# Influence of combined vitamin D3 supplementation and resistance exercise training on musculoskeletal health in older men and women (EXVITD)

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# Influence of combined vitamin $D_3$ supplementation and resistance exercise training on musculoskeletal health in older men and women (EXVITD): protocol for a randomised controlled trial

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## ABSTRACT

**Introduction** Sarcopenia is a progressive loss in muscle mass, strength and function, the adverse consequences of which are severe, affecting quality of life and placing an increasing burden on social and healthcare systems. Vitamin D status is known to be associated with markers of sarcopenia, namely muscle mass, strength and function. Also, resistance exercise training (RET) is currently the only proven intervention to treat sarcopenia. However, very little data exist on the influence of combining the two interventions of vitamin D supplementation and resistance exercise training, although a recent systematic review provides tentative support for the current study's hypothesis that the combined intervention may further improve musculoskeletal function above exercise training alone. The aim of the present study is to determine whether vitamin $D_3$ supplementation is any more effective in improving musculoskeletal function when combined with RET compared with exercise training alone in older adults.

**Methods and analysis** This double-blinded randomised placebo-controlled trial will recruit a target of 127 eligible men and women aged ≥65 years living independently or in sheltered housing within the Birmingham area to two groups: (1) 6 months RET and placebo or (2) 6 months RET and 800 IU/d vitamin $D_3$. Measures of muscle power (Nottingham Power Rig), body composition (dual energy X-ray absorptiometry), muscle function (short physical performance battery, timed up and go), falls and fractures as events will be assessed. Assessments will take place at baseline and postintervention, with intermittent monitoring of bone turnover, calcium and vitamin D. The primary outcome will be lower limb extensor power output. Analyses of within-group changes and between-group differences in outcome measures are planned.

**Ethics and dissemination** The EXVITD study has ethical approval granted by the Black Country National Health Service Research Ethics Committee (14/WM/1220). Results of this trial will be submitted for publication in peer-reviewed journals and presented at conferences. The study is being conducted according to the principles of the Declaration of Helsinki.

## Strengths and limitations of this study

- The present study is a randomised, double-blind, placebo-controlled trial, which is the appropriate design to assess the primary and secondary outcome measures.
- The resistance training aspect of the study uses body weight, ankle weights and physiotherapy bands, which present a feasible daily home or group exercise routine for older adults.
- The study assesses a large number of outcome measures relating to musculoskeletal health, including dual energy X-ray absorptiometry, bone turnover markers, 25(OH)D and calcium monitoring and muscle strength and function parameters.
- A limitation of the study is the lack of a precise and quantifiable measures of exertion and exercise progression/muscle loading.

**Trial registration number**
NCT02467153; Post-results.

## INTRODUCTION

The UK has an ageing population; life expectancy has increased rapidly in the previous two decades, with life expectancy at birth between 2010 and 2012 reaching 82.72 for females and 78.85 years for males.[1] Importantly, healthy life expectancy is not keeping pace; adults over 65 years are expected to spend approximately 7.9 years in poor health.[2] Sarcopenia refers to the age-related loss of muscle mass, strength and function.[3] Using the European Working Group on Sarcopenia in Older People criteria, the prevalence of sarcopenia has been reported to be from 1% to 33% in adults of mean age 59.2–85.8 years. The prevalence is higher in older adults in long term

(eg, care home prevalence was 14%–33%) and acute care (hospital setting prevalence was 10%) settings.[4] In the face of an increasing proportion of older adults and the dramatic increase in pressure on health and social care,[5] many are likely to suffer the adverse consequences of sarcopenia, namely impaired functional ability, increased frequency of falls and fractures, with attendant morbidity and mortality; a higher incidence of hospitalisations and longer length of hospital stay.[6] Sarcopenia, therefore, represents a serious and increasing public health problem. The causes of sarcopenia are unclear, however, there are numerous factors associated aetiology.[7–10]

One such example is vitamin D deficiency; older adults are considered an 'at risk group', with prevalence rates of hypovitaminosis D reaching 89% in residential care.[11] Consequences of vitamin D deficiency include muscle weakness and an increased risk of falls and fractures.[12] While it is known that vitamin D is essential for calcium and phosphorous homoeostasis and bone health,[12] we know relatively little about the direct effects of vitamin D on muscle mass and function in humans. The majority of evidence for an effect on muscle is based on animal models, which have reported increases in muscle protein synthesis in response to vitamin D supplementation but which may not mimic the human condition,[13 14] and cross-sectional epidemiology[15–17] which cannot establish causality.

One recent study of 100 community-dwelling older adults (mean age 69.9 years) with baseline serum 25(OH)D concentrations <50 nmol/L receiving 800 IU $D_3$ or a placebo daily for 12 months found that double leg press and grip strength were more improved and total and appendicular lean mass loss was smaller within the vitamin D group, although there were no significant between-group differences.[18] Meta-analyses examining the effect of vitamin D supplementation on musculoskeletal parameters report conflicting evidence, although supplementation was shown to improve muscle strength, with effects more pronounced in older and vitamin D deficient participants.[19] Another factor associated with sarcopenia is physical activity. Resistance exercise training (RET) is the most promising intervention for improving[20] and also reversing sarcopenia.[21] It is the position of the Society on Sarcopenia, Cachexia and Wasting Disorders that RET should be implemented in the management of sarcopenia,[22] since it is known to improve muscle mass, strength and function.[21 23 24] Although and others have shown that even in very old adults (>75 years), RET improves muscle strength and functional outcomes, the hypertrophic ability of older muscle is blunted compared with younger adults.[25 26] Therefore, in order to help older adults maintain good musculoskeletal health, interventions to optimise responsiveness to physical activity are likely to be most effective if they are multimodal and include resistance exercise. One such example is the combination of RET with vitamin D supplementation.

Very few data exist that test the combined effects of vitamin $D_3$ supplementation and RET on the musculoskeletal health of older adults, as highlighted by two recent systematic reviews.[27 28] The first review included two studies, both of which found no additional effect of vitamin D on muscle mass or strength, although one study reported a further improvement in the timed up and go (TUG) test in participants supplemented with vitamin D.[28] One further systematic review and meta-analysis identified a total of seven studies and concluded that vitamin D supplementation and exercise training significantly improved muscle strength within the lower limb in comparison with exercise training alone (0.98, 95% CI 0.73 to 1.24, p<0.001).[27] However, the limitations of the review serve to highlight the lack of knowledge within this area; only three studies were included in this meta-analysis, and the high weighting of one particular study meant that only tentative conclusions could be drawn.

Therefore, the principal aim of the EXVITD study is to determine whether vitamin $D_3$ supplementation is more effective in improving musculoskeletal function when combined with RET compared with RET alone. We are focusing on the components of sarcopenia such as muscle mass, power and function rather than assessing the direct effects of the intervention on sarcopenic participants since improvements made in these parameters will be beneficial for all older adults, not just those who are sarcopenic. The hypothesis is that the combined intervention may further improve musculoskeletal function above exercise training alone.

The primary aim will be assessed as muscle power (Nottingham rig and Leonardo Mechanography, muscle function (short physical performance battery (SPPB), TUG) and body composition and bone mineral density (dual energy X-ray absorptiometry, DXA). Secondary objectives include: (1) determining the seasonal variation of 25(OH)D in a population of frailer older adults both free living and those living in supported housing; (2) Investigating the association between baseline 25(OH)D and physical activity measured using accelerometry and responsiveness to RET; (3) Determining between-group differences with respect to changes in falls as events and Quality of life (QoL); (4) Determining between-group differences with respect to changes in fractures as events; (5) Determining the influence of RET on serum inflammatory markers (eg, interleukin-6) and (6) Investigating the influence of RET on serum stress markers (cortisol, Dehydroepiandrosterone (DHEAS)).

## METHODS

### Study design

The study protocol is presented in line with the Standard Protocol Items: Recommendations for Interventional Trials guidelines (see Research Checklist). The study start date was April 2016, with study completion anticipated in January 2020.The EXVITD study is a two-arm exploratory double-blinded randomised placebo-controlled trial. 127 participants will be identified, recruited and randomised

1:1 into two groups: (1) RET and 800 IU vitamin $D_3$ per day or, (2) RET and a daily placebo for 6 months. Eligibility will be assessed at screening, with all outcome measures to be collected at baseline and 6 months and venous blood sampling additionally assessed at months 1 and 3.

The EXVITD study will take place within Birmingham, at both the University of Birmingham and the Wellcome Trust Clinical Research Facility (CRF) at the Queen Elizabeth Hospital. Data collection began in July 2017 and collection/analysis is expected to be completed by 31 December 2019.

## Study population

We aim to recruit 127 men and women aged ≥65 years, who are ambulatory (with/without aids) and live independently or within sheltered housing accommodation in Birmingham, West Midlands, UK. We have selected this population as they are more susceptible to sarcopenia and subsequent functional deficits and therefore stand to benefit from interventions aimed to improve musculoskeletal health. Eligibility criteria are summarised in table 1. Since confirmation of eligibility in this low-risk study does not require the interpretation of medical notes/history or a physical examination, the study chief investigator (CI) is suitably qualified to confirm eligibility. However, any queries about eligibility will be raised with the medical expert before a decision is taken.

## Recruitment

Recruitment strategies will be threefold and detailed below.

## Primary care approach

We will work with the West Midlands Clinical Research Network who will assist with recruitment via primary care and help identify additional supported housing facilities under their aegis. Eligible participants from surrounding areas will be identified via an electronic practice-based search of registers using the criteria described in table 1. The general practitioner (GP) will review and exclude anyone they deem unsuitable for reasons other than those identified in the protocol (eg, already taking part in another study).

A patient approach letter will be sent to identified patients from the GP together with a participant information sheet (PIS, see online supplementary file 1), reply form and FREEPOST envelope addressed to the study team. Alternatively, the research team can be contacted directly by phone or email. Patients not responding to the first invitation will receive one reminder after 3 weeks, including an acknowledgement that the letter may be ignored by those that responded to the initial letter. When the study team receive a signed patient contact agreement consent form, they will contact the potential participant via telephone to discuss the study in more detail, go through the questionnaire responses and if eligible, obtain consent.

**Table 1** EXVITD study eligibility criteria*

| | |
|---|---|
| Inclusion criteria | Aged ≥65 years |
| | Ambulatory (with or without walking aids) |
| | Living independently or within sheltered housing accommodation |
| Exclusion criteria | History of myocardial infarction within previous 2 years |
| | Cardiac illness: moderate/severe aortic stenosis, acute pericarditis, acute myocarditis, aneurysm, severe angina, clinically significant valvular disease, uncontrolled dysrhythmia, claudication within the previous 10 years; thrombophlebitis or pulmonary embolus within the previous 2 years |
| | History of cerebrovascular disease (cerebrovascular accidentor transient ischaemic attack) within the previous 2 years |
| | Acute febrile illness within the previous 3 months |
| | Severe airflow obstruction; uncontrolled metabolic disease (eg, thyroid disease or cancer) |
| | Significant emotional distress, psychotic illness or depression within the previous 2 years |
| | Lower limb fracture sustained within the previous 2 years/upper limb fracture within the previous 6 months |
| | Non-arthroscopic lower limb joint surgery within the previous 2 years |
| | Any reason for loss of mobility for greater than 1 week in the previous 2 months or greater than 2 weeks in the previous 6 months |
| | Resting systolic pressure >200 mm Hg or resting diastolic pressure >100 mm Hg |
| | Poorly controlled atrial fibrillation; poor (chronic) pain control |
| | Moderate/severe cognitive impairment (Mini-Mental State Examination score <23) |
| | Vitamin D deficiency (serum 25(OH)D3 <30 nmol/L); current antiresorptive/anabolic treatment for osteoporosis |
| | Treatment with bisphosphonates for osteoporosis in the past 2 years |
| | Current use of glucocorticoids; known primary hyperparathyroidism |
| | Renal impairment (stage 4 or 5) |

*Based on previously published criteria of exercise studies with older adults.[44]

## Sheltered housing approach

Sheltered housing managers and head offices will be contacted directly, and where possible, study information will be presented at residents' meetings, coffee mornings and on communal notice boards. Residents can contact the study team directly or through the housing manager. When a response is received, the participant will be contacted as detailed above.

Table 2 Eligibility screening assessments

| Informed consent | Face-to-face at participant's home or at the University of Birmingham |
|---|---|
| General Health Questionnaire | 1. Telephone call or at participant's home or at the University of Birmingham<br>2. Answering 'yes' to any question outlined in the exclusion criteria shown in table 1 |
| Mini-Mental State Exam | 1. At participant's home or at the University of Birmingham<br>2. A score <23 |
| Venous blood draw to assess serum 25(OH)D status | 1. At participant's home or at the University of Birmingham<br>2. Serum 25(OH)D<30 nmol/L |
| Physical activity monitoring (accelerometry) | 1. At participant's home or at the University of Birmingham<br>2. A descriptive to be used during stratification |

### Independent living approach

We will recruit older adults living independently via several methods. Study information will be displayed at appropriate locations, for example, seniors' groups, community centres and libraries. Additionally, advertisement will be via appropriate and relevant websites, print media (eg, magazines, leaflets, newsletters) and social media. Members of the Birmingham 1000 Elders cohort managed by the University of Birmingham will also be recruited. Study information will be presented at seniors' group meetings and direct contact to a member of the study team will be answered as detailed above.

### Eligibility screening

The assessments completed during eligibility screening are documented in table 2, and will be conducted via one of following methods:

1. For participants identified via the primary care or independent living approach, the health questionnaire (see online supplementary file 2) will be conducted via telephone, with subsequent tests completed at the University of Birmingham.
2. For participants identified via the sheltered housing approach, all eligibility screening tests will be conducted within the participant's own home, provided health and safety requirements for the blood draw are met. Should requirements not be satisfied, transport will be arranged for the participant and the visit will take place at the University of Birmingham.

### Consent

It is the responsibility of the investigator to obtain written informed consent for each participant prior to performing any trial related procedure. A PIS will be provided to facilitate this process and the participant will be given at least 1 week to read the PIS and discuss participation with others outside the research team. For participants recruited via the primary care network approach, a signed patient contact agreement consent form will be received before any contact is made.

Investigators will ensure they adequately explain the aim, trial treatment, anticipated benefits and potential hazards, and the participant will be given the opportunity to ask questions. They will also stress that participation is voluntary and that the participant is free to refuse to take part/withdraw from the trial at any time without it affecting their future care. If interest in participation in the trial is confirmed, they will be asked to sign and date the consent form (see online supplementary file 3).

At each visit the participant's willingness to continue in the trial will be ascertained. Throughout the trial the participant will have the opportunity to ask questions about the trial. Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the participants' decision to continue, participants will be given time to consider and if happy to continue will be reconsented. Reconsent will be documented in the medical notes and the participant's right to withdraw will remain. With the participant's consent, their GP will be informed of their participation.

### Randomisation, allocation and blinding procedures

Participants will be randomised by a University Hospitals Birmingham statistician (PN) to one of two arms: (1) RET +800 IU vitamin $D_3$ daily (intervention) or 2) RET +placebo daily for 6 months (control). Participants will be stratified on the basis of vitamin D status (high ≥50 nmol/L, low=30–50 nmol/L), physical activity (measured prerandomisation using accelerometry, high ≥7000 steps per day, low <7000 steps per day) and sex. Randomisation will be computer generated using the random number function in Microsoft Excel with a mixture of block sizes of four and six. Allocation of participants into study group and labelling and allocation of the tablets into supplement bottles and adherence monitoring will be completed within the University of Birmingham, by an individual with no involvement in the study.

The study team and participants will be blinded to group allocation. Randomisation codes will be kept in individual sealed envelopes to avoid unblinding the whole cohort if an individual participant allocation is requested by the study team's medical expert. In order to avoid assessor unblinding, all blood results will be viewed by the study team's medical expert who may be unblinded as a consequence. Unblinding decisions will be taken by the study medical expert, in consultation with the CI. Arrangements for emergency unblinding if both the medical expert and CI are unavailable will be according to established UHB practice embedded within its governance structure. The CRF does not open 24 hours a day, however, the CRF clinical manager has 24 hours access to the relevant information. The study timeline schematic is shown as figure 1 in online supplementary file 4.

## Study intervention: intervention arm

### Resistance exercise training

A rolling group exercise programme with a maximum of 12 participants per group and no more than 2 groups running concurrently will be established. Group 1 will run alone for 3 months to check for practical issues before completing the 6-month intervention. The exercise training intervention will be delivered by the study team in partnership with a specialist exercise instructor who will deliver initial training, supervision and regular quality assessment. The specialist exercise instructor will provide a copy of their public, personal trainer and coaches liability Insurance certificate to the CI.

The evidence-based Peer Exercise Programme Promotes Independence (PEPPI) programme will be used within the EXVITD study and has been adapted by the specialist exercise instructor to suit a wider range of functional abilities (ie, more standing exercises for higher functioning participants) with permission from the ageing and physical activity expert of the PEPPI programme William Evans.[29] Balance and coordination exercises from the OTAGO programme[30] will also be incorporated since it has been reported that a combination of RET and balance exercises were more effective at reducing the rate of falls than balance or function exercise alone.[31] The specialist exercise instructor has over 10 years of experience of delivering these exercises to older adults across the range of functional abilities, including those with very limited mobility, within the community and population from which we will recruit. The programme has the support of experts in the field including Janet Lord, Professor of Immune Cell Biology and director of the Institute for Inflammation and Ageing at Birmingham University Medical School and a director of the Medical Research Council-Versus Arthritis Centre for Musculoskeletal Ageing Research. The programme has been approved by the Falls Prevention Lead nurse for University Hospitals Birmingham and has been utilised within the National Health Service (NHS), University of Birmingham, the Royal Voluntary Service, St Giles Hospice and Age UK. Move It Or Lose It! have the support of an advisory board of experts within the field (including JL, chartered physiotherapists and the Head of Strategy and Development at the Royal Voluntary Service).

The EXVITD RET programme will follow the same format as the PEPPI programme including a dynamic warm-up and aerobic section with range of motion stretches (approximately 15 min), balance and coordination section (approximately 10 min), resistance training section (approximately 20–25 min) and a cool down with stretches (approximately 10–15 min). Each session will last for approximately 60 min, with two sessions per week for 6 months. The sessions will be tailored and progressed individually to a range of abilities within the target group. The warm-up and aerobic section and cool down will be performed to music. We will be using resistance bands (colours ranging from red to black) and ankle weights (participants can start without and can gradually progress to using 0.5, 0.75 and 1 kg ankle weights) during the strength/resistance section of the group sessions, with a focus on, although not exclusively, the lower body since this is our primary outcome measure. Types of resistance work are shown on the Move It Or Lose It website (https://www.moveitorloseit.co.uk/about-us/). As standard, all class attendees will complete a Physical Activity Readiness Questionnaire prior to beginning the intervention.

Attendance at group sessions will be monitored via a register, and participants will be asked to report any non-attendances to a member of the study team. Progression will be assessed via the 30 s sit to stand challenge, band colour/ankle weight used and repetitions of resistance exercises. Groups will run throughout the year to mitigate for seasonal variation in vitamin D status. Exercise sessions will be held in communal living spaces for participants recruited via the sheltered housing route or within the Morris Club Centre, an NHS health, fitness and wellbeing centre located on the Queen Elizabeth Hospital campus, for participants recruited via the independent living or primary care approach. Prepayed transport to and from the exercise sessions will be offered to all participants in order to remove a potential barrier to participation and promote participant retention. During the study, participants will be asked to continue with their usual daily activities but not to start any additional physical activity or supplements; after the study is completed a book or DVD of the training exercises will be given to encourage continued physical activity as a lifestyle choice.

### Vitamin $D_3$ supplementation

In line with the current Institute Of Medicine[32] and Royal Osteoporosis Society[33] guidelines, the daily dose of vitamin $D_3$ is 800 IU. This is below the UK Food Standards Agency publicly stated safe limit for daily vitamin D intake at 1000 IU,[34] although this has been criticised as overly conservative.[35] The Institute of Medicine set a Tolerable Upper Intake Level for vitamin D of 4000 IU per day[32] and the European Food Safety Agency Panel on Dietetic Products, Nutrition and Allergies have set a no observed adverse effect level of 10 000 IU per day.[36] Additionally, hypercalcaemia, the hallmark of vitamin D intoxication, has only been consistently observed in anecdotal evidence when 25(OH)D concentrations are between 375–500 nmol/L.[37] Therefore, assessment and monitoring of serum 25(OH)D and calcium will occur throughout the study although we do not anticipate any reason for early termination of the study.

Individual supplies of over the counter vitamin D supplements provided by IVC Brunel Healthcare will be given to participants in tablet form packed in pots; pots will contain a 4-week supply of supplements (28 tablets) and one 800 IU tablet is to be taken per day. Tablets will be stored at ambient temperature by the study team within the University of Birmingham, and distributed to participants every 4 weeks. Tablet manufacture will be undertaken by Brunel Healthcare in a Medicines and Healthcare products Regulatory Agency (MHRA)

licensed facility, labelling and allocation of tablets into pots will take place within the University of Birmingham by an individual with no involvement in the study. Labels will contain the following information: number of tablets (28); dose (20 µg/800 IU); schedule and directions of use; storage information; date; participant ID; batch information; trial name (EXVITD) and study team contact number. Compliance will be monitored by the return of used tablet pots, with gentle compliance reminders given to participants during the exercise sessions.

### Study intervention: control arm

Participants randomised to the control arm of the trial will receive the RET intervention alongside the intervention group and a daily placebo supplement distributed and to be taken in the same way as the vitamin $D_3$ supplements.

### Outcome assessments

A list of scheduled outcome assessments is presented in table 3. Outcome measures will be assessed by the study team, with the exception of the DXA scan (performed by a radiographer). For the reliability and validity of outcome measures in older adults, see online supplementary file 5.

### Sample size calculation

We estimate n=114 participants will give 80% power at the 5% level (two-sided test) to detect an additional 19% improvement in the primary outcome measure (lower limb power output) above that expected as a result of RET alone (ie, 29%, assuming SD of 26% and 43% in the two groups). This represents a gain of over 10 'mobility years' assuming an annual loss of power of 1.5%. This sample size also allows detection of a 1.0-point increase on the

**Table 3** EXVITD study outcome measures

| | Trial period | | | | | |
|---|---|---|---|---|---|---|
| | Enrolment | Allocation | Post-allocation | | | Follow-up |
| Time point | −56 to −7 days (Screening) | −7 to 0 days (Baseline) | Month 1 | Month 3 | Month 6 | +1 to +7 days |
| Enrolment | | | | | | |
| Informed consent* | X | | | | | |
| Health questionnaire | X | | | | | |
| MMSE | X | | | | | |
| Venous blood sampling | X | X | X | X | X | X |
| Blood pressure | | X | | | | X |
| Physical activity monitoring (accelerometery) | X | | | | | X |
| Allocation | | X | | | | |
| Interventions | | | | | | |
| Resistance exercise training | | | ← | — | → | |
| Vitamin D or placebo | | | ← | — | → | |
| Outcome assessments | | | | | | |
| Lower limb extensor power (Nottingham power rig)† | | X | | | | X |
| Body composition and BMD (DXA)‡ | | X | | | | X |
| Chair rise (Leonardo force plates)‡ | | X | | | | X |
| Functional ability (SPPB and TUG)‡ | | X | | | | X |
| Falls as events† | X | X | X | X | X | X |
| Fractures as events† | X | X | X | X | X | X |
| Quality of life (SF-36)† | | X | | | | |
| Musculoskeletal pain questionnaire† | | X | | | | X |
| Food diary† | | X | | | | X |

Food diary: see online supplementary file 6.
*Informed consent form will be signed during the screening visit and will be reconfirmed verbally at each following time point.
†Primary outcome measure.
‡Secondary outcome measures.
BMD, bone mineral density; DXA, dual energy X-ray absorptiometry; MMSE, Mini-Mental State Examination; SF-36, 36 item Short Form Survey; SPPB, short physical performance battery; TUG, timed up and go.

SPPB score over and above an assumed 1.5-point increase due to exercise training alone. These calculations are based on a combination of our own pilot data and previously published data.[25 38–40] Informed by our experience of exercise interventions with older adults and patient groups we have added 13 participants to cover an anticipated 10% drop-out rate, giving a total of n=127 participants to be recruited.

### Statistical analysis

All data will be entered into a database and analysed using IBM SPSS Statistics for Windows, V.25.0. Data analysis will be conducted on both an intention-to-treat and per-protocol basis. Normality will be assessed by visual inspection of Q-Q plots and the characteristics of participants at baseline will be summarised using means and SD, medians and quartiles or counts and percentages, as appropriate. The comparison of primary interest is the difference at baseline and 6-month follow-up between the intervention and control groups. Appropriate log transformations will be applied prior to analysis of covariance (ANCOVA) for primary and secondary outcome measures. Covariates applied to the analysis will include age, sex, physical activity and baseline serum 25(OH)D. All statistical tests conducted will be two sided with an alpha level of p=0.05 with missing data addressed using multiple imputation. There are no planned subgroup or interim analyses.

### Data collection, management and monitoring

All personal data will be handled and stored with the strictest confidence and in accordance with the Data Protection Act 2018. Personal details such as home address, name, date of birth and contact number will be provided by the participant in the signed participant contact agreement form or in person during an introductory meeting, with the purpose of future contact. Potential participants will be made aware that personal data collected during the study will be kept confidential and stored securely at the University of Birmingham in a locked cabinet accessible only to members of the study team. Additionally, participants will be aware that relevant sections of medical notes and data collected during the study may be looked at by responsible individuals from the University Hospitals Birmingham NHS Foundation Trust.

Once allocated to one of the study groups, participants will be assigned a unique personal identification code, which will be used from this point onwards to identify them in all documentation, correspondence between the participating sites and the case report form (see online supplementary file 7). In the case of specific issues and/or queries from regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected. Personal data will be kept for 10 years after the last data capture in line with University of Birmingham policy to allow for verification.

### Missing data

Data reported on each case report form will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried. Individual data sets will be checked by the CI at regular intervals and discrepancies highlighted and listed. These will be viewed and discussed by the trial management group.

### Storage and analysis of samples

In total, five blood samples (10 mL) will be taken from participants completing the study; time points are shown in table 3. The samples will be analysed at the Queen Elizabeth clinical haematology laboratory (full blood count, blood biochemistry, liver and renal function, serum 25(OH)D), the University of Birmingham Institute of Inflammation and Ageing (stress and inflammatory markers) under the supervision of a member of the study team and at the University of Liverpool (bone turnover markers) following a material transfer agreement. Blood to be analysed at the Queen Elizabeth hospital will be sent for processing immediately, bloods to be analysed by the University of Birmingham and Liverpool will be stored at the Wellcome Trust CRF at the Queen Elizabeth hospital at −80°C for analysis once data collection is complete. Collection, analysis, storage and destruction of residual blood samples will be according to local policy and standard operating procedures aligned to the University of Birmingham Quality Management System.

### Monitoring and auditing

This is a low-risk single centre trial, and thus, the study team do not consider the support of a data monitoring committee to be necessary; however, monitoring of the study by the University of Birmingham Clinical Research Compliance Team, including access to source documents as requested, will be permitted. They will review at intervals agreed with the CI.

### Patient and public involvement

No patient was involved in the design of this study, although a trial steering committee will comprise the trial management group, one external senior academic, one representative from a Housing Trust and two older adults from the Birmingham 1000 Elders database.

All study team members have received necessary training and will conduct the study in accordance with Good Clinical Practice guidelines.

### Safety monitoring

Serious adverse events (SAEs), defined as any event that could be related to the study that caused injury or hospitalisation, will be reported to the CI and the CRF's clinical manager for review within 24 hours after first becoming aware of the event. All SAEs will be reviewed formally every 2 weeks during CRF operations meetings, which include representation from the trust research, development and innovation office.

### Amendment

Should the authors wish to make any substantial amendments to the REC application or supporting documentation, a notice of amendment will be submitted for REC consideration.

### Dissemination policy

Results of this trial will be submitted for publication in peer-reviewed journals. The manuscript will be prepared by the study team led by the CI. Authors will acknowledge that the trial was performed with the support of the Royal Osteoporosis Society. Participants will be contacted and provided with a copy of the publication.

## DISCUSSION

Although exercise is currently the only proven mechanism to improve the symptoms of sarcopenia,[41] the anabolic response to RET is blunted in older compared with younger adults[25 26] and strategies to potentially overcome this effect are lacking. A recent systematic review highlighted the lack of data in this area[27] and provided tentative support for the combined intervention of vitamin D and RET.[27] Very few studies to date have been appropriately designed to test the combined effects of vitamin D and exercise in older adults, and of the studies which have, poor exercise compliance[42] and small sample sizes have been reported,[43] limiting interpretation of the data.

Therefore, the EXVITD study aims to address these issues and bridge the gap in knowledge regarding the potential enhancement of the effects of RET by vitamin D supplementation. A sample size of n=127 represents a substantial addition to the current data and as the study team will be delivering the intervention (both the supplements and the RET sessions), adherence will be monitored closely and encouraged in person. A finding that RET and vitamin D supplementation is effective compared with RET alone will support the development of future multimodal interventions to maintain bone and muscle health in old age and pave the way for further mechanistic and intervention studies examining the effects of RET/vitamin D in conjunction with other promising anabolic agents.

The strengths of this study include the design; a randomised double-blinded placebo-controlled trial is the most appropriate methodology to use to assess the primary and secondary outcomes. A range of outcome measures will provide a wealth of information regarding the musculoskeletal health of the participants. Additionally, the present study aims to recruit older men and women, meaning that the results of the trial will be generalisable with respect to sex.

One limitation of the study is the lack of a precise and quantifiable measure of exertion, exercise progression or muscle loading. Exertion will not be assessed in the present study; the use of objective measures such as heart rate monitors or rate of perceived exertion scales were rejected due to additional participant burden. Exercise progression and muscle loading would be more objectively measured if gym-based resistance equipment were to be employed, however, the benefit of using body weight, ankle weights and physiotherapy bands is that these equipment will be more familiar and readily adapted to daily practice, so that new-found exercise habits may be maintained following the close of the study. Additionally, previous studies have emphasised benefit of vitamin D supplementation in deficient participants[19]; since vitamin D deficiency is an exclusion criterion, we may be less likely to observe meaningful clinical effects of supplementation in our vitamin D insufficient or replete participants.

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**Contributors** The chief investigator (CAG) designed the study protocol in collaboration with AEW. SL-N advised regarding the vitamin D3 supplementation, JL provided advice about inflammatory markers, AD and JR had substantial input regarding the resistance exercise training programme, PN advised regarding statistical approaches, NG advised in his capacity as study medical expert. AEW drafted the protocol and all other named authors critically revised, contributed to the intellectual content of the protocol and approved the final version for publication. With thanks to the Wellcome Trust Clinical Research Facility staff for their support, particularly Trish Brady, the Clinical Research Network for recruitment assistance, the Royal Osteoporosis Society for funding the study and our grateful thanks to IVC Brunel Healthcare for providing the study with vitamin D3 and placebo supplementation.

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**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

**Patient consent for publication** Not required.

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## REFERENCES


1 Office for National Statistics. Life expectancy at birth and at age 65 by local areas in England and Wales: 2012 to 2014 2015.
2 Office for National Statistics. Changes in healthy life expectancy (HLE): office for national statistics, 2014. Available: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/datasets/changesinhealthylifeexpectancyhle [Accessed 24 Jul 2019].
3 Cruz-Jentoft AJ, Bahat G, Bauer J, *et al*. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* 2019;48:16–31.
4 Cruz-Jentoft AJ, Landi F, Schneider SM, *et al*. Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International sarcopenia initiative (EWGSOP and IWGS). *Age Ageing* 2014;43:748–59.
5 Janssen I, Shepard DS, Katzmarzyk PT, *et al*. The healthcare costs of sarcopenia in the United States. *J Am Geriatr Soc* 2004;52:80–5.
6 Beaudart C, Zaaria M, Pasleau F, *et al*. Health outcomes of sarcopenia: a systematic review and meta-analysis. *PLoS One* 2017;12:e0169548.
7 Bano G, Trevisan C, Carraro S, *et al*. Inflammation and sarcopenia: a systematic review and meta-analysis. *Maturitas* 2017;96:10–15.
8 Steffl M, Bohannon RW, Sontakova L, *et al*. Relationship between sarcopenia and physical activity in older people: a systematic review and meta-analysis. *Clin Interv Aging* 2017;12:835–45.
9 Robinson S, Cooper C, Sayer AA. *Nutrition and sarcopenia: a review of the evidence and implications for preventive strategies*. Clinical Nutrition and Aging: Apple Academic Press, 2017: 3–15.
10 De Spiegeleer A, Beckwée D, Bautmans I, *et al*. Pharmacological interventions to improve muscle mass, muscle strength and physical performance in older people: an umbrella review of systematic reviews and meta-analyses. *Drugs Aging* 2018;35:719–34.
11 Schilling S. Epidemic vitamin D deficiency among patients in an elderly care rehabilitation facility. *Deutsches Ärzteblatt International* 2012;109:33.
12 Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. *Am J Clin Nutr* 2008;87:1080S–6.
13 Garcia LA, King KK, Ferrini MG, *et al*. 1,25(OH)2vitamin D3 stimulates myogenic differentiation by inhibiting cell proliferation and modulating the expression of promyogenic growth factors and myostatin in C2C12 skeletal muscle cells. *Endocrinology* 2011;152:2976–86.
14 Srikuea R, Zhang X, Park-Sarge O-K, *et al*. Vdr and CYP27B1 are expressed in C2C12 cells and regenerating skeletal muscle: potential role in suppression of myoblast proliferation. *Am J Physiol Cell Physiol* 2012;303:C396–405.
15 Wicherts IS, van Schoor NM, Boeke AJP, *et al*. Vitamin D status predicts physical performance and its decline in older persons. *J Clin Endocrinol Metab* 2007;92:2058–65.
16 Visser M, Deeg DJH, Lips P, *et al*. Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (sarcopenia): the longitudinal aging study Amsterdam. *J Clin Endocrinol Metab* 2003;88:5766–72.
17 Houston DK, Cesari M, Ferrucci L, *et al*. Association between vitamin D status and physical performance: the InCHIANTI study. *J Gerontol A Biol Sci Med Sci* 2007;62:440–6.
18 Shea MK, Fielding RA, Dawson-Hughes B. The effect of vitamin D supplementation on lower-extremity power and function in older adults: a randomized controlled trial. *Am J Clin Nutr* 2019;109:369–79.
19 Beaudart C, Buckinx F, Rabenda V, *et al*. The effects of vitamin D on skeletal muscle strength, muscle mass, and muscle power: a systematic review and meta-analysis of randomized controlled trials. *J Clin Endocrinol Metab* 2014;99:4336–45.
20 Kosek DJ, Kim J-S, Petrella JK, *et al*. Efficacy of 3 days/wk resistance training on myofiber hypertrophy and myogenic mechanisms in young vs. older adults. *J Appl Physiol* 2006;101:531–44.
21 Cruz-Jentoft AJ. Sarcopenia: Preventable and Reversible. In: *Prevention of chronic diseases and age-related disability*. Springer, 2019: 47–52.
22 Bauer J, Morley JE, Schols AMWJ, *et al*. Sarcopenia: a time for action. An SCWD position paper. *J Cachexia Sarcopenia Muscle* 2019;10:956–61.
23 Nascimento CM, Ingles M, Salvador-Pascual A, *et al*. Sarcopenia, frailty and their prevention by exercise. *Free Radic Biol Med* 2019;132:42–9.
24 Beckwée D, Delaere A, Aelbrecht S, *et al*. Exercise interventions for the prevention and treatment of sarcopenia. A systematic umbrella review. *J Nutr Health Aging* 2019;23:494–502.
25 Greig CA, Gray C, Rankin D, *et al*. Blunting of adaptive responses to resistance exercise training in women over 75y. *Exp Gerontol* 2011;46:884–90.
26 Raue U, Slivka D, Minchev K, *et al*. Improvements in whole muscle and myocellular function are limited with high-intensity resistance training in octogenarian women. *J Appl Physiol* 2009;106:1611–7.
27 Antoniak AE, Greig CA. The effect of combined resistance exercise training and vitamin $D_3$ supplementation on musculoskeletal health and function in older adults: a systematic review and meta-analysis. *BMJ Open* 2017;7:e014619.
28 Beaudart C, Dawson A, Shaw SC, *et al*. Nutrition and physical activity in the prevention and treatment of sarcopenia: systematic review. *Osteoporos Int* 2017;28:1817–33.
29 Arkansas Department of Health. *Arkansas PEPPI peer leader manual*. Arkansas Department of Health, 2005.
30 Campbell A, Robertson MC. *Otago exercise programme to prevent falls in older adults*. Wellington: ACC Thinksafe, 2003: 3.
31 Sherrington C, Fairhall NJ, Wallbank GK, *et al*. Exercise for preventing falls in older people living in the community. *Cochrane Database Syst Rev* 2019;1:CD012424.
32 Ross AC, Taylor CL, Yaktine AL, *et al*. Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. In: *Dietary reference intakes for calcium and vitamin D*. Washington, DC: National Academies Press, 2011.
33 The Royal Osteoporosis Society. Vitamin D: the Royal osteoporosis Society, 2019. Available: https://theros.org.uk/information-and-support/looking-after-your-bones/vitamin-d/ [Accessed 26 Jul 2019].
34 Food Standards Agency. *Safe upper levels for vitamins and minerals*. London, UK: UK Foods Standards Agency, 2003.
35 Vieth R. Critique of the considerations for establishing the tolerable upper intake level for vitamin D: critical need for revision upwards. *J Nutr* 2006;136:1117–22.
36 EFSA Panel on Dietetic Products N, Allergies. Scientific opinion on the tolerable upper intake level of vitamin D. *EFSA J* 2012;10:2813.
37 Jones G. Pharmacokinetics of vitamin D toxicity. *Am J Clin Nutr* 2008;88:582S–6.
38 Skelton DA, Young A, Greig CA, *et al*. Effects of resistance training on strength, power, and selected functional abilities of women aged 75 and older. *J Am Geriatr Soc* 1995;43:1081–7.
39 Young A, Stokes M, Round JM, *et al*. The effect of high-resistance training on the strength and cross-sectional area of the human quadriceps. *Eur J Clin Invest* 1983;13:411–7.
40 Perera S, Mody SH, Woodman RC, *et al*. Meaningful change and responsiveness in common physical performance measures in older adults. *J Am Geriatr Soc* 2006;54:743–9.
41 Offord NJ, Witham MD. The emergence of sarcopenia as an important entity in older people. *Clin Med* 2017;17:363–6.
42 Bunout D, Barrera G, Leiva L, *et al*. Effects of vitamin D supplementation and exercise training on physical performance in Chilean vitamin D deficient elderly subjects. *Exp Gerontol* 2006;41:746–52.
43 Agergaard J, Trøstrup J, Uth J, *et al*. Does vitamin-D intake during resistance training improve the skeletal muscle hypertrophic and strength response in young and elderly men? - a randomized controlled trial. *Nutr Metab* 2015;12:32.
44 Greig CA, Young A, Skelton DA, *et al*. Exercise studies with elderly volunteers. *Age Ageing* 1994;23:185–9.