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Original Study

Effects of High-Intensity Progressive Resistance Training and Targeted Multidisciplinary Treatment of Frailty on Mortality and Nursing Home Admissions after Hip Fracture: A Randomized Controlled Trial

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A B S T R A C T

Rationale: Excess mortality and residual disability are common after hip fracture.
Hypothesis: Twelve months of high-intensity weight-lifting exercise and targeted multidisciplinary interventions will result in lower mortality, nursing home admissions, and disability compared with usual care after hip fracture.
Design: Randomized, controlled, parallel-group superiority study.
Setting: Outpatient clinic
Participants: Patients (n = 124) admitted to public hospital for surgical repair of hip fracture between 2003 and 2007.
Intervention: Twelve months of geriatrician-supervised high-intensity weight-lifting exercise and targeted treatment of balance, osteoporosis, nutrition, vitamin D/calcium, depression, cognition, vision, home safety, polypharmacy, hip protectors, self-efficacy, and social support.
Outcomes: Functional independence: mortality, nursing home admissions, basic and instrumental activities of daily living (ADLs/IADLs), and assistive device utilization.
Results: Risk of death was reduced by 81% (age-adjusted OR [95% CI] = 0.19 [0.04–0.91]; $P < .04$) in the HIPFIT group (n = 4) compared with usual care controls (n = 8). Nursing home admissions were reduced by 84% (age-adjusted OR [95% CI] = 0.16 [0.04–0.64]; $P < .01$) in the experimental group (n = 5) compared with controls (n = 12). Basic ADLs declined less ($P < .0001$) and assistive device use was significantly lower at 12 months ($P = .02$) in the intervention group compared with controls. The targeted improvements in upper body strength, nutrition, depressive symptoms, vision, balance, cognition, self-efficacy, and habitual activity level were all related to ADL improvements ($P < .0001$–$.02$), and improvements in basic ADLs, vision, and walking endurance were associated with reduced nursing home use ($P < .0001$–$.05$).
Conclusion: The HIPFIT intervention reduced mortality, nursing home admissions, and ADL dependency compared with usual care. Australian New Zealand Clinical Trials Registry (ACTN12605000164695).

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Ethics approval was granted by the University of Sydney Human Research Ethics Committee and Sydney South West Area Health Service Ethics Review Committee in 2002. This trial was registered with the Australian New Zealand Clinical Trials Registry (ACTN12605000164695).

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Approximately 1.6 million hip fractures occur worldwide annually and are predicted to reach up to 6.3 million by 2050,[1] with increases geographically distinct.[2–4] One-year mortality after hip fracture is significantly elevated, and this excess risk persists for at least 10 years.[5] The risk of institutionalization after hip fracture is 5 times greater than for age- and sex-matched individuals.[6] We have reported that 80% of recurrent fallers preferred *death* to nursing home residence subsequent to hip fracture,[7] emphasizing the substantial personal and societal cost of this outcome.

We,[8] and others[9,10] have identified a large burden of potentially treatable risk factors for mortality, frailty, and recurrent injurious falls in this cohort. However, current clinical treatment pathways still focus primarily on repair and rehabilitation of the fracture itself rather than the underlying frailty.[11] Few physical therapists prescribe robust resistance training to improve muscle strength,[12] despite its recognized role in osteoporotic fracture and frailty. Poor outcomes may theoretically be improved via inclusion of robust strategies designed to target modifiable predictors of frailty; however, as recent systematic reviews document,[13–15] most clinical trials have been uni-modal and/or short term, there is no consensus on optimal long-term treatment. No interventions have yet been reported to reduce long-term nursing home admissions. This recognized controversy both forms the rationale and supports the clinical equipoise of this trial.[13]

Therefore, we designed the Hip Fracture Intervention Trial (HIPFIT) to test a novel, evidence-based treatment strategy to improve long-term outcomes after hip fracture by targeting sarcopenia with 12 months of high-intensity progressive resistance training. Concomitantly, we diagnosed and treated the major *previously identified* and potentially modifiable[7,16–30] predictors of frailty, mortality, and nursing home admission in this cohort. We hypothesized that patients randomized to the HIPFIT intervention would have improved functional outcomes over 12 months, defined as reduced mortality, nursing home use, need for assistive devices/persons, and impairment in activities of daily living (ADLs) compared with usual-care controls. Furthermore, we hypothesized that greater improvements in the targeted deficits (strength, balance, sarcopenia, depression, self-efficacy, nutritional status, vision, cognition, social support) would occur, and would explain significant portions of the variance in nursing home use and disability over 12 months.

Methods

Trial Design

This was a randomized, parallel-group superiority trial with an intention-to-treat analytic strategy, irrespective of dropout or discontinuation of intervention.[31] There were no missing data for primary outcomes of mortality and nursing home admissions, and missing data for other primary outcomes were handled via imputation as recommended.[32] We conducted blinded assessment of 2 disability outcomes: the Functional Independence Measure (FIM)[33] and the Assessment of Living Skills and Resources (ALSAR)[34] and unblinded assessment of other outcomes. Written informed consent was obtained from each participant. Ethics approval was granted by the University of Sydney Human Research Ethics Committee and Sydney South West Area Health Service Ethics Review Committee in 2002. This trial was registered with the Australian New Zealand Clinical Trials Registry (ACTN12605000164695).

Participants and Recruitment Method

Participants were recruited from all patients admitted to a 700-bed public teaching hospital affiliated with the University of Sydney, Australia, as well as surrounding geriatric and rehabilitation hospitals, for surgical repair of minimal-trauma hip fracture.

Broad inclusionary criteria included age older than 55 years, and sufficient cognitive ability and English-language skills sufficient to understand the informed consent process. Exclusionary criteria included only terminal illness, pathological fracture, no surgical repair, or geographical distance precluding participation.

Interventions

The experimental participants were prescribed high-intensity progressive resistance training (80% of peak upper and lower body muscle strength) supervised by research staff in the outpatient clinic of the aged care hospital 2 days per week for 12 months as the core treatment. Weight lifting began after standard physiotherapy ceased, approximately 6 to 8 weeks after fracture. Other intervention arms began as soon as assessed in hospital or at home (see Table 1). All interventions were coordinated by the research staff via weekly interdisciplinary team meetings.

All experimental participants received a monthly phone call and a monthly residential visit by their trainer. Thus, total experimental contacts prescribed in addition to usual care averaged 80 supervised exercise training sessions, 10 home visits, and 10 phone calls over 12 months.

Control Group Usual Care Treatment

All participants underwent standard care as offered for hip fracture in the area health service, including orthogeriatric care, rehabilitation service, other medical and allied health consultation as required, and physiotherapy.

Primary Outcomes

Date and cause of death (if relevant), nursing home residence at time of acute and rehabilitation hospital discharge, 4 months, and 12 months were extracted from medical records and/or family interviews, with no missing data. Participants who resided in a nursing home at any 1 or more of these 4 assessment time points were classified as having used a nursing home during the year.

The Katz index of ADLs[35] was used to reflect *prefracture* basic ADL function, and Part C (ADL) of the National Health and Nutrition Examination Survey (NHANES) I Epidemiologic Follow-Up Study, 1986[36] reflected *prefracture* ADL/instrumental ADL (IADL) function. The FIM[33] and ALSAR[34] (reflecting *postfracture* ADL and IADL function, respectively) were administered by certified occupational therapists blinded to group allocation, at the place of residence following discharge from hospital after index hip fracture at baseline, and at 4 and 12 months.

Clinical Characteristics

Health status and demographics

Medical records were abstracted to collect medical and surgical history and postoperative care. Demographic information was collected via interview.

Nutritional status

Serum albumin, 25-hydroxyvitamin D_3 level, total lymphocyte count, the Mini-Nutritional Assessment,[37] score and anthropometry

(height, fasting body weight, and circumference measures) were collected. Bioelectrical impedance analysis was used for body composition classification.

Physical activity history and physical capacities

Prefracture habitual physical activity level was assessed via the Harvard Alumni Physical Activity Index[38] and the Physical Activity Scale for the Elderly.[39] Peak isometric elbow extension (triceps), hip abduction, and knee extension strength, 6-minute walk distance, habitual and maximal gait velocity, and static and dynamic balance were assessed,[40–42] as well as vision (acuity, contrast sensitivity, depth perception).[43]

Neuropsychological/Social Characteristics

Cognition was assessed via the Mini-Mental State Examination (MMSE), depressive symptoms via the Geriatric Depression Scale (GDS), fear of falling via the Tinetti Falls Efficacy Scale,[44] confidence for functional independence via the Self-efficacy Gauge,[45] satisfaction with social support network via the 11-item Duke Social Support Index,[46] and health-related quality of life via the Medical Outcomes Study Short-Form Health Survey (SF-36 v. 1).

Randomization and Masking

Participants were individually randomized to 1 of 2 parallel groups in a 1:1 ratio, stratified by gender via computer-generated randomly permuted blocks (available at www.randomization.com). Masked randomization assignments were generated by an offsite investigator and sent electronically to research assistants, who then distributed the written treatment assignments to participants in sequentially numbered opaque sealed envelopes within 1 to 2 days of consent.

Blinding

The postfracture disability outcomes (FIM and ALSAR scores) were collected by an otherwise uninvolved blinded assessor after discharge. All laboratory data were blindly analyzed. All other outcomes (prefracture disability, health status, strength, vision, physical performance, body composition, psychosocial scales) were collected by unblinded research assistants.

Power Calculations

Sample size estimate was driven by hypothesized differences between the experimental and control participants in the primary outcome: nursing home residential status in the 12 months after fracture. Estimates of nursing home residence at 12 months in controls were derived from the most recently published figures from the Northern Sydney Area Health Service across 5 different hospitals at the time the trial was planned in 2001.[47] Estimates of treatment effect were based on data from the 5 randomized controlled trials that had assessed residential status as an outcome after hip fracture interventions.[29,48–51] In these 5 studies, the mean reduction in nursing home residence in the experimental group was 30% ± 22% compared with the control condition. We conservatively proposed a 33% reduction in the rate of nursing home residence after hip fracture (ie, from the 33% control rate to 22% in the experimental group). Setting alpha at 0.05 and beta at 0.20, 258 subjects were estimated required per group for nursing home use (total n = 516) using the G*Power computer program (version 3.1.22009) (http://www.psycho.uni-duesseldorf.de/aap/projects/gpower/). The final sample size (n = 126) was smaller than planned because of significant funding reductions and fewer numbers of hip fractures than projected by the area health service report during the years of enrollment[47]; however, post hoc power calculations indicated that we had achieved greater than 99% power for these primary outcomes (nursing home admission and mortality) with the sample size recruited.

Statistical Methods

Data were assessed for normality visually and statistically, and log transformed if necessary for use with parametric statistics. Missing data at any time point were imputed via the maximum expectation algorithm in SPSS (version 17; SPSS, Chicago, IL), using age, data at other time points, and group assignment as predictors. Categorical outcomes (nursing home residence, death) were used as events to calculate relative and absolute risk reduction, number needed to treat, and adjusted odds ratios (95% confidence intervals [CIs]) via logistic regression models adjusted for age (selected a priori as covariate based on previous literature). Time and group × time interactions for continuous outcomes were analyzed via repeated measures analysis of variance for normally distributed or logged variables. Wilcoxon signed rank tests and analysis of covariance models of change scores adjusted for baseline value were substituted if log transformation was not possible. Adjusted mean differences and relative effect sizes (calculated as change in treatment group minus change in control group divided by pooled standard deviation, corrected for sample size [Hedge's bias corrected ES]) were calculated for continuous outcomes. Relationships between baseline characteristics or change scores and study outcomes were performed via analysis of variance, logistic, or linear regression models as appropriate. All analyses were performed using StatView Version 5.0 (SAS Institute Inc., Cary, NC) or SPSS, v. 18 (IBM-SPSS, Inc.) and procedures of Armitage and Berry.

Results

Flow of Participants

Participants were recruited between February 2003 and April 2007, closing when funding ceased. All but one hip fracture patient admitted during recruitment (773/774; 99.9%) were assessed for eligibility, and 47% (124) of the 262 potentially eligible hip fracture patients consented (Figure 1). Hip fracture patients who were ineligible (n = 512), eligible but refused (n = 138), and consented (n = 124) were similar in age (79, 80, and 79 years, respectively; $P = .79$) and gender (67%, 67%, and 69% female; $P = .53$).

Nine (15%) and 4 (6%) experimental and control subjects respectively ($P = .14$) dropped out at a median of 24 days (1–348 days), but mortality and nursing home status were obtained in 100% of the cohort.

Baseline Participant Characteristics and Acute Hospital Treatment

Baseline characteristics of participants and details of initial hospitalization are shown in Tables 1 and 2. There were no statistically significant or clinically meaningful differences between groups in any characteristic.

Primary Outcomes

Mortality

Four (6.5%) experimental subjects and 8 (12.9%) controls died over 12 months. Mortality rate was reduced by 81% (age-adjusted odds ratio [OR] [95% CI] = 0.19 [0.04, 0.91]; $P < .04$) in the experimental group compared with controls (see Table 3 for absolute and

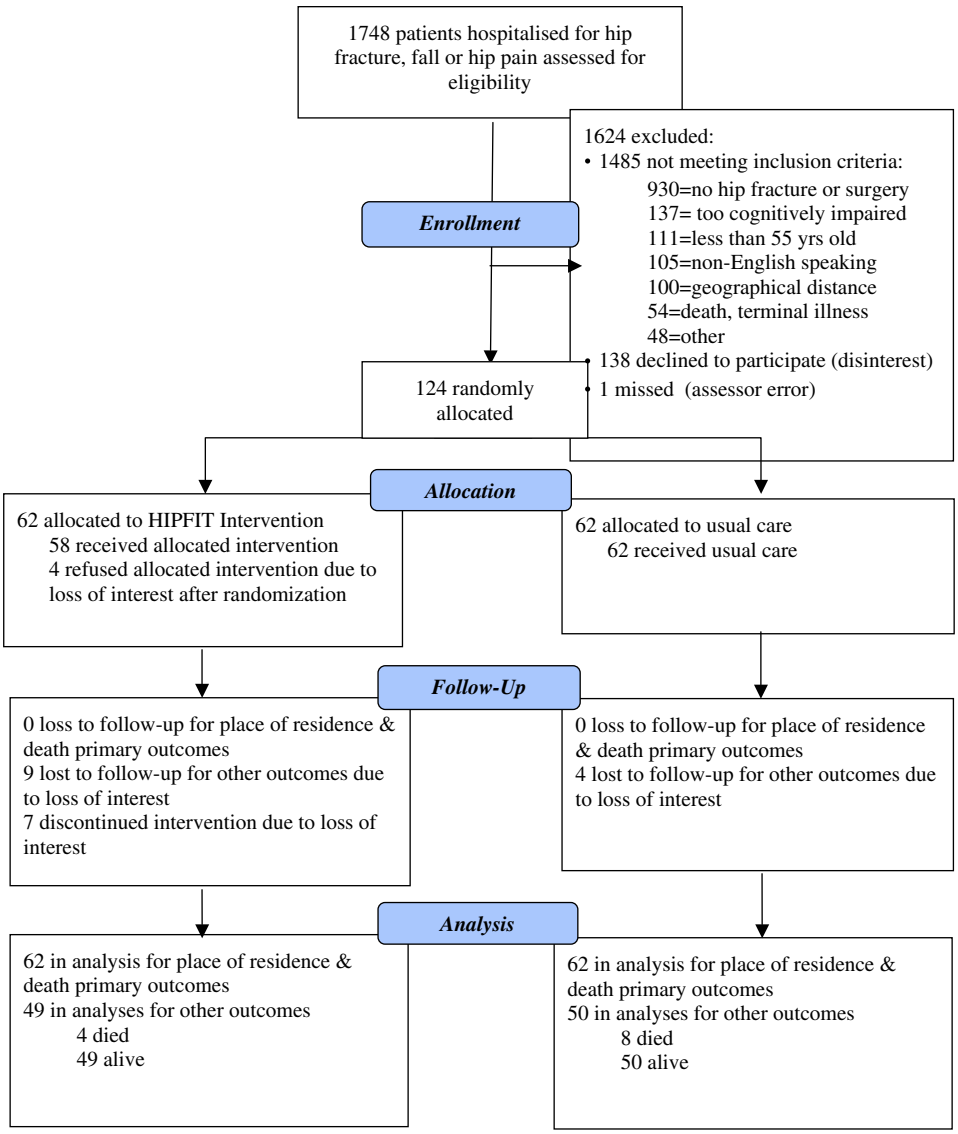

Fig. 1. Flow of Participants

adjusted risk reductions and number needed to treat). Cause of death was attributed to cardiovascular events (n = 4 control, 1 intervention), infection (n = 2 control, 1 intervention), cancer (n = 2 intervention), or unknown (n = 2 control), with the number of events precluding survival analysis or intergroup statistical comparisons of causality.

Nursing home use

Five (8.1%) experimental participants and 12 (19.4%) controls resided in a nursing home during at least 1 of the assessment time points in the year after fracture. The odds of requiring a nursing home at any time during the year were reduced by 84% (age-adjusted OR [95% CI] = 0.16 [0.04, 0.64]; $P < .01$] in the experimental group compared with controls (see Table 3). Similarly, risk for the commonly reported combined end point of death *or* any nursing home use (ie, "poor outcome"[14,52]) was 82% lower in the experimental group (age-adjusted OR [95% CI] = 0.18 (0.05, 0.59); $P = .005$].

Predictors of nursing home use

At baseline, older age ($P < .001$), as well as worse age-adjusted cognition ($P < .02$), ADL/IADLs (Katz, NHANES, FIM, and ALSAR scores; $P = .04–.0001$), physical activity level ($P < .02$), 6-minute walk distance ($P < .02$), and fear of falling ($P < .0001$) were each predictive of nursing home use across all participants. Over time, greater age-adjusted declines in Katz ADL scores (total, continence, bathing, transferring, and dressing; $P < .01–.0001$), vision-contrast sensitivity ($P < .001$), and less improvement in 6-minute walk distance ($P < .05$) were each significantly associated with greater nursing home use. Similarly, smaller improvements in triceps strength ($P = .08$), maximal gait velocity ($P = .07$), satisfaction with social support ($P < .08$), and nutritional index ($P < .09$) tended to predict nursing home use.

ADLs and IADLS and use of assistive devices

The experimental subjects used fewer assistive devices for mobility, function, and safety at 12 months compared with controls ($P < .01$), as hypothesized (Table 4). The experimental group had significantly less decline in Katz ADL toileting and transferring than controls at 12 months, with a similar trend for overall Katz score. Beneficial reductions in total Katz score ($r = -0.25$, $P = .02$), toileting ($r = -0.26$, $P = .02$) and transferring ($r = -0.30$, $P < .008$) were all significantly related to increases in triceps strength, but not

to any other physical or neuropsychological changes assessed, including leg strength. When the analysis of covariance models of ADL transfer and toileting changes were adjusted for changes in triceps strength, the intervention group effect was attenuated and no longer significant ($P = 0.43$ and 0.54, respectively), suggesting that these strength improvements partially mediated the ADL improvements associated with the HIPFIT intervention.

The FIM, NHANES, and ALSAR ADL/IADL scores did not change differentially between groups over time (Table 4).

Adverse Events

There were no major adverse events attributable to the study. No dropouts or deaths were related to adverse events.

Discussion

Interpretation

One year of high-intensity progressive resistance training combined with a targeted multifactorial intervention directed at major predictors of frailty reduced mortality and nursing home use over 12 months by more than 80% after hip fracture. Additionally, independence in toileting and transferring and assistive device usage were significantly improved by HIPFIT compared with usual care.

Notably, usual care included inpatient orthogeriatric and allied health consultation, followed by 6 to 12 weeks of standard inpatient/outpatient physical therapy. Usual care, however, did *not* include weight-lifting exercise or robust and progressive balance training, long-term nutritional support, treatment of depression, cognitive impairment, home evaluation and enhancement of social support and self-efficacy, correction of visual impairment, or use of hip protectors. As hypothesized, improvements in upper body strength, walking endurance, vision,[43,53] and ADL independence partially mediated the reduced need for institutional care. No other clinical trial has provided 12 months of high-intensity, whole-body, progressive resistance and balance training and nutritional supplementation after hip fracture, integrated with multidisciplinary geriatric care. We suggest that this novel feature of HIPFIT may underlie the clinically relevant benefits observed, compared with 1 year of home-based exercise, for example.[54] Future trials including all health care use and cost reductions achieved with similar interventions are warranted.

Effects on Mortality and Nursing Home Use

Age-adjusted mortality was 81% lower in the intervention group by 12 months. The explanation for this reduced mortality rate is likely multifactorial. All participants received similar acute hospital/perioperative and early rehabilitative care, and had similar lengths of stay and complication rates, so it is unlikely that these perioperative factors explain the risk reduction. Given the previously demonstrated associations of mortality with cognition, depression, nursing home use, and malnutrition after hip fracture,[5] it is possible that our targeting and improvement in all of these outcomes contributed to the lower risk of death in experimental subjects.

Long-term reductions in *both* mortality and nursing home residence after hip fracture have not been reported previously. Only the study by Kennie et al[48] in 1988 of comprehensive geriatric consultation in the United Kingdom has demonstrated significantly reduced nursing home residence after fracture. In that study, however, nursing home residence was determined *only* at acute hospital discharge, and the greater cognitive and functional impairment at baseline in the control group (which were not adjusted for), limit the interpretation of that study. Following evidence-based clinical pathways perioperatively has also *not* been shown to significantly reduce new nursing home admissions or 4-month mortality.[15] A recent meta-analysis of trials of comprehensive multidisciplinary care, pooling results across 2498 patients in 13 trials,[52] similarly showed no statistically significant difference between intervention and control groups for “poor outcome” (death or nursing home residence), mortality, nursing home residence, or hospital readmission. Similarly, high-dose vitamin D supplementation, and/or extended physiotherapy have recently been reported to reduce rehospitalizations and falls, respectively, but not nursing home use or mortality over 1 year.[55] The theoretically grounded[7,16–30] targeting and prioritization of sarcopenia, nutrition, and other treatments to address frailty for the entire year may have contributed to observed clinical benefits.

Effects on Activities of Daily Living

Basic ADL improvements were observed compared with pre-fracture status in the HIPFIT group, and the effect sizes were moderate to very large for transferring and toileting independence as well as need for assistive devices. Upper-body strength changes were directly and significantly related to physiologically plausible ADL improvements (total, transferring, and toileting), and tended to predict nursing home use. This linkage is logical, given the increased demand on the upper body when lower extremity impairment and pain are present, such as after hip fracture and surgery. Dependence in toileting and transferring is extremely prevalent at nursing home admission in other studies,[56] lending further support to our findings.

By contrast, we did not find a significant improvement in IADL function attributable to the HIPFIT intervention, with both groups changing similarly over time, compared with either pre- or post-fracture status. Such improvement may require even more robust augmentation of social support, muscle mass, walking endurance, and translation of physiological gains into functional activities than achieved in this study.

Limitations

One limitation of this study is the smaller than planned sample size owing to funding reductions and fewer than expected hip fractures in Australia during the recruitment period,[57] similar to trends in Canada[58] and France.[59] The much greater than expected effect on mortality and nursing home admission (84% observed vs 33% hypothesized), however, allowed us to achieve a very high level of statistical power for these primary outcomes (>99%) despite the reduced sample size. Although the substantial risk reductions and low numbers needed to treat support the clinical meaningfulness of these findings, we acknowledge that the confidence intervals for nursing home and mortality risk reductions are wide, and the total number of events is limited by the sample size.

Second, we cannot state which intervention components were responsible for beneficial outcomes, as the study was intentionally *not* designed to evaluate the individual effects of each treatment arm.

Generalizability

The generalizability of our findings is supported by the following: (1) the demographic similarity of the HIPFIT cohort to noneligible/noninterested hip fracture patients screened, (2) clinical similarity to other published cohorts internationally, (3) screening of 99.9% of potential participants, (4) use of few

exclusionary criteria, (5) the 47% consent rate among eligible patients, and (6) retention of the *least* healthy subjects for the 12-month trial. The HIPFIT intervention was carried out by allied health professionals working as a team with a geriatrician and conducted in an outpatient geriatric clinic of a public hospital, and included the recommended rehabilitation targets in the current National Institute for Health and Clinical Excellence guidelines.[11] HIPFIT provides the first evidence that these recommendations will improve standard care if applied robustly in the year after hip fracture.

Conclusions

We have shown for the first time that provision of 12 months of supervised high-intensity progressive resistance training, with simultaneous targeting and treatment of other deficits related to frailty in a typical hip fracture cohort is feasible and effective. The HIPFIT intervention resulted in statistically significant and clinically meaningful reductions in mortality, nursing home use, ADL dependency, and assistive device usage. Rehabilitation withdrawn when prefracture levels of mobility and function are regained (as is current usual care) is suboptimal. Lowering the burden of excess morbidity and mortality after hip fracture requires treatment of the underlying frailty itself, not just the broken bone.

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Supplementary Data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jamda.2011.08.005.

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