

Supplementary File 1: Details of included studies

Study reference	Design, country	Participants	Outcomes analysed	Summary of findings
Binder 2002 [26, 33]	2 group RCT (3:2 allocation) USA	<p>n=115 provided post-intervention data (119 randomised)</p> <p><i>Inclusion:</i> 78+yrs, mild-moderate frailty</p> <p><i>Exclusion:</i> medical condition contraindicating vigorous exercise, neuromuscular disorders unlikely to improve with exercise, chronic use of corticosteroids, immunosuppressants, androgen-, oestrogen- or progestin-containing compounds, cigarette use within previous year, cancer diagnosis within previous year, sensory impairments interfering with following test instructions, significant cognitive impairment</p> <p>83yrs (4), 60F/55M</p> <p>Frailty definition: mPPT score 18-32 plus either difficulty with ≥ 2 IADLs/1 ADL or VO_{2peak} 10-18ml/kg/min</p> <p>Baseline frailty: average mPPT score 28.4(4.7) (exercise) and 28.3(5.9) (control)</p>	<p>3, 6 and 9 months.</p> <ol style="list-style-type: none"> Modified physical performance test (mPPT) (Primary outcome) Activities of daily living (ADL) questionnaires (Primary outcome) <ol style="list-style-type: none"> Older American Resources and Services instrument Physical function subscale of Functional Status Questionnaire (FSQ) Peak oxygen uptake (VO_{2peak}, graded treadmill walking) (primary outcome) Range of motion of hip, ankle, knee and shoulder (goniometry) Balance <ol style="list-style-type: none"> Functional reach test Balance beam Single limb stance time Berg balance instrument Short Form-36 Geriatric depression scale Maximal voluntary muscle strength (Cybex isokinetic dynamometry) 	<p>Significant improvements in exercise group vs control in modified PPT score (29.2 vs 31.8 at test 4, groupxtest p=0.02), VO_{2peak} (15.2 vs 17.4 at test 4, groupxtest p=0.0001) and FSQ score (27.0 vs 30.4 at test 4, groupxtest p=0.01). No significant changes on Older American Resources and Services instrument ADL scale (data not reported in paper), but some changes in balance, muscle strength and health Short Form-36 subscale. No significant differences between groups for other outcomes.</p>
Brown 2000 [17]	2 group RCT USA	<p>n=84 provided post-intervention data (n=87 randomised)</p> <p><i>Inclusion:</i> sedentary, >78yrs, living independently but with difficulty, PPT score 18-32.</p> <p><i>Exclusion:</i> PPT score >32 or ≤ 17</p> <p>83yrs (4), 57%F/43%M</p> <p>Frailty definition: mPPT score 18-32</p> <p>Baseline frailty: mPPT scores Exercise 29(4), Control 29(6)</p>	<p>3 months. Primary outcome not specified</p> <ol style="list-style-type: none"> Physical Performance Test Strength (lower: Cybex isokinetic dynamometer, upper: Micro-Fet dynamometer) <ol style="list-style-type: none"> Knee extensors and flexors ankle plantar and dorsiflexors shoulder flexion and abduction elbow flexion grip strength hip extension and abduction Range of motion (goniometric measures) <ol style="list-style-type: none"> Passive shoulder flexion shoulder external rotation hip flexion with the knee extended hip internal rotation knee flexion ankle dorsiflexion trunk rotation 	<p>Significant improvements in mPPT from 29(4) to 31 (4) in exercise compared to home group (29(6) to 29(6), 2x2 ANOVA, p<0.05). Some significant changes in knee extensors and flexors and shoulder abductors but no other changes. Flexibility increased in both groups (no significant differences). Significant improvements in balance in the exercise group, but no significant changes in gait apart from preferred walking cadence. No changes in coordination or response time and no differences in sensation (both groups showed mild sensory loss).</p>

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			h. distance from fingertips to floor while bending i. hip flexor tightness 4. Balance a. Static - Romberg test b. Dynamic - balance beam, obstacle course, fast gait speed c. Berg balance test 5. Gait analysis (pressure-sensitive foot switches to collect gait velocity, stride length, cadence, swing, stance time, double support time and percentage of gait cycle spent in each phase) 6. Coordination and response speed a. Purdue peg board b. Response time 7. Sensation a. Light touch and pressure (monofilaments pressed against plantar surface of toes and heel) b. Proprioception (tuning fork placed on foot. Scored if felt for 5seconds or more)	
Daniel 2012 [30]	3 group pilot RCT USA	N=19 provided post-intervention data (n=23 randomised) <i>Inclusion:</i> 65+yrs, pre-frail (Fried criteria) <i>Exclusion:</i> not reported 77yrs (5.3), 14F/9M Frailty definition: Fried phenotype (no further details) Baseline frailty: 100% pre-frail	15 weeks. Primary outcome not specified. 1. Senior Fitness Test a) chair stands b) timed up and go c) arm curls d) sit and reach e) step 2 f) back scratch g) 6 minute walk 2. Community Healthy Activities Model Programme for Seniors 3. Activities-specific confidence scale 4. Late life function and disability index – function total, disability frequency, disability limitations	Within-group improvements in some aspects of the Senior Fitness test for seated exercise and Wii groups. Between group changes not assessed. Increase in energy expenditure for Wii group (Community Healthy Activities Model Programme for Seniors) and reduction in disability frequency (Late life function and disability index) across all groups.
Drey 2012 [28, 34]	3 group RCT Germany	n=69* provided 3mo data (n=69 randomised) <i>Inclusion:</i> independent community-dwelling older adults aged 65-94, pre-frail (Fried criteria)	12, 24, 36 weeks 1. Primary outcome: Short Physical Performance Battery (SPPB) 2. Sit-to-stand transfer power	Significant differences in SPPB score changes at 12 weeks between each power training and control (+0.9points (CI 0.48-2.73), p=0.004) and strength training and control (+1.0points (CI

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		<p><i>Exclusion:</i> depression (Geriatric Depression Scale>5), dementia (Mini-mental state examination<25), Body mass index >35, taking immunosuppressants, history of kidney stones, sarcoidosis, plasmacytoma, chronic obstructive pulmonary disease, inflammatory bowel disease, angina pectoris, history of cancer, current attendance at muscle training Control 76yrs, 73%F/27%M Power training 78yrs, 67%F/33%M Strength training 77yrs, 70%F/30%M</p> <p>Frailty definition: Fried phenotype, with unintentional weight loss self-reported rather than directly measured</p> <p>Baseline frailty: 100% pre-frail</p>	<p>3. Short Form Late Life Function and Disability Instrument 4. Appendicular lean mass</p>	<p>0.44-2.58), p=0.005), but not power vs strength training (Kruskal Wallis p=0.301). Effects were not maintained at 24 or 36 weeks. No differences in sit-to-stand power or Short Form Late Life Function and Disability Instrument between groups at 12, 24 or 36 weeks.</p>
Kwon 2015 [29]	3 group RCT Japan	<p>N=79 provided 3 month data (n=89 randomised) <i>Inclusion:</i> community-dwelling women aged 70+, pre-frail (modified Fried criteria) <i>Exclusion:</i> serum albumin >=4.5mg/dL, serious musculoskeletal conditions, taking vitamin D or calcium supplements. 76.8yrs (range 70-84), 100%F</p> <p>Frailty definition: 2 Fried criteria: muscle weakness (handgrip strength in lowest quartile at baseline =<23kg) and slow gait speed (lowest quartile at baseline =<1.52m/s).</p> <p>Baseline frailty: 100% pre-frail</p>	<p>3, 9 months 1) Physical performance a) Muscle strength (handgrip strength, Smedley's Hand Dynamometer) b) Balance (stork stand time with eyes open) c) Walking (usual walking speed over 5m) 2) Health-related quality of life (8 domains of Short Form-36)</p>	<p>No significant differences between groups in physical performance apart from improved handgrip strength in exercise group at 3 month (not maintained at 6month). No significant differences between groups in quality of life apart from role emotional score at 3 months (not maintained at 6 month) in exercise+nutrition group.</p>

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Lustosa 2011 [31,34]	2 group randomised crossover trial Brazil	n=32 provided post-intervention data** (n=32 randomised) <i>Inclusion:</i> community-dwelling women aged 65+, pre-frail (Fried criteria) <i>Exclusion:</i> men, orthopaedic surgery or history of lower limb fracture, unable to walk without an aid, neurological conditions, acute musculoskeletal inflammatory conditions, already performing physical activity >=2x weekly, active neoplasia in the last 5 yrs, using drugs with a broad immune system action, cognitive alterations (based on Mini-mental state examination). Exercise 72yrs (4), 100%F Control 72yrs (3.5), 100%F Frailty definition: Fried phenotype (no further details) Baseline frailty: 100% pre-frail	10, 20 weeks 1. Functional performance (primary outcome***) a) Timed up and go b) 10 metre walk test (6m are timed) 2. Muscle strength of knee extensors (isokinetic dynamometer Byodex System).	Both exercise phases (n=32) compared to first control phase (n=16) in paper. Significant improvements in functional performance (Timed up and go F=9.54, p=0.01, 10 metre walk test F=3.80 p=0.01) in exercise training group and muscle power at 180 degrees/s (tending toward significant at 60 degrees/s).
Upatising 2013 [32]	Secondary analysis of Tele-ERA RCT USA	n=87 out of 194 with complete frailty data used in per-protocol analysis (n=205 randomised). <i>Inclusion:</i> 60+, score of 16+ on elder risk assessment <i>Exclusion:</i> living in a nursing home; dementia; score of <=29 on the Kokmen short mental status test, unable to give informed consent; inability to use telemonitoring equipment. 80.4yrs (8.3), 105F/89M Frailty definition: Fried phenotype with modifications: unintentional weight loss within previous six months recorded within medical records, an exhaustion question from the Patient Health Questionnaire-9 and the Short Form-12 physical score for low activity. Baseline frailty: non-frail 75, pre-frail 87, frail 32	6, 12 months 1. Primary outcome: hospitalisations and emergency department visits**** 2. Transition to a worse frailty state (Fried criteria)	Slightly higher transitions from pre-frail to non-frail in usual care compared to telemonitoring (12/38 (32%) vs 9/35 (26%)) and from pre-frail to frail (6/38 (16%) vs 3/35 (9%)) between baseline and 6 months. Similar numbers remained pre-frail (20/38 (53%) vs 21/35 (60%)). 2 telemonitoring and 9 usual care deaths.

*Further data supplied from the authors.

**n=32 analysed in original paper from (period 1 exercise and period 2 exercise groups combined vs 1st period control). N=16 results obtained from authors for meta-analysis.

*** as reported in this paper, protocol states this was a secondary outcome

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***reported in separate paper, without frailty stratification

Abbreviations: ADL= activities of daily living; ANOVA = analysis of variance; CI = confidence interval; dL = decilitre; F=female; FSQ = functional status questionnaire; kg = kilograms; M=male; m = metre; m/s = metres per second; mPPT: modified physical performance test; SPPB = Short Physical Performance Battery; VO_{2peak} = peak oxygen consumption; yrs=years.

Supplementary file 2: Ongoing studies

Studies identified from searches 6.6.16 of Clinicaltrials.gov search, UK Clinical Trials Gateway and HTA database plus database searches.

Pre-frail populations					
Title	Lead author	Status	Pre-frailty criteria	Intervention	Identifier or location
Clinical and Economic Assessment of a Pre-frail Screening Program	M Serra-Prat Spain	Completed, published 7.1.17	Pre-frailty using Fried criteria	Nutritional assessment and physical activity programme vs usual care	Serra-Prat et al. <i>Age and Ageing</i> . 2017. 0:1-7. ⁴⁴
Training and de-training effects: One year follow-up of a 3-month resistance exercise program in the pre-frail elderly	P Lin	Completed, published as conference abstract	Pre-frailty (criteria not reported)	Muscle resistance training vs control (not specified)	Lin et al. <i>Physiotherapy</i> . 2015. 101: eS882.
The Effect of SOD Enzyme on Frailty and HRQOL Among Indonesian Pre-frail Elderly: A Double Blind Randomized Controlled Trial	S Setiati Indonesia	Recruiting	Pre-frailty on FI-40 item questionnaire	Superoxide Dismutase enzyme and Gliadin supplement vs placebo	NCT02753582 Clinicaltrials.gov
Resistance Training to Optimize Health in Pre-frail Older Adults	A Tang Canada	Recruiting	Pre-frailty (criteria unclear)	Higher intensity resistance training vs lower intensity resistance training	NCT02593084 Clinicaltrials.gov
Home-based health promotion for vulnerable older people	K Walters UK	Completed	"Mild frailty" on Clinical Frailty Scale	Home-based multidimensional health promotion and behaviour change intervention vs treatment as usual	ISRCTN11986672 UK Clinical Trials Gateway

Pre-frail and frail populations*					
Title	Authors	Status	Pre-frailty criteria	Intervention	Identifier or location
Immune Benefits of WGP in Elderly	Nestle Germany	Completed	Frail or pre-frail (Fried criteria)	Food fibres dietary supplement plus influenza vaccine vs placebo (maltodextrin) plus influenza vaccine	NCT02262091 Clinicaltrials.gov
Effectiveness of a Program Using Video Games Associated With Conventional Physiotherapy in Physical Functioning in Frail Elderly Compared to Conventional Physiotherapy	M Perracini Brazil	Recruiting	Frail or pre-frail (Fried criteria)	Exergames and conventional physiotherapy vs conventional physiotherapy	NCT02333214 Clinicaltrials.gov
Effects of Community Health Programs by Nurses for Older Adults	L Huang Taiwan	Completed	Fried frailty criteria: Frail or pre-frail	Comprehensive community nursing care, including physical activity training, community resources referrals, health education and health promotion vs usual care	NCT01972958 Clinicaltrials.gov

*insufficient information to determine whether pre-frail results would be reported separately

Updated search 10.1.17 of Clinicaltrials.gov, UK Clinical Trials Gateway and HTA database

Pre-frail and frail populations*					
Title	Authors	Status	Pre-frailty criteria	Intervention	Identifier or location
Exercise Intervention to Reverse Frailty (ERF)	G Jones Canada	Recruiting	Women with gait speed 1-1.5m/s and pre-frail according to the CHS and "Vulnerable" and/or "Mildly Frail"	Exercise intervention (resistance, aerobic, flexibility and balance) vs usual activity	NCT02952443 Clinicaltrials.gov

			according to the CFS		
Home-Based Technologies Coupled to Teleassistance Service in the Elderly (DOMOLIM)	T Dantoine France	Recruiting	Frail or pre-frail (Fried criteria)	Home automation pack with teleassistance vs teleassistance only	NCT01697553 Clinicaltrials.gov
Implementing Resistance Exercise to Reduce Frailty for Older Adult Medicaid Waiver Recipients	M Danilovich USA	Not yet open for recruitment	Frail or pre-frail (SHARE-FI)	Resistance exercise vs usual care	NCT02942992 Clinicaltrials.gov
A person-centred approach to health promotion for persons 70+ who have migrated to Sweden: promoting aging migrants' capabilities	S Gustafsson Sweden	Completed	Eight physical frailty indicators assessed as outcomes in community-dwelling migrants aged 70+ born in Finland or the Balkan Peninsula not dependent on informal or formal help in daily activities.	Senior meetings (multidimensional, delivered by nurses, physiotherapists, occupational therapists and social workers) followed by a home visit vs usual care	NCT01841853 Clinicaltrials.gov

*insufficient information to determine whether pre-frail results would be reported separately