

BMJ Open The effect of combined resistance exercise training and vitamin D₃ supplementation on musculoskeletal health and function in older adults: a systematic review and meta-analysis

Anneka Elizabeth Antoniak,¹ Carolyn A Greig^{1,2}

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¹School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Birmingham, UK

²MRC-Arthritis Research UK Centre for Musculoskeletal Ageing Research, Birmingham, UK

Correspondence to

Mrs. Anneka Elizabeth Antoniak; aea423@bham.ac.uk

ABSTRACT

Objectives In older adults, there is a blunted responsiveness to resistance training and reduced muscle hypertrophy compared with younger adults. There is evidence that both exercise training and vitamin D supplementation may benefit musculoskeletal health in older adults, and it is plausible that in combination their effects may be additive. The aim of this systematic review was to evaluate the effectiveness of combined resistance exercise training and vitamin D₃ supplementation on musculoskeletal health in older adults.

Data sources A comprehensive search of electronic databases, including Science Direct, Medline, PubMed, Google Scholar and Cochrane Central Register of Controlled Trials (Cochrane CENTRAL accessed by Wiley Science) was conducted. Eligible studies were randomised controlled trials including men and women (aged ≥65 years or mean age ≥65 years); enlisting resistance exercise training and vitamin D₃ supplementation; including outcomes of muscle strength, function, muscle power, body composition, serum vitamin D/calcium status or quality of life comparing results with a control group. The review was informed by a preregistered protocol (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015020157).

Results Seven studies including a total of 792 participants were identified. Studies were categorised into two groups; group 1 compared vitamin D₃ supplementation and exercise training versus exercise alone (describing the additive effect of vitamin D₃ supplementation when combined with resistance exercise training) and group 2 compared vitamin D₃ supplementation and exercise training versus vitamin D₃ supplementation alone (describing the additive effect of resistance exercise training when combined with vitamin D₃ supplementation). Meta-analyses for group 1 found muscle strength of the lower limb to be significantly improved within the intervention group (0.98, 95% CI 0.73 to 1.24, p<0.001); all other outcomes showed small but non-significant positive effects for the intervention group. The short physical performance battery (SPPB), timed up and go (TUG), muscle strength of the lower limb and femoral neck bone mineral density showed significantly greater improvements in the intervention group for group 2 comparisons.

Strengths and limitations of this study

- To the best of our knowledge, this study represents the first review evaluating the combined effects of vitamin D₃ supplementation and exercise in older adults.
- Generally, outcome measure data could be graded as representing moderate quality.
- Only seven studies were found to be eligible for inclusion, highlighting the lack of literature available on the topic.
- The inclusion of one high-risk study was deemed necessary due to the lack of eligible studies.

Conclusions This review provides tentative support for the additive effect of resistance exercise and vitamin D₃ supplementation for the improvement of muscle strength in older adults. For other functional variables, such as SPPB and TUG, no additional benefit beyond exercise was shown. Further evidence is required to draw firm conclusions or make explicit recommendations regarding combined exercise and vitamin D₃ supplementation.

INTRODUCTION

Sarcopenia, originally defined as the age-related loss of muscle mass,¹ now also encompasses low muscle strength and/or muscle function.² The efficacy of resistance training in preventing or alleviating age-related musculoskeletal loss is well established; cited as the most promising intervention for improving symptoms of sarcopenia.³

Clear evidence exists demonstrating an association between resistance exercise training (RET) and muscle hypertrophy, which is maintained in older age.³⁻⁵ However, in older adults there is a blunted responsiveness to RET in comparison with younger adults; a blunted muscle protein synthetic rate in response to a single bout of resistance exercise has been reported,⁶ and

others demonstrate a reduction in muscle hypertrophy in comparison to younger adults.^{7–10} This ‘anabolic resistance’ may be due to changes in gene expression and anabolic signalling; an attenuated anabolic hormone response to resistance exercise is observed in comparison to younger adults.¹¹

Losses in muscle strength are associated with losses in functional ability, independence and increases in frailty, falls and disability in older adults^{12–15}; therefore, there may be merit associated with a combination of interventions to boost responsiveness of older muscle to resistance exercise and combat anabolic resistance.

Vitamin D₃ supplementation in humans has been shown to positively influence musculoskeletal health in older adults: increases in relative number and cross-sectional area (CSA) of muscle fibres (type II in particular) has been reported,^{16–18} and muscle strength increased and fall rates decreased after treatment with vitamin D₃.¹⁷ Vitamin D receptor concentration significantly increased with vitamin D₃ supplementation¹⁸; conversely, supplementation conferred no benefits on strength, functioning and balance.^{19–21} Moreover, a systematic review examining the effects of vitamin D₃ supplementation in vitamin D replete adults aged over 18 years found no significant effect on grip or proximal lower limb muscle strength; however, pooled data including vitamin D deficient participants (serum 25(OH)D < 25 nmol/L) demonstrated a large effect on hip muscle strength.²²

There is conflicting evidence surrounding the efficacy of vitamin D₃ supplementation alone or in combination with exercise on musculoskeletal health, with no clear consensus regarding the management or prevention of sarcopenia. Although epidemiological data suggest a relationship between vitamin D₃ and muscle weakness,²³ this association is not well understood, and evidence in published literature is lacking and contradictory. Considering the beneficial effects of both RET and vitamin D₃ on muscle tissue, it is plausible an additive effect would exist if combined, optimising the potential for healthy ageing muscle.²⁴ Thus, the aim of this study was to assess the combined effect of RET and vitamin D₃ supplementation on musculoskeletal health in older adults.

MATERIALS AND METHODS

A systematic review of peer-reviewed literature relating to the effect of RET and vitamin D₃ supplementation on musculoskeletal health in older adults was conducted in accordance with a study protocol registered on the PROSPERO database (record number CRD42015020157). The protocol was informed by the Cochrane Handbook for Systematic Reviews of Interventions,²⁵ and reporting conformed to the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement.²⁶

Eligibility criteria

Randomised controlled trials were sought for this study. Journal studies included: (1) male and/or female

participants (aged ≥ 65 years or mean age ≥ 65 years), (2) enlisted RET and vitamin D₃ supplementation (studies using vitamin D₃ and calcium supplementation were included), (3) included measures of muscle strength, function, muscle power, body composition, serum vitamin D/calcium status or quality of life, (4) compared results with a control group (sedentary/usual care/no vitamin D₃ supplementation). Articles were excluded if participants were supplemented with additional protein or any supplement/medication with a known anabolic effect on muscle tissue.

Search methods for identification of studies

Articles published before March 2016 were included. A computerised search of Science Direct, Medline, PubMed, Google Scholar and Cochrane Central Register of Controlled Trials (Cochrane CENTRAL accessed by Wiley Science) databases was conducted. Table 1 shows the Medline search strategy, devised by AEA and LH.

Data items and collection

Data were extracted independently by two reviewers (AEA and ASA) using a standardised data extraction sheet; any disagreements were discussed and resolved with a third person (CAG). The inter-rater reliability assessed using Cohen’s Kappa, was found to be excellent (86% agreement).²⁷ Data items including general information, participant characteristics and details of the intervention were extracted. For key outcomes, the definition used by the authors, methodology, results, mean differences and the presence/absence of statistical significance were reported.

Risk of bias analysis

Two reviewers (AEA and CAG) independently assessed the validity of included studies, with provisions for moderation from a third reviewer. The Cochrane Collaboration’s tool for assessing risk of bias was used, as described in the Cochrane Handbook for Systematic Reviews of Interventions²⁵; the use of scales for assessment is explicitly discouraged.^{28–29} Prespecified consensus points were devised and agreed by reviewers to ensure consistency. It was acknowledged that by nature of design, blinding of participants and personnel would be difficult in certain studies; therefore, grading was based on the likelihood that outcome measures were influenced by the potential lack of blinding.²⁵

Grading the quality of evidence

The Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) handbook³⁰ was used to evaluate the quality of evidence of outcomes assessed within the meta-analyses. The GRADE approach uses systematically produced questions to reach conclusions on degree of confidence in the estimate of the effect. GRADE assesses patient important outcomes across five areas: risk of bias, inconsistency, indirectness, imprecision and publication bias and grades outcomes as

Table 1 Example Ovid Medline search, to be adapted for other databases

1	Aging/
2	Exp aged/
3	(65 adj2 (years or age* or old*))
4	(old* adj (adult* or people or person* or population* or men or women))
5	(elder* or senior* or geriatric* or ?enarian or ag?ing)
6	((age* or aging or old* or elder*) adj1 (musc*))
7	1 or 2 or 3 or 4 or 5 or 6
8	Vitamin D/
9	(cholecalciferol* or calciferol* or ergocalciferol*)
10	(supplements or dietary supplements)
11	((vitamin D* or cholecalciferol or calciferol* OR ergocalciferol) adj supplementation)
12	8 or 9 or 10 or 11
13	Muscle Development/
14	Muscle, Skeletal/
15	(Skeletal muscle adj2 (atrophy or sarcopenia or wasting or loss or deterioration))
16	Muscle Strength/
17	(skeletal muscle mass or size or fibres or fibers or area)
18	(musc* adj2 (function* or power or strength))
19	(musc* adj2 (grow* or hypertrophy or size or mass or csa or cross sectional area or volume))
20	Body Composition/
21	(lean adj3 mass)
22	(protein adj2 (turnover or synthesis or breakdown))
23	(nitrogen adj2 (balance or turnover or synthesis or breakdown or retention or loss or retain*))
24	Sarcopenia/
25	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26	Exp exercise/
27	(resistance exercise or resistance exercise training)
28	((resistance or strength or weight or cardio or aerobic) adj3 (train* or condition* or exercise* or lift*))
29	(physical adj3 (activit* or exercise* or train* or exertion* or endurance* or therap* or conditioning or fitness))
30	(exercise adj3 (train* or intervention* or protocol* or program* or therap* or regim* or activit*))
31	26 or 27 or 28 or 29 or 30
32	7 and 12 and 25 and 31
33	Limit 32 to humans
34	Remove duplicates from 33

demonstrating high, moderate, low or very low quality of evidence.

RESULTS

Study selection

Seven studies were included within the review: Agergaard *et al*³¹, Bunout *et al*³², Drey *et al*³³, Gianoudis *et al*³⁴, Jessup *et al*³⁵, Uusi-Rasi *et al*²¹ and Verschueren *et al*³⁶; the study flow diagram is presented in figure 1.

On reading full-text articles, it became clear that there were two separate groups of interventions; group 1, in which all participants took part in RET and the intervention arm was supplemented with vitamin D₃ (describing

the additive effect of vitamin D₃ supplementation when combined with resistance exercise training), group 2 in which all participants were supplemented with vitamin D₃ and the intervention arm took part in RET (describing the additive effect of resistance exercise training when combined with vitamin D₃ supplementation); and studies using a combination of the two interventions (table 2).

Study demographics

Seven eligible studies included a total of 792 participants of mean age 72.8 years (table 2). Of these, one included only males³¹ and three included only females.^{21 35 36} All studies included healthy participants living independently,

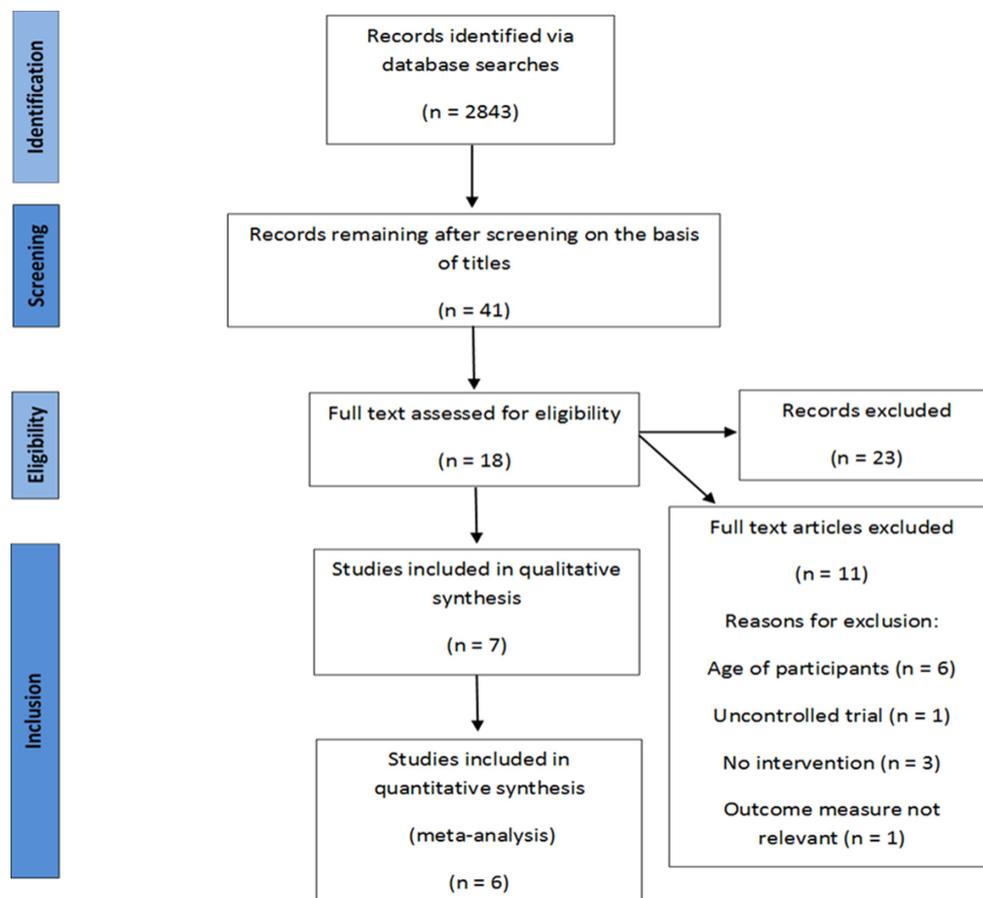


Figure 1 Study flow chart.

except for two studies³⁵; included participants living within a retirement community and³⁶ included institutionalised participants living in nursing homes, service flats or cloistered communities.

Interventions

Studies assigned to group 1 included: Agergaard *et al*³¹, Bunout *et al*³² and Uusi-Rasi *et al*²¹. In group 1, all participants took part in RET; incorporating a warm-up and strengthening exercises using commercial weight machines^{21 31} or Thera-bands.³¹ Two studies included balance challenging aspects.^{21 32} All studies included supervised, progressive exercise sessions; progression was monitored by a five rep max test,³¹ Borg scale³² or metabolic equivalents (METs).²¹ Total number of sessions delivered ranged from 36³¹ to 156,²¹ over a duration of 16 weeks³¹ to 24 months.²¹ All administered a vitamin D₃ supplement, orally in tablet form; doses ranged from 400 IU/day³² to 1920 IU/day³¹; in two studies participants were supplemented with 800mg calcium per day^{31 32} and one study supplemented the control group with a placebo.²¹

Six studies assigned to group 2 included: Bunout *et al*³², Drey *et al*³³, Gianoudis *et al*³⁴, Jessup *et al*³⁵, Uusi-Rasi *et al*²¹ and Verschueren *et al*³⁶. Within group 2, all participants took a vitamin D₃ supplement, orally in tablet form. Doses ranged from 400 IU/day^{32 35} to 2000 IU/day³³; one study

monitored serum 25(OH)D at baseline to determine supplement dosage.³³ In four studies,^{32 34–36} all participants were supplemented with calcium; doses ranged from 700 mg/day³⁴ to 1000 mg/day^{35 36}. The intervention group took part in RET. Studies used machine weights and pulleys,^{21 33–35} Thera-bands,³² weighted vests³⁵ and whole body vibration machines³⁶ for resistance. Five studies included balance challenging aspects.^{21 32–35} All studies employed supervised, progressive exercise sessions monitored via a Borg scale,^{32–34} addition of weights to weighted vests,³⁵ estimation of METs or individual ability.³⁶ Total number of sessions delivered ranged from 24³³ to 156,²¹ over a duration of 12 weeks³³ to 24 months.²¹ Note that two studies included comparators which allowed allocation to both groups.^{21 32}

Outcome measures

All outcomes are listed in table 3. Group 1 studies had few outcomes in common; however, all measured muscle strength^{21 31 32}; isometric knee extensor strength was measured using a strain gauge^{21 31} and isometric quadriceps strength was measured using a quadriceps table.³² Hand grip strength was measured using a hand grip dynamometer.³² MRI was used to measure the CSA of the quadriceps,³¹ while³² analysed fat and lean mass using dual-energy X-ray absorptiometry (DXA). Two studies measured timed up and go (TUG), femoral

Table 2 Study demographics

Author, year	N included in analyses	Mean age (y)	Sex (M:F)	Study design	Intervention group protocol	Control group protocol	Duration
Group 1: all participants exercised, intervention group received vitamin D supplementation							
Agergaard <i>et al.</i> , 2015 ³¹	17	66.9	17:0	RCT	RET 3x per week and 1920 IU D3+800 mg Ca/day	RET 3x per week and 800 mg Ca/day	16 weeks
Group 2: all participants received vitamin D supplementation, intervention group exercised							
Drey <i>et al.</i> , 2011 ³³	45	77	13:32	RCT	RET 2x60 min per week and >20 ng/mL=1000 IU D3/day <20 ng/mL=2000 IU D3/day	Sedentary and >20 ng/mL=1000 IU D3/day <20 ng/mL=2000 IU D3/day	12 weeks
Gianoudis <i>et al.</i> , 2014 ³⁴	162	67	119:43	RCT	HV-PRT 3x per week and 1000 IU D3+700 mg Ca/day	Sedentary and 1000 IU D3+700 mg Ca/day	12 months
Jessup <i>et al.</i> , 2003 ³⁵	18	69	0:18	RCT parallel	RET 3x60–90 min per week and 400 IU D3+1000 mg Ca/day	Sedentary and 400 IU D3+1000 mg Ca/day	32 weeks
Verschueren <i>et al.</i> , 2011 ³⁶	111	79	0:111	RCT	WBV 3x per week and High-dose=1600 IU Or Conventional dose=800 IU D3/day +1000 mg Ca/day	Sedentary and High-dose=1600 IU Or Conventional dose=800 IU D3/day +1000 mg Ca/day	6 months
Assigned to groups 1 and 2: participants took part in a combination of exercise and vitamin D interventions							
Bunout <i>et al.</i> , 2006 ³²	92	77	9:83	RCT	RET 2x1.5 hour per week Or sedentary and 400 IU D3+800 mg Ca/day	RET 2x1.5 hours per week Or sedentary and 800 mg Ca/day	9 months
Uusi-Rasi <i>et al.</i> , 2015 ²¹	409	74	0:409	RCT	RET 2x/week for 12 months, 1x/week for next 12 months or sedentary and 800 IU D3/day	RET 2x/week for 12 months, 1x/week for next 12 months or sedentary and Placebo/day	2 years

*RCT, randomised controlled trial, RET, resistance exercise training, IU, international units, Ca, calcium, HV-PRT, high-velocity progressive resistance training; WBV, whole body vibration.

Table 3 Summary of included study outcome measures and significant results

Author, year	Outcome measures	Significant results
Agergaard <i>et al</i> ³¹	Muscle strength Muscle CSA Muscle quality	Muscle strength: no between-group difference Muscle CSA: no between-group difference Muscle quality: N/S
Bunout <i>et al</i> ³²	Muscle strength Muscle function BMD Body sway Endurance	Muscle strength: increased with exercise ($p<0.001$), no effect of vitamin D Muscle function: SPPB increased with exercise ($p=0.002$), no effect of vitamin D, TUG: increased in both groups ($p=0.004$) BMD: femoral neck increased with vitamin D, decreased without ($p=0.006$). Spine was N/S Body sway: lower with vitamin D than without ($p=0.05$) Endurance: N/S
Drey <i>et al</i> ³³	Muscle power Muscle function Body composition	Muscle power: increased with vitamin D intake ($p=0.017$) Muscle function : SPPB increased with exercise ($p=0.009$), SF-LLFDI was N/S Body composition: aLM was N/S
Gianoudis <i>et al</i> ³⁴	Muscle strength Muscle power Muscle function BMD Body composition Dynamic balance	Muscle strength: intervention increased strength relative to controls ($p<0.001$) Muscle power: Intervention increased power relative to controls ($p<0.05$) Muscle function: intervention improved sit-to-stand relative to controls ($p<0.05$) TUG: no between-group difference BMD: intervention increased femoral neck relative to controls ($p<0.05$) Spine: intervention increased relative to controls ($p<0.05$) Body composition: lean and fat mass: N/S Dynamic balance: intervention increased relative to controls ($p<0.05$)
Jessup <i>et al</i> ³⁵	Muscle strength BMD Body sway	Muscle strength: increased with intervention ($p=0.0156$) BMD femoral neck: increase with intervention ($p=0.00001$) Spine: no between-group difference Body sway: significantly reduced in intervention group ($p=0.0027$)
Uusi-Rasi <i>et al</i> ²¹	Muscle strength Muscle function BMD Dynamic balance	Muscle strength: increased with exercise ($p<0.001$) Vitamin D supplementation N/S Muscle function : SPPB=N/S TUG: vitamin D without exercise increased relative to placebo without exercise ($p=0.01$) BMD: femoral neck Vitamin D maintained BMD ($p=0.02$) as did exercise ($p=0.01$) Spine: N/S Dynamic balance: improved with exercise (placebo: $p=0.001$, vitamin D: $p=0.03$). No additive effect of vitamin D
Verschuere <i>et al</i> ³⁶	Muscle strength BMD Muscle mass	Muscle strength: isometric: N/S Dynamic: N/S Vitamin D=no effect BMD: improved in all groups. No between-group difference Muscle mass: N/S

aLM, appendicular Lean Mass; BMD, bone mineral density; CSA, cross-sectional area; DXA, dual-energy X-ray absorptiometry; N/S, not significant; SPPB, short physical performance battery; SF-LLFDI, Short Form of the Late-Life Function and Disability Instrument; TUG, timed up and go.

Table 4 Summary of risk of bias analysis for each included study

Author, year	Components of risk of bias							Summary	Comments on high-risk components
	1	2	3	4	5	6	7		
Agergaard <i>et al</i> ³¹	L	U	L	L	U	L	L	High (0) Unclear (2) Low (5)	N/A
Bunout <i>et al</i> ³²	L	U	U	U	U	U	U	High (0) Unclear (6) Low (1)	N/A
Drey <i>et al</i> ³³	L	L	U	U	L	L	U	High (0) Unclear (3) Low (4)	N/A
Gianoudis <i>et al</i> ³⁴	L	U	U	U	H	L	L	High (1) Unclear (3) Low (3)	One high-risk component, 5 ITT analysis used, but no data entered for participants with missing data
Jessup <i>et al</i> ³⁵	L	U	U	U	U	U	L	High (0) Unclear (5) Low (2)	N/A
Uusi-Rasi <i>et al</i> ²¹	L	U	U	U	U	L	L	High (0) Unclear (4) Low (3)	N/A
Verschueren <i>et al</i> ³⁶	L	U	U	U	U	L	L	High (0) Unclear (4) Low (3)	N/A

ITT, intention to treat; N/A, not available.

neck and spine bone mineral density (BMD).^{21 32} One study analysed fibre type and muscle quality.³¹

Group 2 studies^{21 32 34 36} assessed lower limb strength^{32 35} and measured grip strength. Muscle power was measured as sit-to-stand transfer power³³ and the stair climb test.³⁴ The short physical performance battery (SPPB) was assessed by,^{32 34} and the TUG by.^{21 32 34} BMD of the femoral neck^{21 32 34–36} and spine^{21 32 34 35} were measured using DXA. Lean mass was measured using DXA^{32–34} and X-ray CT.³⁶ Balance was assessed via the Romberg ratio,³² four-square step test,³⁴ an AcuSway platform³⁵ and backwards walking.²¹ Other outcomes included endurance (12 min walk³²), the 30 s sit-to-stand test,³⁴ normal walking speed and the 5-time chair stand test.²¹

Risk of bias within studies

The risk of bias analyses are displayed in [table 4](#). For all studies, a high proportion of components were assigned an unclear risk of bias due to insufficient information and the unknown effect on study outcome measures. Many studies reported insufficient information on concealment and blinding procedures, or whether procedures were in place in the event of unblinding. In total, six studies were judged to have an unclear risk of bias.^{21 31–33 35 36} Component 1 was assessed as having a low risk of bias for all studies. One study was assessed as having an overall high risk of bias³⁴ due to component 5, as no data were entered into the analyses for participants with missing data.

GRADE analysis

The GRADE summary of findings for groups 1 and 2 are shown in [tables 5 and 6](#).

Within group 1, all studies were evaluated as moderate quality of evidence; no serious risk of bias was detected. Due to the nature of the studies included within this review, no serious indirectness was detected; all outcomes were measured directly without the use of a surrogate. Publication bias was not detected, and due to the number of studies included, it was not possible to produce funnel plots for any outcomes. Although publication bias was ‘not detected’, it is difficult to conclude that there was a complete absence of bias since studies with significant results are more likely to be published than those reporting null or non-significant results.²⁵ Published, peer-reviewed articles were included in this review, since the Cochrane Handbook for Systematic Reviews of Interventions further suggests that the inclusion of unpublished studies may introduce additional bias, as these studies have not been strengthened by the peer-review process and may be of lower methodological quality.²⁵ Reasons for downgrading the quality of evidence included serious inconsistency due to substantial heterogeneity, and serious imprecision due to CIs crossing the line of no effect.

Within group 2 studies, five outcomes were graded as high-to-moderate quality of evidence (SPPB, TUG, muscle strength of the lower limb, hand grip strength and BMD of the femoral neck). Remaining outcomes were graded as low or very low quality, meaning that one could

Table 5 GRADE analysis of group 1 measurement outcomes included in the quantitative synthesis

Outcome	Quality assessment						Summary of findings				
	Included studies (design)	ROB	Inconsistency	No serious indirectness	Imprecision	Publication bias	Groups (intervention/control)	Effect size (direction)	p Value	95% CI	Quality
Muscle strength (lower limb)	(RCT) ^{21, 31, 32}	No serious ROB	Serious inconsistency (substantial heterogeneity)	No serious indirectness	No serious imprecision	Undetected [^]	131/135	0.98 (intervention)	<0.00001	(0.73 to 1.24)	⊕⊕⊕○ Moderate
TUG	(RCT) ^{21, 32}	No serious ROB	No serious inconsistency	No serious indirectness	Serious imprecision (CIs crossline of no effect/OIS not reached)	Undetected [^]	124/125	0.37 (intervention)	0.37	(-0.68 to 0.26)	⊕⊕⊕○ Moderate
BMD (femoral neck)	(RCT) ^{21, 32}	No serious ROB	No serious inconsistency	No serious indirectness	Serious imprecision (CIs crossline of no effect/OIS not reached)	Undetected [^]	124/125	0.02 (intervention)	0.15	(-0.01 to 0.05)	⊕⊕⊕○ Moderate
BMD (spine)	(RCT) ^{21, 32}	No serious ROB	No serious inconsistency	No serious indirectness	Serious imprecision (CIs crossline of no effect/OIS not reached)	Undetected [^]	124/125	0.02 (intervention)	0.41	(-0.03 to 0.07)	⊕⊕⊕○ Moderate

[^] Insufficient

BMD, bone mineral density; RCT, randomised controlled trial; OIS, Optimal Information Size; ROB, Risk Of Bias.

have little or very little confidence in the effect estimate. Common reasons for downgrading outcomes included a combination of serious risk of bias (due to the inclusion of study³⁴), serious imprecision or serious inconsistency.

Results of individual studies and synthesis of results

Results of the two groups of studies are reported separately. Qualitative syntheses were conducted for studies with similar interventions and outcomes measures using RevMan V.5.3 software. Study outcomes reporting results in the same units were pooled using a fixed-effect meta-analysis. Effect sizes are expressed as percentage mean differences or standardised mean differences (when outcomes were measured using different methods), with 95% CIs. Higher weighting was assigned to studies with smaller SD and a larger sample size.²⁵ Analyses were completed from extracted data, where necessary data were estimated from statistics or figures, or requested from the authors of the article. Heterogeneity was assessed via X^2 test (figures 2–14 and tables 5 and 6). One article³⁶ was not included in any of the quantitative analyses, since the exercise intervention modality was considered to be too dissimilar to compare with the other included articles. Within each group, there were outcomes unsuitable for quantitative synthesis, due to a lack of studies with common outcomes or aspects of studies too dissimilar for comparison; therefore, a narrative analysis was used.

Quantitative synthesis

Outcomes compared for group 1 included muscle strength of the lower limb, TUG and BMD of the femoral neck and spine (figures 2–5). Only muscle strength of the lower limb was found to be significant, with a large effect size in favour of the intervention group (figure 2; 0.98, 95% CI 0.73, to 1.24, $p < 0.00001$).

Group 2 comparisons included the SPPB (figure 6), TUG (figure 7), muscle strength of the lower limb (figure 8), hand grip strength (figure 9), weight (figure 10), lean mass (figure 11), fat mass (figure 12), BMD of the femoral neck (figure 13) and spine (figure 14). Of these outcomes, hand grip strength, weight, lean mass, fat mass and the BMD of the spine were found to be non-significant. However, SPPB score was more improved in the intervention group (1.09, 95% CI 0.15 to 2.03, $p = 0.02$), with a significant and large effect. Similarly, TUG was significantly reduced within the intervention group (-1.57 , 95% CI -2.50 to -0.64 , $p = 0.0010$). The results of the quantitative analysis also supported the combined intervention for muscle strength of the lower limb (2.69, 95% CI 0.95 to 4.42, $p = 0.002$), and BMD of the femoral neck (0.04, 95% CI 0.01 to 0.06, $p = 0.002$).

Qualitative synthesis

Referring to the narrative synthesis guidelines provided by the Cochrane Consumers and Communication Review Group,³⁷ it was appropriate to apply two steps listed; developing a preliminary synthesis and exploring the relationships within and between studies. To develop a

Table 6 GRADE analysis of group 2 measurement outcomes included in the quantitative synthesis

Outcome	Quality assessment						Summary of findings				
	Design, included studies	ROB	Inconsistency	Indirectness	Imprecision	Publication bias	Groups (intervention/control)	Effect size (direction)	p Value	95% CI	Quality
SPPB	(RCT) ^{32,33}	No serious ROB	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected [^]	45/46	1.09 (intervention)	0.02	(0.15 to 2.03)	⊕⊕⊕⊕ High
TUG	(RCT) ^{21,32}	No serious ROB	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected [^]	124/126	-1.57 (intervention)	p=0.001	(-2.50 to -0.64)	⊕⊕⊕⊕ High
Muscle strength (lower limb)	(RCT) ^{21,32}	No serious ROB	Serious inconsistency (substantial heterogeneity)	No serious indirectness	No serious imprecision	Undetected [^]	124/126	2.69 (intervention)	0.002	(0.96 to 4.42)	⊕⊕⊕⊕ Moderate
Hand grip strength	(RCT) ^{32,35}	No serious ROB	No serious inconsistency	No serious indirectness	Serious imprecision (crossline of no effect, OIS not reached)	Undetected [^]	31/33	0.85 (intervention)	0.55	(-1.93 to 3.63)	⊕⊕⊕⊕ Moderate
Weight	(RCT) ^{32,34,35}	Serious ROB ⁴ (was evaluated as high risk for incomplete outcome data)	No serious inconsistency	No serious indirectness	Serious imprecision (crossline of no effect, OIS not reached)	Undetected [^]	112/114	-0.12 (intervention)	0.37	(-0.38 to 0.14)	⊕⊕⊕⊕ Low
Lean mass	(RCT) ^{32,34}	Serious ROB ⁴ (was evaluated as high risk for incomplete outcome data)	No serious inconsistency	No serious indirectness	Serious imprecision (crossline of no effect, OIS not reached)	Undetected [^]	103/105	0.02 (intervention)	0.98	(-1.31 to 1.35)	⊕⊕⊕⊕ Low
Fat mass	(RCT) ^{32,34}	Serious ROB ⁴ (was evaluated as high risk for incomplete outcome data)	No serious inconsistency	No serious indirectness	Serious imprecision (crossline of no effect, OIS not reached)	Undetected [^]	103/105	-0.39 (intervention)	0.76	(-2.82 to 2.05)	⊕⊕⊕⊕ Low
BMD (femoral neck)	(RCT) ^{21,32,34,35}	Serious ROB ⁴ (was evaluated as high risk for incomplete outcome data)	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected [^]	124/126	0.04 (intervention)	0.002	(0.01 to 0.06)	⊕⊕⊕⊕ Moderate
BMD (spine)	(RCT) ^{21,32,34,35}	Serious ROB ⁴ (was evaluated as high risk for incomplete outcome data)	Serious inconsistency (substantial heterogeneity)	No serious indirectness	Serious imprecision (crossline of no effect, OIS not reached)	Undetected [^]	124/126	0.02 (intervention)	0.24	(-0.001 to 0.05)	⊕⊕⊕⊕ Very low

[^]Insufficient data to produce funnel plots.
BMD, bone mineral density; RCT, randomised controlled trial; SPPB, short physical performance battery; TUG, timed up and go.

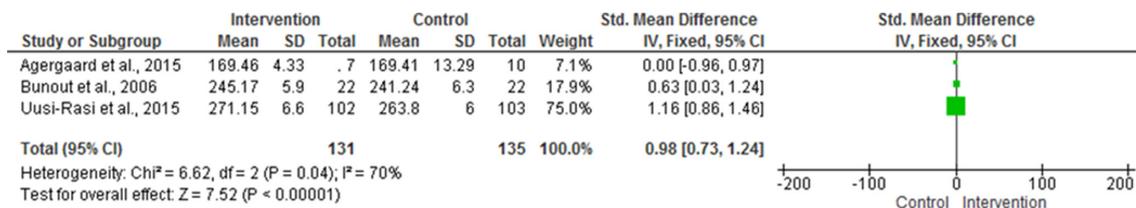


Figure 2 Group 1 analysis of muscle strength of the lower limb.

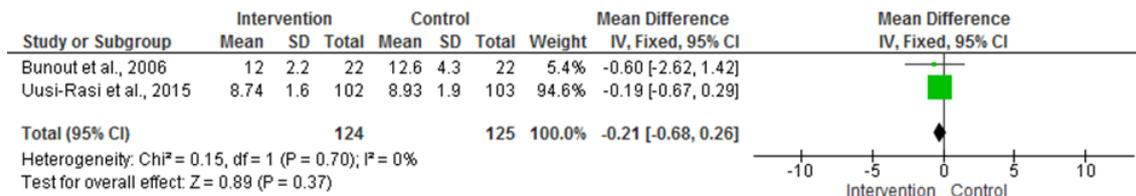


Figure 3 Group 1 analysis of the TUG test.

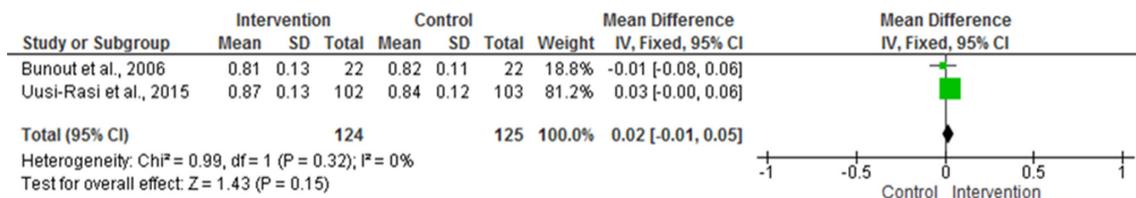


Figure 4 Group 1 analysis of BMD of the femoral neck.

primary synthesis, results were systematically tabulated to identify patterns across studies (tables 7–9). Exploring the relationships between and within studies for group 1, the control group in study³¹ demonstrated a significant percentage increase in CSA of the quadriceps from baseline in comparison with the intervention group (+8.46% vs +4.94%, p<0.05).

Comparing primary outcomes for group 2, the percentage increase in isometric knee extensor strength for study³⁶ was greater in the intervention group (+3.01% vs +0.11%), although not statistically significant. Muscle power was compared in studies³³ and expressed as sit-to-stand transfer power and functional stair climbing muscle power, respectively³⁴. Both studies reported a significant percentage increase in muscle power within

the intervention groups, and smaller, non-significant increases within the control groups (sit-to-stand transfer power intervention group +8.00% vs +2.61%, p=0.017; functional stair climbing muscle power intervention group +10.51% vs +7.32%, p<0.05).

The 30s sit-to-stand test showed significant favourable results for the combined intervention of exercise and vitamin D₃ (+10.40% vs +6.20%, p<0.05). Within study,²¹ normal walking speed declined in both groups and the 5-time chair stand time was improved non-significantly in both groups. The 12min walk test in study³² was further improved within the control group, although this did not achieve statistical significance. The four-square step test, body sway and backward walking were significantly more improved in the intervention groups. Only Romberg

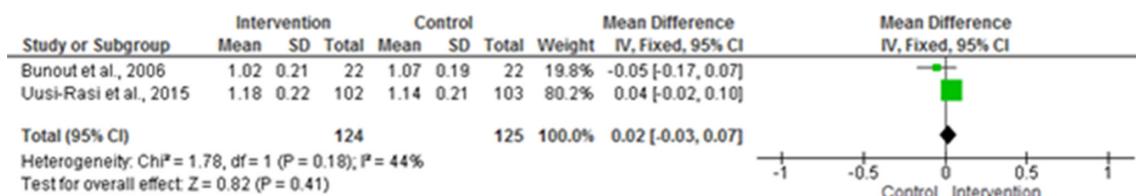


Figure 5 Group 1 analysis of BMD of the spine.

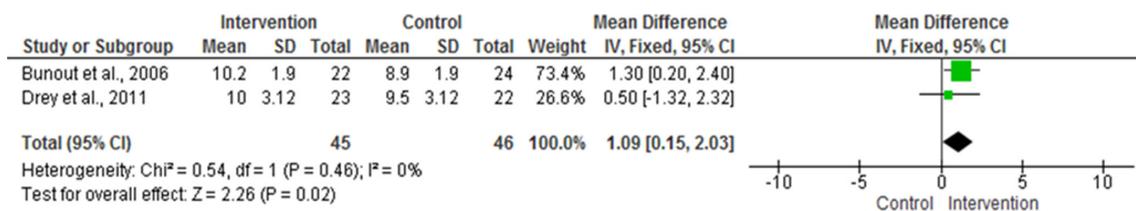


Figure 6 Group 2 analysis of the SPPB test.

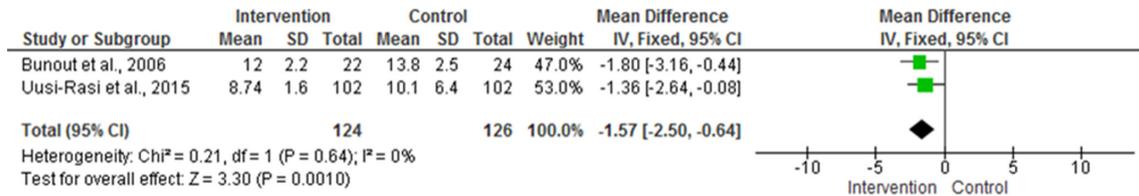


Figure 7 Group 2 analysis of the timed up and go test.

ratio showed the greatest improvement within the control group; Romberg ratio was decreased in comparison with the intervention group, although the results were non-significant (+2.8% vs -0.60%).

For group 2 secondary outcomes, small and non-significant gains in appendicular lean mass were demonstrated in the intervention group of study.³³ In study,³⁶ muscle mass of the upper limb decreased non-significantly in both the intervention and control groups, although to a lesser extent in the intervention group. BMD of the femoral neck was gained in both groups, although by a higher percentage in the control group; both trends were non-significant.

In summary, meta-analyses for group 1 found muscle strength of the lower limb to be significantly improved within the intervention group (0.98, 95% CI 0.73 to 1.24, $p < 0.001$). All other outcomes showed small but non-significant positive effects for the intervention group. The SPPB, TUG, muscle strength of the lower limb and femoral neck BMD all showed significantly greater improvements in the intervention group for group 2 comparisons.

The narrative analysis revealed significant differences in body composition, muscle power, muscle function and balance. A significant percentage increase in quadriceps CSA was observed in the control group of study.³¹ The combined intervention of RET and vitamin D₃ supplementation resulted in a greater percentage increase in muscle strength and power, and a greater improvement in the 30s sit-to-stand test, the four-square step test, body sway and backward walking. However, vitamin D₃ supplementation alone resulted in a greater improvement in the 12 min walk test and Romberg ratio.

DISCUSSION

The aim of this systematic review was to assess the combined effect of RET and vitamin D₃ supplementation on musculoskeletal health in older adults. Only seven studies were eligible for inclusion, with a total of 792 participants, highlighting the lack of available literature on the topic. Studies were categorised into two groups: studies in which all participants took part in RET and the intervention group was supplemented with vitamin D₃, or studies in which all participants were supplemented with vitamin D₃ and the intervention group took part in RET. Two studies were categorised into both group 1 and group 2.

Quantitative analysis

Data analysis conducted for this review included meta-analyses and narrative reviews. Meta-analyses for group 1 included muscle strength of the lower limb, TUG and BMD of both the femoral neck and spine. Evidence of additional benefit was shown for all outcomes within the intervention group; however, the effect size was small and non-significant for TUG and BMD of the femoral neck and spine. Muscle strength of the lower limb was the only significant outcome of group 1, with a large effect size observed within the intervention group (0.98, 95% CI 0.73, to 1.24, $p < 0.00001$). Although numerous studies have demonstrated the beneficial effect of RET on muscle strength in older adults,³⁻⁵ this result provides evidence that vitamin D₃ supplementation may enhance these effects in older adults. Skeletal muscle myopathies associated with vitamin D deficiency are well documented,³⁸ and symptoms of significant muscle

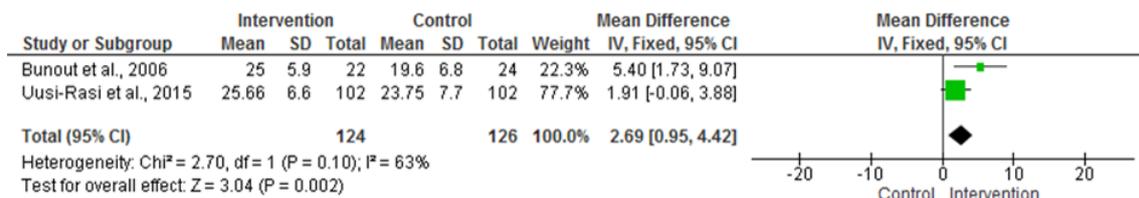


Figure 8 Group 2 analysis of the muscle strength of the lower limb.

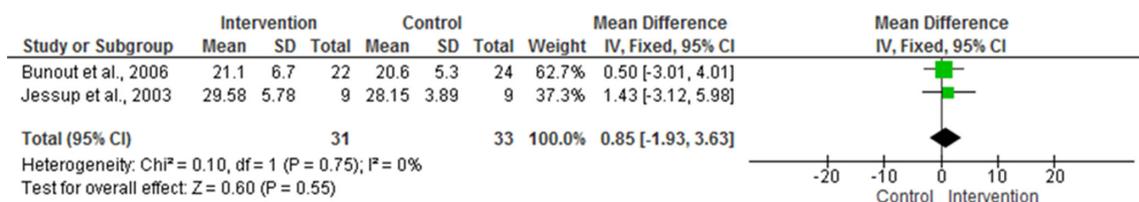


Figure 9 Group 2 analysis of hand grip strength.

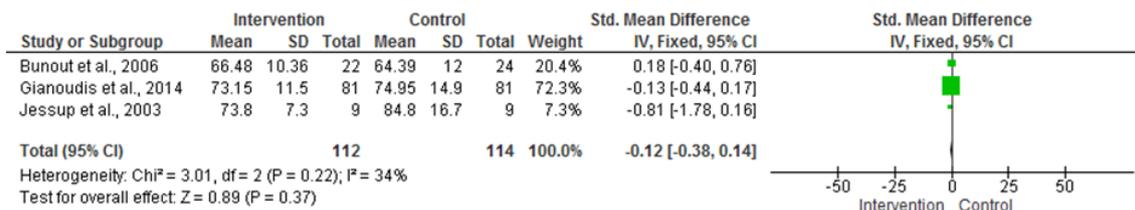


Figure 10 Group 2 analysis of total body weight.

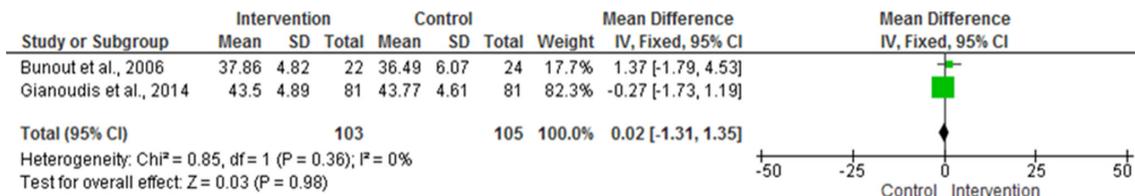


Figure 11 Group 2 analysis of lean mass.

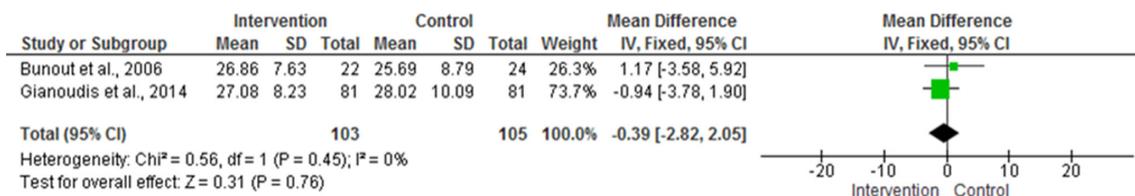


Figure 12 Group 2 analysis of fat mass.

weakness are reversed with treatment of the deficiency.³⁹ A systematic review and meta-analysis reported a gain in lower extremity strength with vitamin D supplementation only in vitamin D deficient older adults; no effect was observed in replete adults.²² Similarly, no effect of vitamin D₃ supplementation on isometric quadriceps strength was demonstrated after 6 months in vitamin D replete older adults.⁴⁰ Interestingly, although the studies included within group 1^{21 31 32} did not specify serum 25(OH)D levels as inclusion/exclusion criteria, baseline and postintervention serum 25(OH)D were within the 'sufficient' range (>30 nmol/L). A greater increase of

muscle strength in replete older adults represents a novel finding of this review. Preliminary support for combined vitamin D supplementation and RET was demonstrated in a 3-month longitudinal study examining the effect of serum 25(OH)D and exercise training on functional performance in older men and women aged 65 years and over. No significant improvements in function were reported in participants with lower serum 25(OH)D (<47.5 nmol/L); however, higher serum 25(OH)D (>67.5 nmol/L) was associated with greatest improvements in functionality and muscle strength.⁴¹

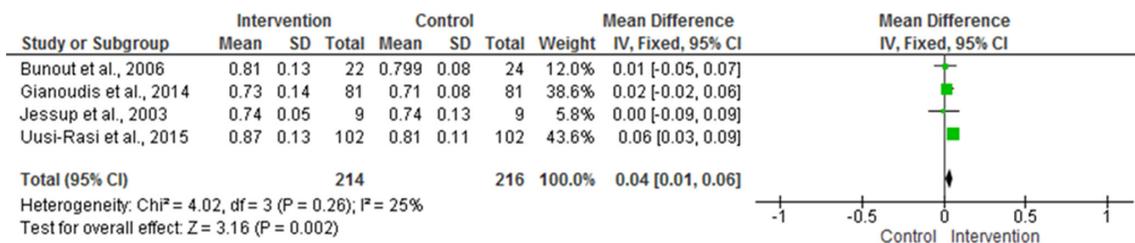


Figure 13 Group 2 analysis of bone mineral density of the femoral neck.

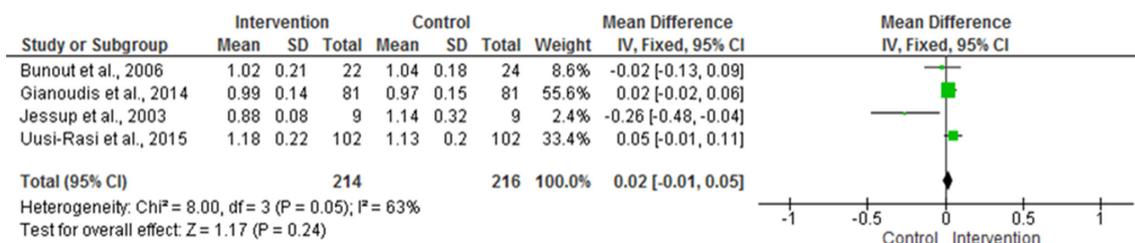


Figure 14 Group 2 analysis of bone mineral density of the spine.

Table 7 Narrative analysis summary of findings for group 1 secondary outcome measures

Category	Outcome measure	Assessment point	Study	Intervention group % change from baseline			Control group % change from baseline		
				M	SD	N	M	SD	N
Body composition	CSA of quadriceps muscles (cm ²)	16 weeks	Agergaard <i>et al</i> , 2015 ³¹	+4.94	5.28	7	+8.46*	6.80	10

Group 1 studies compared vitamin D3 supplementation and exercise training vs exercise alone.

* $p < 0.05$

CSA, cross-sectional area.

This finding must be considered within the context of the risk of bias and GRADE analyses. The risk of bias analysis showed an overall unclear risk of bias for the included studies, and the GRADE analysis concluded that the evidenced was

of moderate quality; however, serious inconsistency due to moderate heterogeneity ($I^2=70\%$) was detected. This heterogeneity may have been due to the differing duration of interventions (12 weeks to 24 months), differences

Table 8 Narrative analysis summary of findings for group 2 primary outcome measures

Category	Outcome	Assessment point	Study	Intervention group % change from baseline			Control group % change from baseline		
				M	SD	N	M	SD	N
Muscle strength	Isometric knee extensor strength (Nm)	6 months	Verschueren <i>et al</i> , 2011 ³⁶	+3.01	2.67	28	+0.11	3.18	28
Muscle power	Sit-to-stand transfer power (W)	12 weeks	Drey <i>et al</i> , 2011 ³³	+8.99*	5.51	23	+2.61	2.49	22
	Functional stair climbing muscle power (W)	12 months	Gianoudis <i>et al</i> , 2014 ³⁴	+10.40*	13.00	81	+6.20	12.70	81
Muscle function	30s sit-to-stand (n. stands)	12 months	Gianoudis <i>et al</i> , 2014 ³⁴	+18.30*	23.60	81	+2.70	17.2	81
	5-time chair stand time (s)	24 months	Uusi-Rasi <i>et al</i> , 2015 ²¹	-6.95	2.50	102	-3.49	3.30	102
	Normal walking speed (m/s)	24 months	Uusi-Rasi <i>et al</i> , 2015 ²¹	-1.80	0.20	102	-3.30	0.21	102
	Endurance: 12 min walk (m)	9 months	Bunout <i>et al</i> , 2006 ³²	+8.80	17.60	22	+20.90	27.70	24
Balance	Romberg ratio (%)	9 months	Bunout <i>et al</i> , 2006 ³²	+2.80	33.80	22	-0.60	35.80	
	Four-square step test (s)	12 months	Gianoudis <i>et al</i> , 2014 ³⁴	-12.00*	14.10	81	-5.20	14.90	81
	Body sway (cm)	32 weeks	Jessup <i>et al</i> , 2003 ³⁵	-26.39*	0.52	9	+2.90	0.49	9
	Backwards walking (% able to complete)	24 months	Uusi-Rasi <i>et al</i> , 2015 ²¹	+25.47*	13.59	102	+9.48	15.58	102

Group 2 compared vitamin D₃ supplementation and exercise training vs vitamin D₃ supplementation alone.

* $p < 0.05$

Table 9 Narrative analysis summary of findings for group 2 secondary outcomes

Category	Outcome measure	Assessment point	Study	Intervention group % change from baseline			Control group % change from baseline		
				M	SD	N	M	SD	N
Body composition	Appendicular lean mass (kg)	12 weeks	Drey <i>et al</i> , 2011 ³³	+1.65	0.71	23	+0.00	0.87	22
	Muscle mass of upper limb (cm ³)	6 months	Verschueren <i>et al</i> , 2011 ³⁶	-0.16	0.57	28	-0.25	0.38	28
	BMD of femoral neck (g/cm ²)	6 months	Verschueren <i>et al</i> , 2011 ³⁶	+0.71	0.42	28	+0.99	0.51	28

Group 2 compared vitamin D₃ supplementation and exercise training vs vitamin D₃ supplementation alone.

BMD, bone mineral density.

between measurement methodologies, differences between exercise regimens (although all adopted progressive RET), doses of vitamin D₃ (400–1920 IU/day) or may indicate that these studies were unsuitable for comparison.

Significant effects for the SPPB, TUG, muscle strength of the lower limb and the BMD of the femoral neck were observed within the intervention groups of group 2 studies; unsurprisingly, RET was found to have a positive influence. In a recent systematic review and meta-analysis, exercise significantly increased SPPB score and decreased TUG time, with large effect sizes (1.87 and -2.47, respectively⁴²); similar results are reported within this review. Vitamin D is a regulator of BMD, proliferating calcium and phosphate absorption in the intestine and acting directly on bone cells.⁴³ Vitamin D has previously been shown to influence BMD, fracture rate and risk⁴⁴; studies of patients who have sustained a hip fracture typically demonstrated low serum vitamin D (≤ 30.0 nmol/L⁴⁵). Supplementation of vitamin D and calcium has been shown to significantly decrease the rate of bone loss in the hip and spine.⁴⁶ GRADE analyses for these outcomes concluded the quality of evidence to be high (SPPB and TUG) or moderate (muscle strength of the lower limb and BMD of the femoral neck).

Closer examination of the control groups within significant outcomes for group 2 was undertaken to evaluate the effect of vitamin D₃ supplementation alone. Intriguingly, although the intervention groups (RET and vitamin D₃ supplementation) showed evidence of benefit in number of outcomes, the control groups (vitamin D₃ supplementation alone) showed mixed, or even negative impacts on the same outcomes. SPPB score was decreased postintervention compared with baseline by 0.30% and 0.50% in the control groups of studies³² and³³, respectively. Muscle strength of the lower limb and BMD of the femoral neck showed mixed results for the intervention groups, with some studies reporting small increases and others reporting small losses (non-significant). Previous reports of the effect of vitamin D supplementation on muscle strength and physical functioning are mixed; the InCHIANTI study of people aged 65 years or over reported a significant association between serum 25(OH)D < 25 nmol/L and SPPB score.⁴⁷ Similarly, a large prospective cohort of older adults aged 65 years or over found those with low (< 25 nmol/L) 25(OH)D were significantly more likely to experience losses in grip strength and higher rates of appendicular lean mass loss compared with those with higher (> 50 nmol/L) 25(OH)D.²³ Conversely, another large, prospective study found no association between serum 25(OH)D, walking speed and time for repeated chair stands.⁴⁸ The TUG test time increased in all groups of study,³² and was significantly increased in the vitamin D without exercise group in study (p=0.01).²¹ Again, participants included in studies³² and²¹ had sufficient serum 25(OH)D levels, indicating that supplementation in replete older adults may not confer additional benefits to neuromuscular function unless combined with exercise.

Narrative analysis

Studies in group 1^{21 31 32} had few body composition outcomes in common, therefore, a narrative analysis was conducted. The CSA of the quadriceps was analysed within study,³¹ and results showed that although the intervention group did experience a +4.94%, increase from baseline, the control group (not supplemented with vitamin D₃) actually showed a significantly higher increase in quadriceps CSA (+8.46%, p<0.05).

These results do not provide evidence for the additive effects of combined exercise training and vitamin D₃. Other study groups have reported changes in muscle CSA consequent to RET, which are both smaller^{8 49} and comparable⁵⁰ to those reported in study.³¹ Interestingly, study³¹ also assessed 'muscle quality' (muscle strength/CSA), although non-significant, the intervention group improved their muscle quality to a greater degree than the control group (+9.61% vs +0.66% change from baseline), indicating an increased functionality of the muscle to produce force; conceptually more relevant in combatting the effects of sarcopenia than muscle size and strength alone.⁵¹

Results of the narrative analysis for group 2 showed that the combined intervention of RET and vitamin D₃ supplementation was significantly more beneficial than vitamin D₃ supplementation alone for sit-to-stand transfer power, functional stair climbing muscle power, 30s sit-to-stand, 5-time chair stand, the four-square step test, body sway and backward walking. Only body sway was negatively affected by vitamin D₃ supplementation, although the within-group change was non-significant. Other outcomes of interest included normal walking speed, which deteriorated in both groups, the distance walked in 12 min and Romberg ratio, in which the control groups made the most improvement, although not significantly.

Limitations

Few published studies were eligible for inclusion within this review, although this serves to highlight the knowledge gap with respect to this topic. The inclusion of a high-risk study was deemed necessary due to the lack of available literature, although this had a negative effect on the perceived quality of evidence for the outcomes in which it was reported. Generally, outcome measure data could be graded as representing moderate quality, although there were several outcome measures graded as low or very low quality, due to the high variability of participant numbers, duration of interventions, exercise methodologies or differing vitamin D₃ doses and period of supplementation employed within the studies. Furthermore, data produced from meta-analyses including study²¹ may have been skewed due to the high weighting assigned for this study as a result of the large number of participants recruited.

Of the individual studies included within this review, none reported inclusion/exclusion criterion for vitamin D status, and although at baseline serum vitamin D was not significantly different between the groups in five

studies,^{21 31–33 36} two studies reported no data for serum vitamin D preintervention or postintervention.^{34 35} Additionally, analysis methods used within five studies included did not account for confounding factors,^{31–34 36} and participants were not stratified on the basis of any characteristics in three studies,^{21 31 35} although these were single-sex studies. Unfortunately, several outcome measures were unsuitable for inclusion within the qualitative analysis due to differing measurement methodologies used or too few outcome measures in common. A recent systematic review and meta-analysis investigating the effects of vitamin D on neuromuscular remodelling following exercise or injury similarly found few eligible studies and high levels of heterogeneity due to methodological differences, resulting in the authors to suggest more high-quality evidence is needed to reach a result that is conclusive.⁵²

CONCLUSION

This review provides tentative support for the additive effect of combined RET and vitamin D₃ supplementation for the improvement of muscle strength in older adults. For other aspects of musculoskeletal function, such as SPPB and TUG, no additional benefit beyond that gained from exercise training was found. This review showed no evidence of benefit of vitamin D₃ supplementation alone, however, few studies were identified during the literature search, highlighting that further evidence is required to draw any firm conclusions or make explicit recommendations regarding vitamin D₃ supplementation for musculoskeletal health and function in older adults.

Our recommendations to enable future studies to definitively answer questions regarding the additive effects of the combined vitamin D₃ supplementation and RET include common outcomes relevant to the condition studied, for example, the SPPB, 400 m walk and gait speed are recommended to assess physical performance,⁵³ which would allow for a more detailed assessment of results. Additionally, exercise interventions of similar durations would allow for a more accurate comparison between studies; it has been suggested that interventions with older adults should be of a minimum duration of 3 months to obtain significant differences in relevant outcomes.⁵³ Reporting of confounding factors would allow for adjustment of results via the use of covariates, for example, objective measures of physical activity using accelerometers, baseline serum vitamin D₃ status and participant characteristics, which may bias the participant pool. Separate analysis of male and female participants, or the addition of sex as a covariate in any analysis models would help to address sex-related differences in performance. Regarding study design, four-armed RCT studies are best placed to answer combined effects research questions, that is, exercise intervention, vitamin D intervention, both exercise and vitamin D, neither exercise nor vitamin D (true control). A true control group was

lacking from a number of the included studies within this review.

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Contributors AEA has planned, conducted and written the report for this study. CAG has been involved in all stages, particularly in critically reviewing and approving the final draft of the report. Asma Alrushud was involved in the search for literature and data extraction stages. Lynn Harris assisted in formulating the search strategy.

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