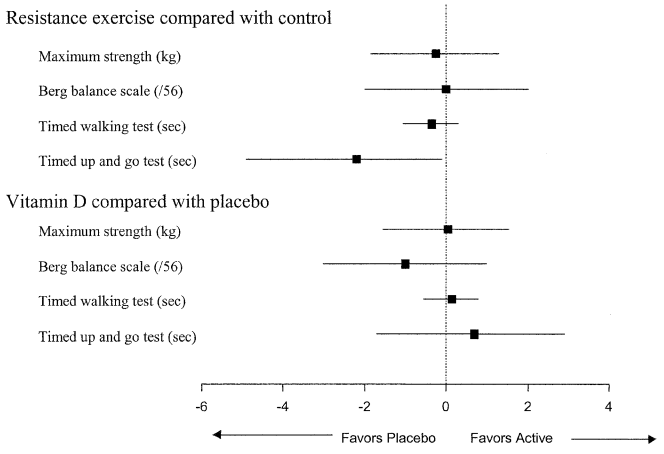

Figure 2. Comparison of physical performance measures in treatment and control groups at 3-month follow-up. Points are median differences between groups for change in measures from baseline to 3 months. Bars are 95% confidence intervals. Difference is significant where confidence intervals do not overlap the vertical line.

were clearly defined and systematically monitored in this trial. Because the physical therapists in this study had equal contact with patients in each treatment group, it is possible that the patients derived a therapeutic benefit from this contact that could have decreased the difference in the treatment effect between groups. However, the use of an attention control group strengthens the validity of these findings about the true effect of resistance exercise on recovery.

Several studies of home-based strength training exercises have been undertaken that have included frail but medically stable older people.[31–33] With the exception of the Fitness Arthritis and Seniors Trial study[32] and a recently published trial,[34] the exercises used have generally been of a low intensity and have used elastic bands instead of weights. Compared with the FITNESS trial, the participants in these studies were also slightly younger and, in the two trials that measured gait speed,[31,33] appeared to have faster mobility. Given that these studies have shown modest positive effects on strength and physical function, the home-based program of high-intensity resistance exercise was considered to be practical and beneficial for older people. Yet no significant effect was found for physical health and performance in this study. There are several possible reasons for this.

First, the exercise program might have been inadequate to achieve the desired gains in strength and subsequent outcomes. The study was designed so that the interventions could be easily incorporated into existing community rehabilitation services. As such, a simple exercise program of limited duration was used. The authors chose a strength training program that specifically targeted the quadriceps muscles because of their pivotal role in mobility, particularly standing, transfers, and walking, and because the exercise could be undertaken safely in a seated position. Exercise to a wider range of muscle groups including the hips and shoulders adds complexity to a program and therefore has the potential to reduce adherence and increase the risk of injury in frail and older patients at home. Because compliance with exercise programs is known to decrease in older people when more exercises are added,[35] the decision was made to limit this program to one exercise performed at a high intensity. However, it is possible that an exercise program involving more muscle groups or performed for a longer duration would have resulted in greater improvements in performance. Also, a different form of exercise might have been more effective, because there is evidence that exercise in a weight-bearing position is more effective in reducing falls.[6] It is possible that a different mode of resistance training would have resulted in larger functional gains, because seated resistance training with ankle weights does not overload the quadriceps muscles through the full range of motion and therefore might limit carryover to some functional tasks.

Second, use of high-intensity exercise in a home-based program might have had a greater risk of injuries and adverse events in these patients than a program of lower intensity. Although resistance exercises adapted from published protocols were used, most high-intensity programs for older people have been conducted under highly supervised conditions, often in clinics, and with specialized equipment.[8] There is limited information about the relative safety of the different forms of exercise, although there is some evidence to indicate that cuff weights are associated with more injuries than resistance exercise involving machines.[36] Although high-intensity exercise might offer benefits to frail older people in supervised gym-based programs, these data would suggest that the risks associated with this form of high-intensity resistance exercise appear to outweigh any potential benefits at home.

Third, the population was different from most previous studies of resistance exercise, because it involved older people who had been recently ill and hospitalized. There is strong rationale for attempting to increase the muscle strength of older people after they leave the hospital, because hospitalization often results in rapid declines in strength and function, but the exercise program appeared to impair rather than enhance recovery, with increased levels of fatigue and injury in the exercise group. One recent study showed that a complex exercise program of balance, functional training, and resistance exercise had positive effects on function and physical performance of older people attending a geriatric out-patient clinic after discharge from hospital.[37] Nevertheless, in that study, the resistance exercise component of the program involved the use of specialized exercise machines, and all sessions were supervised. It would seem therefore that it is inappropriate for frail older people to attempt this high-intensity resistance exercise without supervision while they are in a period of recovery from illness and readjusting to their home environment.

With regard to vitamin D, previous clinical trials that have examined effects on physical function have reported mixed results. Three trials, two using daily calciferol[16,38] and the other using a vitamin D analog,[17] showed no effect on physical performance or function. Three other trials showed a reduction in falls or improved physical function when vitamin D and calcium supplements were compared with calcium supplementation alone in older people with low vitamin D levels.[18,39,40]

In this study, there was no effect of vitamin D supplementation on the physical function of older people, even though the majority of patients were deficient in this vitamin; no effect was observed even in those patients with low 25-OH-D levels. However, given the smaller numbers in this latter subgroup, it cannot be excluded that there was a modest effect of vitamin D supplementation in people with extremely low vitamin D (25-OH-D) levels. It seems plausible that calcium needs to be added to vitamin D to produce a beneficial effect on physical performance, but this needs to be confirmed in further clinical trials.

This trial was one of the first studies to attempt resistance training as a therapeutic rehabilitation intervention. Although most previous studies have involved medically stable older people, this trial targeted frail older people who had been recently ill and in the hospital. In addition, it used a simple program that could be implemented in most healthcare environments. Given the pragmatic design and the broad characteristics of patients recruited across multiple centers, the results can be generalized to the wider population of frail older people. Although the benefits of physical activity on health are well established[7] and some exercise programs have been shown to reduce falls in older people,[6] these data indicate that a cautious approach to high-intensity resistance exercise for frail older people is warranted. In view of aging populations around the world, further clinical trials and meta-analyses are required to establish the effectiveness and safety of simple and widely applicable exercise programs for frail older people in rehabilitation and community settings.

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REFERENCES

1. Hughes VA, Frontera WR, Wood M et al. Longitudinal muscle strength changes in older adults: Influence of muscle mass, physical activity and health. J Gerontol A Biol Sci Med Sci 2001;56A:B209–B217.
2. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. N Engl J Med 1988;319:1701–1711.
3. Guralnik JM, Ferrucci L, Simonsick EM et al. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. N Engl J Med 1995;332:556–561.
4. Buchner D, de Cress M, Lateur B et al. The effect of strength and endurance training on gait, balance, fall risk and health services use in community-living older adults. J Gerontol A Bio Sci Med Sci 1997;52A:M218–M224.
5. Gillespie LD, Gillespie WJ, Robertson MC et al. Interventions for Preventing Falls in Elderly People. In: Gillespie WJ, Swiontkowski M, Madhok R et al., eds. The Cochrane Library, Issue 3. Oxford: Update Software, 2002.
6. Robertson MC, Devlin N, Gardner MM et al. Effectiveness and economic evaluation of a nurse delivered home exercise programme to prevent falls. 1: Randomised controlled trial. BMJ 2001;322:697–701.
7. Mazzeo R, Cavanagh P, Evans W et al. Exercise and physical activity in older adults. Med Sci Sports Exerc 1998;30:992–1008.
8. Fiatarone MA, O'Neill EF, Doyle Ryan N et al. Exercise training and nutritional supplementation for physical frailty in very elderly people. N Engl J Med 1994;330:1769–1775.
9. Nelson ME, Fiatarone MA, Morganti CM et al. Effects of high-intensity strength training on multiple risk factors for osteoporotic fractures: A randomized controlled trial. JAMA 1994;272:1909–1914.
10. Mahoney JE. Acute hospital care—immobility and falls. Clin Geriatr Med 1998;14:699–726.
11. Sager MA, Franke T, Inouye SK et al. Functional outcomes of acute medical illness and hospitalization in older persons. Arch Intern Med 1996;156:645–652.
12. Stein MS, Wark JD, Scherer SC et al. Falls related to vitamin D and parathyroid hormone in an Australian nursing home and hostel. J Am Geriatr Soc 1999;47:1195–1201.
13. Reid IR. Therapy of osteoporosis: Calcium, vitamin D, and exercise. Am J Med Sci 1996;312:278–286.
14. Gillespie WJ, Avenell A, Henry DA et al. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis (Cochrane Review). In: Gillespie WJ, Swiontkowski M, Madhok R et al., eds. The Cochrane Library, Issue 3. Oxford: Update Software, 2002.
15. Simpson RU, Thomas GA, Arnold AJ. Identification of 1, 25-dihydroxyvitamin D3 receptors and activities on muscle. J Biol Chem 1985;260:8882–8891.
16. Corless D, Dawson E, Fraser F et al. Do vitamin D supplements improve the physical capabilities of elderly hospital patients? Age Ageing 1985;14:76–84.
17. Grady D, Halloran B, Cummings S et al. 1,25-Dihydroxyvitamin D3 and muscle strength in the elderly: A randomized controlled trial. J Clin Endocrinol Metab 1991;73:1111–1117.
18. Pfeifer M, Begerow B, Minne HW et al. Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. J Bone Miner Res 2000;15:1113–1118.
19. Winograd CH, Gerety MB, Chung M et al. Screening for frailty: Criteria and predictors of outcomes. J Am Geriatr Soc 1991;39:778–784.
20. Ware JD. SF-36 Physical and Mental Health Summary Scales: A User's Manual. Boston, MA: The Health Institute, 1994.
21. Richardson J, Stratford P, Cripps D. Assessment of reliability of the handheld dynamometer for measuring strength in healthy older adults. Physiother Theory Pract 1998;14:49–54.
22. Berg KO, Wood-Dauphinee SL, Williams JI et al. Measuring balance in the elderly: Validation of an instrument. Can J Public Health 1992;83:7–11.
23. Podsiadlo D, Richardson S. The timed 'Up and Go': A test of basic functional mobility for frail elderly persons. J Am Geriatr Soc 1991;39:142–148.
24. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
25. Hachisuka K, Ogata H, Ohkuma H et al. Test-retest and inter-method reliability of the self-rating Barthel index. Clin Rehabil 1997;11:28–35.
26. Hill KD, Schwarz JA, Kalogeropoulos AJ et al. Fear of falling revisited. Arch Phys Med Rehabil 1996;77:1025–1029.
27. Clark MS, Bond MJ. The Adelaide Activities Profile: A measure of the lifestyle activities of elderly people. Aging Clin Exp Res 1995;7:174–184.
28. Day SJ, Graham DF. Sample size estimation for comparing two or more treatment groups in clinical trials. Stats Med 1991;10:33–43.
29. Campbell MJ, Gardner MJ. Calculating confidence intervals for some nonparametric analyses. BMJ 1988;296:1454–1456.
30. Campbell AJ, Buchner DM. Unstable disability and the fluctuations of frailty. Age Ageing 1997;26:315–318.
31. Chandler JM, Duncan PW, Kochersberger G et al. Is lower extremity strength gain associated with improvement in physical performance and disability in frail, community-dwelling elders? Arch Phys Med Rehabil 1998;79:24–30.
32. Ettinger WH Jr, Burns R, Messier SP et al. A randomized trial comparing aerobic exercise and resistance exercise with a health education program in older adults with knee osteoarthritis. The Fitness Arthritis and Seniors Trial (FAST). JAMA 1997;277:25–31.
33. Jette AM, Lachman M, Giorgetti MM et al. Exercise—it's never too late: The strong-for-life program. Am J Public Health 1999;89:66–72.
34. Baker KR, Nelson ME, Felson DT et al. The efficacy of home based progressive strength training in older adults with knee osteoarthritis: A randomized controlled trial. J Rheumatol 2001;28:1655–1665.
35. Henry KD, Rosemond C, Eckert LB. Effect of number of home exercises on compliance and performance in adults over 65 yrs of age. Phys Ther 1998; 78:270–277.
36. Judge JO, Whipple RH, Wolfson LI. Effects of resistance and balance exercises on isokinetic strength in older persons. J Am Geriatr Soc 1994;42:937–946.
37. Hauer K, Rost B, Rutschle K et al. Exercise training for rehabilitation and secondary prevention of falls in geriatric patients with a history of injurious falls. J Am Geriatr Soc 2001;49:10–20.
38. Johnson KR, Jobber J, Stonawski BJ. Prophylactic vitamin D in the elderly. Age Ageing 1980;9:121–127.
39. Bischoff HA, Staehelin HB, Dick W et al. Fall prevention by vitamin D and calcium supplementation: A randomized controlled trial. J Bone Miner Res 2001;16:S163.
40. Gloth FM III, Smith CE, Hollis BW et al. Functional improvement with vitamin D replenishment in a cohort of frail, vitamin D–deficient older people. J Am Geriatr Soc 1995;43:1269–1271.

APPENDIX 1

The FITNESS study group Steering Committee: Craig Anderson, Nancy Latham, Anne Moseley, and Ian Cameron; Independent Data and Safety Monitor: Phillippa Poole; Study and Data Management Committee: Jan Douglas, Rina Prasad, Deanne Douglas, Aimee Santos, and Terry Holloway; statisticians: Derrick Bennett, Joanna Broad, Kristie Carter, and Arier Lee; and research field staff: Sherilyn Coulston, Sue Hawkins, Jen Hughes, Stephanie Lanzarone, Keri Lockwood, Faith Mahony, John Parsons, Caroline Stretton, Edmund Santos, and Lee Taylor. The clinical centers involved were Auckland Hospital, North Shore Hospital, and Middlemore Hospital in Auckland, New Zealand, and Hornsby Ku-ring-gai Hospital and the Royal Rehabilitation Center Sydney in Sydney, Australia.