Feasibility of a high-protein Mediterranean-style diet and resistance exercise in cardiac rehabilitation patients with sarcopenic obesity (PRiMER): Study protocol for a randomised control trial.

Names of protocol contributors

Deaglan McCullough[1,2,3]*, Richard Kirwan[2,4]*, Tom Butler[5], Fatima Perez de Heredia[2,4], Dick Thijssen[1,2], Gregory Y. H. Lip[6,7], Joseph Mills[6], Ian G. Davies[1,2]

[1] Research Institute of Sport and Exercise Science, Liverpool John Moores University, Liverpool, UK.

[2] Institute for Health Research, Liverpool John Moores University, Liverpool, UK.

[3] Carnegie School of Sport, Leeds Beckett University, Leeds, UK

[4] School of Biological and Environmental Sciences, Liverpool John Moores University, Liverpool, UK.

[5] Faculty of Health, Social Care and Medicine, Edge Hill University, Ormskirk, UK

[6] Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, UK.

[7] Department of Clinical Medicine, Aalborg University, Aalborg, Denmark.

* Co-first authors

Corresponding author

Tom Butler: Butlert@edgehill.ac.uk

Abstract

Background. Cardiac rehabilitation (CR) is an essential component of long-term recovery following a cardiac event. Typical CR may not be optimal for patients presenting with sarcopenic obesity (SO) who present with reduced muscle mass and elevated adipose tissue, and may indicate greater cardiovascular disease (CVD) risk. Resistance exercise and high-protein diets are known to increase muscle mass, while Mediterranean-style diets have been shown to reduce CVD risk. A high-protein Mediterranean-style diet combined with resistance exercise intervention is yet to be trialled in cardiac rehabilitation populations.

Objectives. Primary outcome: to determine the feasibility of such an intervention by investigating the perceptions, acceptance and adherence to a resistance exercise protocol and high-protein Mediterranean style diet in a UK cardiac rehabilitation population with SO. Secondary outcome: to trial this protocol ahead of a fully powered clinical study.

Methods. Eligible cardiac rehabilitation patients will be randomised to one of the following: 1) a control group (standard CR), 2) high-protein Mediterranean-style diet, 3) resistance exercise group, or 4) both high-protein Mediterranean-style diet and resistance exercise group. The pilot study will last 12 weeks. Measures of body composition (dual energy x-ray absorptiometry) grip strength, CVD risk (e.g., fasting triglycerides, glucose, cholesterol) and dietary adherence will be assessed at baseline and after 12 weeks. To compare groups, a mixed model ANOVA (time x intervention) will be performed. Patient participant involvement throughout the development of this project will be used to determine the feasibility of a future, fully powered, randomised control trial. A feasibility questionnaire will help establish the proportion of eligible participants, their willingness to be randomised, response rates, and ethical considerations. Furthermore, focus groups, food tasting and telephone interviews will be conducted to assess the acceptability of recipes and exercise protocols provided.

Discussion. This pilot trial will determine whether a fully powered, multi-centred randomised control trial in CR patients with SO can be implemented. The information received from patient

involvement will be invaluable for identifying possible barriers to participation and tailoring interventions to participant needs, helping to increase the likelihood of long-term compliance to health-promoting lifestyle changes.

Registration

This study is registered at clinicaltrials.gov (NCT04272073), registered on 17/02/2020, https://clinicaltrials.gov/ct2/show/NCT04272073.

Date and Version

28/12/20 version 3.0

Keywords

Mediterranean diet, cardiac rehabilitation, high-protein, resistance exercise, sarcopenic obesity, anabolic resistance, cardiovascular disease

Background

Currently 7.4 million people in the UK are living with cardiovascular disease (CVD), which is responsible for more than 1 in 4 deaths in the UK per year (1) and leads to a considerable economic cost (2). Obesity, which is commonly associated with risk markers for cardiometabolic disease (CMD), is a key risk factor in the development of CVD (3,4). Conversely, in adults free of CVD, skeletal muscle mass is shown to have an inverse association with future CVD incidence independent of CVD risk factors such as smoking habits, hypertension, hypercholesterolaemia and diabetes (5). Furthermore, in individuals with CVD, those who have high muscle mass and high fat mass have been shown to have significantly lower rates of mortality compared with individuals with low muscle mass and low fat mass (6). This highlights the importance of skeletal muscle mass preservation for decreasing CVD risk.

Reduced muscle mass observed in individuals with CVD/CMD is likely due to sarcopenia, the age-associated decline in skeletal muscle mass and function which may begin as early as one's fifth decade of life (7). Indeed, sarcopenia determined by appendicular skeletal muscle mass (ASM)/height^2 (kg/m^2) has been associated with higher 5-year all-cause mortality in individuals with CHD (8). Sarcopenia can result from a myriad of factors, including sedentary lifestyle, increased inflammation and age-related endocrine alterations (9). Sarcopenia contributes to CVD risk, and in turn, CVD may also exacerbate sarcopenia severity via increased inflammation, reduced muscle blood flow and dysregulated endocrine function(10). Both skeletal muscle and adipose tissue are metabolically and hormonally active tissues, which contribute to the levels of inflammatory modulators (11). A shift towards decreasing skeletal muscle mass and increasing visceral adipose tissue - a combination termed sarcopenic obesity (SO) - can lead to elevated levels of pro-inflammatory cytokines and decreases in anti-inflammatory cytokines, thereby increasing risk of CVD (12,13). These pro-inflammatory cytokines may also contribute to the progression of SO through their association with reduced muscle mass and strength (14). Consequently, methods of augmenting skeletal

muscle tissue, while diminishing VAT and associated markers of CMD may be useful for reducing CVD risk.

Clinically, following a cardiac event, patients are referred to a supervised exercise and weight management intervention termed cardiac rehabilitation (CR), which has been shown to be a cost-effective strategy for decreasing morbidity, mortality and improving quality of life (15–17). Although current CR guidelines do encourage resistance exercise (RE), they primarily focus on aerobic exercise with an overall aim of increasing physical fitness and energy expenditure in order to reduce CVD risk (15,18). Aerobic exercise has smaller effects on muscle strength or muscle hypertrophy compared to RE, which has been shown to effectively improve muscle mass and strength in a dose-response manner (19–21). In older adults with and without CVD, RE has been shown to effectively diminish the risk of developing and exacerbating CVD symptoms, while also being safe for CR (22,23). To maximise the benefits of RE on muscle hypertrophy, protein intakes greater than the recommended daily allowance may be required (24,25). Increased protein intakes may be especially important considering ageing individuals are shown to have a reduced capacity to increase muscle mass with protein intakes similar to young individuals, a phenomenon referred to as anabolic resistance (26).

Diet plays a key role in the development of obesity, inflammation and CVD risk. Western-type diets, for example, have shown unfavourable relationships with these conditions (27,28). wheras, Mediterranean-style diets (MedDiets) present inverse relationships with obesity, inflammation, CMD and CVD risk (27,28) and mortality (29). Results from studies on secondary prevention of CVD suggest MedDiet-based approaches are effective and are frequently recommended during CR (30,31). However, MedDiets are not necessarily high in protein content, which may not be optimal for increasing muscle mass in CR patients, who are likely to present with SO. Therefore, consumption of a higher protein (1.3-1.5 g/kg per day) Mediterranean-style diet to support a RE programme may be of greater benefit in CR, due to a greater capacity to enhance skeletal muscle hypertrophy and reduce markers of CMD (32).

It is worth noting that an intervention such as that proposed here has never been trialled in CR patients with SO, and there may be barriers that lead to poor adherence. Therefore, an aim of this protocol paper is to describe the design of a feasibility study for a high-PRotein Mediterranean diet and Resistance Exercise in cardiac Rehabilitation patients with SO (PRiMER). The study will also assess the effect of a pilot intervention on skeletal muscle mass and function, in addition to markers of cardiometabolic health in CR patients. It is hypothesized that a CR intervention focused on RE and a modified-MedDiet with increased protein (HPMD) content will be feasible and more effective for improving cardiometabolic health in CR patients with SO, than the current CR guidelines based around aerobic exercise with dietary change focused on weight management (15).

Methods/Design

The study is designed as a pilot, 12-week, four-arm, randomised control trial in CR patients with SO (Fig.1) and conforms with the SPIRIT 2013 statement (33).

Patient participant involvement and feasibility of study design

Prior to beginning recruitment, patient participant involvement (PPI) will be used as a tool to inform future research design and implementation of a fully powered research study using questionnaires, focus groups and interviews, which are described below. Use of a feasibility questionnaire will help establish the number of eligible participants, their willingness to be randomised to different protocol arms, response rates to questionnaires, acceptability of nutritional and exercise protocols, and ethical considerations. A trial oversight committee will be formed, consisting of the academic investigators, Liverpool Heart and Chest Hospital clinical leads, and community centre leads. Equally, there will be a trial steering group (TSG), consisting of patients engaging with CR (phase III and phase IV), the academic investigators, and staff employed on the trial. The TSG will be responsible for reviewing the protocol design and ethical considerations such as participant information, and valuable feedback on patient

friendliness and acceptability. Any changes made to the protocol will be reported and documented.

Figure 1. Study flow-chart. *CR; cardiac rehabilitation, HPMD; high-protein Mediterranean-style diet, LHCH; Liverpool heart and chest hospital, PPI; patient participant involvement, SO; sarcopenic obesity, TSG; trial steering group.*

As the study design involves dietary and exercise changes, a recipe booklet and the RE training protocol will be presented to a focus group of CR patients (*n* = 10-12) who are eligible for, but not necessarily taking part, in the study. Recipes have been designed based on MedDiet criteria as described in the validated English version of the 14-item Mediterranean Diet Adherence Screener (MEDAS) used in the PREDIMED study (34) but have been adapted to include high-protein dishes typical to England in order to aid adherence in this UK-based population. Focus group questions will be based on the food guidelines and exercises provided in the recipe book (Table 1) and training protocol (Table 2), respectively. Additionally, CR patients will be asked to prepare and taste recipes from the recipe book and complete a hedonic food scales questionnaire. Exercise videos will also be used to demonstrate the RE training program, and participants will be asked about its suitability for CR. Focus group participants will receive all materials (recipe booklet, training protocol, exercise videos) digitally. Upon review of these materials, participants will participate in recorded phone or web-based focus groups, conducted by one member of the research team. Focus groups will be transcribed and analysed using thematic analysis.

Table 1. Sample focus group questions at the recipe tasting session.

Focus group menu questions:
1. What do you think about the research study we proposed? 2. What were your thoughts of the recipe book you received? 3. Describe your experiences of the dishes you made at home from the recipe books. 4. Why did you choose to make the dishes you made?

5. Which dishes did you dislike and why? 6. How do you think the foods can be improved? 7. What other types of recipes would you like to see in the recipe book? 8. Describe the pros and cons of making these dishes at home 9. What is your opinion on preparing more food at home?

Table 2. Sample focus group questions on the RE programme.

Focus group, exercise training questions:
1. What is your opinion on doing this type of exercise programme for your CR? 2. What do you think about the resistance exercise you've seen today? 3. Are there any exercises you think aren't appropriate and why? 4. What would you expect to be the main advantages of the resistance exercise you've seen here? 5. What would you expect to be the main disadvantages of resistance exercise? 6. Are the number of gym sessions per week reasonable for CR patients, considering work and other life commitments and why? If not, do you have alternative suggestions? 7. What do you think about travelling regularly to your local gym for CR? 8. Would you prefer group exercise sessions or private sessions and why?

This PPI will also be continued throughout the intervention to inform participant adherence/compliance rates and attrition, in order to determine the feasibility of the study (Fig. 1). Qualitative (thematic) analysis will be used to assess responses from focus groups, relating to the dietary and exercise interventions and associated materials/guides, as well as to assess all participant feedback throughout the study. Commonly occurring themes which emerge from

this qualitative analysis will be considered for protocol changes in the development of the fully powered study.

Eligibility and recruitment

In a North-West England setting, participants (male and female) will be recruited from Liverpool Heart and Chest Hospital Cardiac Rehabilitation unit. Individuals will have recently completed phase III CR, be deemed as cardiac stable, and referred to phase IV CR. Phase III CR may begin 2 to 6 weeks after a cardiac event and can last between 4 weeks to 6 months depending on the patient and the specific CR centre (35). It primarily consists of a graduated exercise programme and is supplemented by education on heart disease and leading a healthier lifestyle (35). There is no "one size fits all" approach, and as such a range of physical activities are encouraged such as group exercises, walking, swimming or cycling. When the risk level of the patient is deemed low, patients can proceed to phase IV of CR, which is primarily a continuation of the new lifestyle habits (35).

Inclusion criteria include the following: minimum age 40 years old, cardiac function deemed stable after phase III CR, referral to a CR programme and meeting the criteria for defining sarcopenic obesity. Eligible participants will be assessed by whole body dual-energy X-ray absorptiometry (DXA) (Hologic, Manchester, UK) to determine body composition; as no consensus definition of sarcopenic obesity exists we will use the following definition based on the criteria for sarcopenia as defined by the EWGSOP2 (36) and including a measure of abdominal adiposity:

i) Grip strength <27kg in men or <16kg in women

ii) Appendicular skeletal muscle (ASM)/height^2 <7 kg/m^2 in men or <6 kg/m^2 in women

iii) Waist circumference ≥ 94 cm in men or ≥ 80 cm in women (37).

Exclusion criteria include the following (as determined by medical records): individuals with electric implants (i.e. pacemakers), inability to perform RE (determined by primary care team), presenting with chronic kidney disease stage 3-5 (eGFR <60 mmol/L) due to concerns with

high-protein intake (38), inability/unwillingness to digest/consume dairy products, admission to CR due to congenital or drug/alcohol-abuse-induced cardiac events, and pregnancy. Potential participants will receive written study information before being asked to provide informed consent.

Sample size estimation

This pilot investigation will aim to recruit a sample size of 10-15 participants/group (a total of 40-60 participants). Data collected from this pilot study will help determine the correct sample size for a fully powered study. For the future fully powered randomised control trial, power calculations will be calculated by G*Power 3 (39) based on the effect size of change in lean body mass.

Ethics approval and data management

The NHS Health Research Authority North West - Greater Manchester East Research Ethics Committee (IRAS: 256927) and Liverpool John Moores University Research Ethics Committee (19/NW/0762) reviewed and granted approval for the trial. This study is also registered at ClinicalTrials.gov (NCT04272073). All data will be collected by a trained researcher and pseudo anonymised by providing each participant with a unique ID which will be used on all questionnaires and biological samples. All biological samples and data collected will comply with the Human Tissue Act (2004) and General Data Protection Regulation guidelines. Only authorised researchers will have access to samples and collected data.

Randomisation and blinding

Eligible participants will be randomised by a computerised stratified randomisation programme for allocation to one of the following arms: standard CR (control group, CON); high-protein Mediterranean-style diet (HPMD group); resistance exercise with standard CR (RE group); or high-protein Mediterranean-style diet and resistance exercise (HPMD+RE group). Participants will be stratified based on body composition and their allocation will be sealed in envelopes until assigned to intervention group by lead researcher. Due to the nature of the interventions,

participants cannot be blinded to their allocation. Data analysis will be carried out by a member of the research team blinded to participant allocation.

Intervention

Exercise prescription

If allocated to groups RE or HPMD+RE, participants will be asked to perform RE using weights or weight machines, with the aim of building muscle size and strength. Participants will be shown how to perform the exercises by British Association for Cardiovascular Prevention and Rehabilitation (BACPR) qualified instructors in the community centre where they carry out their current phase III CR. All exercises have been deemed safe for CR patients and will be supervised by the BACPR instructor at all exercise sessions. Participants will be required to attend 3 sessions per week and each session is expected to last approximately 45 minutes (supplementary data 1).

If allocated to groups CON or HPMD, participants will be asked to continue with the standard, aerobic-style exercise (treadmills, rowing machines, elliptical trainers) they have used in phase III of CR. This will also require 3 sessions per week and be supervised by qualified BACPR instructors. Participants will be excluded if they do not achieve a 90% attendance rate at exercise sessions, based on previous studies reporting similar adherence in this population (40–43).

Diet

Participants allocated to groups HPMD or HPMD+RE will be asked to make changes to their eating habits to adapt to a HPMD adapted from the PREDIMED (Prevención con Dieta Mediterránea) study (34), by applying the following guidelines:

- increasing fruit and vegetables
- reducing intake of commercial pastries
- replacing refined carbohydrate foods (white bread, white rice, white pasta) with wholegrains (wholegrain bread, rice and pasta)
- replacing butter and margarine with olive oil as the main culinary fat

- reducing fatty meat and replacing with other high-protein, low-fat foods, such as lean meat, fish, legumes (peas, beans, lentils), low-fat dairy products (44,45).

The diet will be supplemented by provision of 2 high-protein yoghurts (providing approximately 20g of milk protein each) per day in order to increase per-meal protein intake.

Participants will receive personalised guidance to help follow the new diet during baseline data collection appointments, along with guidebooks and a recipe guide (supplementary data 2). All foods included will be designed to be affordable, with ingredients that are easy to find in local supermarkets (shopping guides will be provided).

If allocated to groups CON or RE, participants will be asked to follow the dietary recommendations given during phase III of CR.

Researchers will be in contact with all participants weekly, regardless of intervention allocation, by phone to encourage adherence. Any adverse events will be recorded via this phone contact and reported to the ethics committee.

Outcome assessments

Primary outcome

The primary outcome of the study will be the feasibility of conducting a larger, fully powered, multicentre study aimed at determining the effectiveness of a HPMD and RE protocol for CR patients. This will be based on rates of recruitment, adherence to dietary and exercise guidelines, and feedback from patient focus groups prior to and throughout the intervention.

Compliance with the dietary recommendations over the course of the intervention will be assessed via 3-day food diaries (on two weekdays plus one weekend day) being completed prior to starting the intervention, midpoint and at the end of the 12-weeks. Analysis of food diaries will be completed with Dietplan 7 (Forestfield Software Ltd, UK). Consistent with the National Audit of Cardiac rehabilitation, participants will also complete a brief 14-question questionnaire regarding the frequency of their intake of certain foods to determine their MedDiet score (34).

Adherence to the exercise guidelines will be assessed through participant exercise logs, completed at the same time points of the food questionnaires.

Secondary outcomes

Secondary outcomes will be measured at baseline and at 12 weeks of intervention and will include the following:

Anthropometrics will be collected including; weight which will be measured using a digital scale (Seca 704, Birmingham, UK), height will be recorded using a stadiometer (Seca 213, Birmingham, UK) and waist circumference will be recorded 3 times to the nearest 0.1 cm at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest (46). Blood pressure will be measured 3 times consecutively using a digital sphygmomanometer (Dianamap; GE Pro 300V2, Tampa, FL, USA) with systolic and diastolic measures being recorded. For waist circumference and blood pressure, the average of all 3 measurements will be used for data analysis. Changes in body composition will be determined by a whole body DXA system (Hologic, Manchester, UK) (47,48). Participants will be instructed to lay supine on the DXA table with arms adequately separated from the trunk and instructed to remain still throughout the scanning procedure.

To assess changes in muscle strength, participants will be instructed to perform isometric contractions using a hand-held grip dynamometer (Takei Kiki Kogyo, Tokyo, Japan) (49,50). The hand grip strength test will be done seated with their elbow by their side and flexed to right angles, and a neutral wrist position for 3 s. The maximum value of 3 consecutive measurements in the non-dominant arm will be registered.

To assess changes in markers of cardiometabolic health, fasted (12 hours) venous blood samples will be collected from the antecubital vein. Markers including plasma glucose, insulin, triglycerides, total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, C-reactive protein and whole blood HbA1c will be determined by an automated random-access clinical chemistry analyser (Daytona, Randox Laboratories Ltd, UK).

To assess changes in quality of life due to sarcopenia, participants will also complete the validated sarcopenia quality of life questionnaire (SarQol) (51).

Statistical analysis

Comparisons between intervention groups for all outcome measures will be performed by means of mixed model ANOVA, to account for inter-subject (differences between treatments) and intra-subject (differences between baseline and endpoint) variability. The non-parametric equivalent will be used if data are not normally distributed as determined by Shapiro Wilks test. Since a sample size calculation will not be conducted for this component, interpretation of the results will be largely descriptive and focused on confidence limits around parameter estimates. In the case of non-compliance or participant dropout, intention to treat analysis will be carried out to maintain the effect of randomisation and avoid selection bias (52). Moreover, per protocol analysis will also be carried out to investigate the effect of treatments on subpopulations who fully adhere to the protocol. Statistical significance will be set at $P < 0.05$, and all analyses will be conducted using IBM SPSS Statistics v25 (SPSS Inc., Chicago, IL).

Discussion

This study aims to determine if it is feasible to implement a RE and high-protein modified-MedDiet in phase IV CR patients with SO in the North-West of England. If the primary outcome measures deem the intervention to be feasible, and if the pilot intervention shows improvements in the secondary measures (body composition, strength and cardiovascular health), we will seek to implement a fully powered, multi-centred, randomised control trial in CR patients, in order to confirm the findings of the pilot study and inform future CR exercise and dietary recommendations. CR is an essential component of long-term recovery following a cardiac event; however, an overall aim of increasing physical fitness and energy expenditure primarily through aerobic exercise, may not be optimal for the secondary prevention of CVD in individuals presenting with SO (15,18). Preservation of muscle mass via RE, supplemented with a high-protein diet may be of greater benefit. For example, individuals with CHD and low skeletal mass were associated with reduced physical fitness and increased 5-year all-cause mortality risk (8). Furthermore, following a Mediterranean-style diet may also reduce CVD risk,

as MedDiets show an inverse relationship with obesity, inflammation, CMD and CVD risk (27,28) and are recommended for secondary prevention of CVD (30,31).

In addition, the potential information received from PPI will be invaluable for identifying possible barriers in CR patients and allow for future interventions to be tailored to their needs to help increase the likelihood of long-term compliance to health-promoting lifestyles. The results will also be compared with similar research investigating potential barriers of implementing exercise program in CR patients (53), and Mediterranean-style diets in northern European populations (54). Previous barriers reported by CR patients on engaging with exercise consisted of lack of education on benefits, lack of resources, and motivation (53). Furthermore, barriers reported on following a MedDiet were lack of knowledge on MedDiets, lack of cooking skills and resistance to dietary change (54). This pilot study has been developed with some of these barriers in mind: dietary guides have been created to facilitate dietary changes using local-style dishes which have been designed to follow Mediterranean-diet guidelines; educational materials regarding the benefits of Mediterranean and high-protein diets will be included; easy recipe booklets focused on convenience and recipes familiar to this population will be provided; and weekly phone calls to maintain motivation will be carried out.

In conclusion, results of a feasibility study on the implementation of RE and high-protein modified-MedDiet in phase IV CR patients with SO will allow potential barriers to be addressed and allow for a fully powered randomised control trial to be performed. A fully powered study of a RE and high-protein modified-MedDiet in phase IV CR patients will determine if such a protocol is of greater benefit for improving muscle mass and strength while also improving CVD risk compared to current aerobic style CR recommendations.

Trial status

Start of recruitment, 05/03/2021. Planned completion, 01/12/2021.

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Authors' contributions

DM wrote the manuscript. RK, TB, IGD and FPdH conceived and designed the study. DT, GYHL and JM advised on clinical and logistical aspects of the study design. All authors read and approved the final manuscript.

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Liverpool Clinical Commissioning Group (LCCG) and Liverpool John Moores University, Institute of Health and Research. The role of LCCG is to support the future design of a larger study for subsequent National Institute of Health Research (NIHR) support.

Availability of data and materials

Not applicable as no datasets were generated or analysed during this study

Ethics approval and consent to participate

The trial has been reviewed and approved by the NHS Health Research Authority North West - Greater Manchester East Research Ethics Committee (19/NW/0762). Potential participants will receive written study information before being asked to provide informed consent to the lead researcher.

Competing interests

RK is a beneficiary of a postgraduate stipend from the Institute for Health Research from Liverpool John Moores University. RK has received a guarantee of support for the planned dietary intervention in the form of food product from Grahams' Family Dairy. RK has received a speaker honorarium for a symposium hosted by the British Association for Parenteral and Enteral Nutrition.

Abbreviations

ASM - appendicular skeletal muscle mass

BACPR – British Association for Cardiovascular Prevention and Rehabilitation

CHD - coronary heart disease

CMD – cardiometabolic disease

CON - control

CR - cardiac rehabilitation

CVD – cardiovascular disease

DXA - dual-energy X-ray Absorptiometry

EWGSOP2 - European Working Group on Sarcopenia in Older People 2

HPMD – high protein Mediterranean diet

MedDiet – Mediterranean diet

PPI – patient participant involvement

PREDIMED - prevención con dieta Mediterránea

RE – resistance exercise

SO – sarcopenic obese

TSG – trial steering group

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