Train High Eat Low for Osteoarthritis Study (THE LO Study): Protocol for a randomised controlled trial.

Human research ethics approval committee:
Sydney Local Health District Human Research Ethics Committee
Human research ethics approval number:
(CH62/06/2011-030 HREC/11/CRGH/47) by 31st March 2012

BACKGROUND

Osteoarthritis (OA) is one of the most prevalent chronic conditions among older adults [1], with 1.9 million Australians living with this condition [2]. Of the weight-bearing joints, the medial tibiofemoral joint is most frequently affected [3]. Increased join loading in people with knee OA may be due to associated pain, impaired gait, balance, lower-extremity muscle weakness, and/or depression [1]. Osteoarthritis is the most common cause of disability in older adults, which imposes great personal and societal burden [1, 4]. There is no cure for OA currently. Treatment options are often aimed at alleviating symptoms and in some advanced cases with knee replacement surgery maybe the only option [5]. Recent emphasis has been placed on the development of interventions capable of slowing down the progression of disease in an attempt to reduce the burden of OA.

It is well known that a combination of genetic, lifestyle and mechanical factors contribute to the development, clinical expression and progression of OA [1, 6]. Many

potentially modifiable factors have been confirmed to hasten the progression of knee OA, including abnormal dynamic knee joint load during walking [4, 6], obesity [7] and muscle weakness [8]. Lifestyle programs have great potential to target these risk factors, thus acting as disease-modifying interventions rather than simply providing pain relief [4, 9, 10]. This distinguishes lifestyle therapy from pharmacologic/analgesic therapy for OA, justifying its role as central to the treatment of OA. Notably, the standard "public health" lifestyle prescription of a healthy diet and increased physical activity [11] (usually walking) are both insufficient to address the above deficits in OA, as well as unrealistic in individuals who may be morbidly obese and markedly restricted in mobility due to pain. This may explain why lifestyle modification is often ignored in favour of pharmacologic management. Therefore, a theoretically grounded lifestyle modification program that better addresses the aetiology and progression of the disease is needed to successfully alter the underlying pathophysiology of knee OA.

Biomechanical assessment of abnormal joint loading has emerged as one of the key intervention targets is recent years. Medial compartment knee load during walking is commonly measured non-invasively using 3D motion analysis. The primary variable resulting from this analysis is the external Knee Adduction Moment (KAM), which is an indicator of medio-lateral load distribution. [12]. The KAM is a torque, which acts to pull the tibia in a more varus position during the stance phase of gait, thereby increasing medial tibiofemoral joint load. Recent interventions, which aim to reduce the progression of OA, commonly target this variable with the aim of reducing disease progression risk [6].

There are several potential ways to reduce indices of the KAM in people with knee OA, and the optimal approach remains to be defined. One approach is gait modification (gait retraining), which has demonstrated significant reductions in the KAM. Various gait modification strategies can yield a variety of effects. Most of the studies have investigated these effects only immediately [9, 13-18]. However the beneficial biomechanical effects seem to also be translated into short term effects including changes in pain as identified in recent studies [19, 20]. Another approach to targeting reductions in the KAM is muscle strengthening, as strength has been associated with the magnitude of the KAM peak [21]. Since 40% of the gait cycle is unipedal, muscle strength (especially hip abductors) and balance are essential for lower body alignment. Progressive resistance training (PRT), the specific exercise modality targeting muscle weakness has been shown to reduce the KAM by 5-10% in healthy subjects [22], it encourages the preservation of lean tissue in the face of a weight loss program, and can improve balance and reduce pain in individuals with OA [23]. Finally, weight loss has been shown to be highly related to reductions in KAM [24] with each kg lost associated with a 1.4% reduction in KAM. It is important to highlight that hypo-caloric diets with or without aerobic exercise tend to decrease lean tissue as well, thus supporting the additional role for PRT. A high protein (HP)/low glycemic index (GI) energy restricted diet has been shown to be more effective at reducing weight and maintaining weight loss, lean mass and lowering systemic inflammation/insulin resistance than standard energy and fat restriction[25-28], but has never been tested for efficacy in OA specifically.

Thus, we have designed a novel, evidence-based lifestyle intervention, which targets the above treatable aetiological factors in knee OA, by including gait retraining, high intensity PRT, and a HP/ low GI energy restricted diet, in a randomised controlled trial (RCT) known as **THE LO STUDY** (Train High, Eat Low for Osteoarthritis). The present study will be the first RCT of gait retraining in individuals with medial knee OA over 12 months. It will also be the first trial to directly compare the isolated effects of PRT, HP/low GI diet, and gait retraining in this cohort, as well as the first test of a novel intervention combining all three treatments, in comparison to a lifestyle advice control group.

DESIGN

We are currently conducting a single-blinded RCT, **THE LO Study,** over one year to investigate the effects of a unique, targeted lifestyle intervention in overweight/ obese adults with symptomatic medial knee OA. This study is an RCT adhering to CONSORT guidelines for conduct and reporting of clinical trials. Ethical approval was obtained from the Sydney Local Health District Human Research Ethics Committee on the 31st March 2012 (CH62/06/2011-030 HREC/11/CRGH/47) and eligible participants who agree to participate in the study are provided a participant information statement and asked to sign the consent form in person. This study has been lodged with the Australian and New Zealand Clinical Trails Registry (ANZCTR Ref. No. 12612000501842).

Hypotheses

We hypothesise that the effects of the two novel intervention groups: 1) gait retraining, and 2) Combined (HP/low GI energy restricted diet, high intensity PRT, and gait retraining) will result in significant reductions in KAM compared to the lifestyle advice only Control group. We also hypothesise that the Combined group will be superior to the isolated interventions of the 1) HP/low GI diet and 2) PRT groups. Finally, we hypothesise that the Combined group will result in a greater range of improvements in secondary outcomes, including muscle strength, functional status, body composition, metabolic profile, and psychological well-being, compared to any of the isolated interventions or Control group.

METHODS

Settings

The study is being conducted at the Faculty of Health Science, Cumberland Campus of The University of Sydney, NSW, Australia. Training sessions and measurements are conducted on-site, while X-ray films are acquired at the Radiology Department of Concord Repatriation Hospital, Concord, NSW, Australia. Figure 1 shows the flowchart of the study design.

Sample size estimation

Sample size estimates have been calculated to test the hypothesised differences between the experimental and control conditions for the primary outcome (KAM). A weight loss of about 1 kg has been shown to decrease the peak knee adduction moment (KAM) by 0.496Nm [24]. Therefore, the control group change is based on the lifestyle advice-only control group weight loss of 1.1 kg (=KAM reduction of -

0.55 Nm) in the ADAPT trial [10]. Gait retraining benefit is estimated as the average of effects achieved in the literature: Mundermann 2007 (-65%), Fregly 2007 (-39%) [17, 29] and in our pilot 4-week trial (-55%). We acknowledge potential imprecision due to the fact that these published trials included only healthy participants, and our pilot data in 10 participants with OA (the GO study) was limited to 8 sessions over 4 weeks. However, as THE LO study is 12 months rather than 4 weeks in duration, we believe our estimate is conservative. PRT benefit is conservatively estimated as a 10% reduction, similar to the result seen in healthy subjects over 12 weeks [22]. It is expected that the Diet group will reduce their weight by at least 8.9kg as seen in the IDEA study [30]. Again this is a conservative estimate, as the novel High Protein/Low GI diet we are prescribing has been shown to be more effective than typical low fat, energy restricted diets such as that used in the IDEA study [25, 30, 31]. The values used for the KAM at baseline and the Standard Deviation (SD) for the effect size (ES) estimates are taken from the baseline of our pilot study of gait retraining (GO Study).

We have conservatively assumed a less than additive benefit when all three treatments are combined, as shown in Table 1, as they may be working through overlapping pathways to some degree. As there is no similar study in the literature, we have estimated the hypothesised change for the combined group as equal to Diet plus Gait Effect Size (ES 1.63). The sample sizes (n) required with alpha 0.05 and beta at 0.2 for each of the treatment arms is shown in Table 1.

Therefore, 12 people per group would be required for Gat vs. Control hypothesis

testing with allocation of 1:1:1:1:1 for the 5 groups =n of 60 with a 40% dropout we need to recruit 100 participants. However, we will recruit an additional 25 people in the event that there is greater heterogeneity in our cohort than anticipated, due to the inclusion of men and women as well as a broad age range from middle aged to older adults compared to the literature on which the sample size estimates were derived.

We have powered the study to look at the effects of the 2 most novel interventions in THE LO study compared to control group (the two which have never been tested in this cohort): Gait vs. Control (ES= 1.25) and Combined vs. Control (ES= 1.63) as well as Combined vs. Diet (ES= 1.30) and Combined vs. PRT (ES=1.43)

With this sample size of 125, we will also be able to conduct exploratory analyses of the comparisons which are estimated to have small ESs (0.20-0.38): Diet vs. Control, PRT vs. Control and Combined vs. Gait.

Eligibility and recruitment

Participants are community- dwelling persons aged 40 or above, with medial knee OA in at least one knee according to the American College of Rheumatology clinical and radiographic criteria; and have a BMI $\geq$ 25Kg/m^2. Complete inclusion and exclusion criteria are listed in Table 2.

Participants are currently being recruited via Hospital and University intranet advertisements, targeted mail-outs (Arthritis NSW, Concord Hospital) SSWAHS Intranet Arthritis NSW Website, Specialist / GP referral, advertisements in local newspapers and seniors' magazines, brochures distributed to local medical practitioners and pharmacies, as well as social media. We predict that we will need to

screen approximately 2000 people in order to enrol 125 participants.

Screening Procedure

- ***Telephone Screen:***

Potential participants initially contact the research assistant by telephone. To assess participant eligibility for THE LO Study, a 30-minute telephone screening form is utilized. The questions on the form are designed to address inclusion and exclusion criteria as well as the participant's basic demographic and contact information, current medical history, medication and physical activity/exercise levels.

- ***Investigator Review:***

The study's chief investigator reviews telephone-screening questionnaires upon completion. Participants are informed about their eligibility or placed on hold for further medical information and/or investigation(s). An information package is sent to the eligible participants including an appointment with the study physician, brief outline of the assessments procedure, and information regarding the screening and testing venue. If not eligible, the research team asks the participants for permission to retain their contact details, in case their situation changes over time and they become eligible at a later date. To obtain medical clarification for participants, letters are sent to their respective doctors along with a signed permission slip from the participant indicating that the physician may release relevant medical information.

- ***Radiographs:***

To determine the presence of radiographic medial knee OA, potential participants

undergo bilateral weight-bearing postero-anterior knee radiography using a SynaFlexer^{TM} Positioning Frame and Phantom [32] in a standing, semi-flexed position then, the severity of radiographic disease will be rated at baseline and follow-up using two clinical scoring systems: the Kellgren and Lawrence OA score [33] and the Osteoarthritis Research Society International (OARSI) atlas of radiographic features[34]. The index knee is the knee that participant identifies as his/her most painful knee; usually but not always, this is the knee that is worse on x-ray findings and worse on physical exam findings by team leader [35]. If pain and x-ray findings are equal, the study physician makes a clinical judgment based on all data.

- ***Physician Screening:***

To determine final eligibility, a structured clinical interview including physician screening, radiographs' review, clinical history and medication record list is performed by the study physician prior to remainder of baseline testing.

Randomisation

An independent researcher not involved in testing, or training prepares concealed randomisation in variable blocks (block size = 4-8), utilising a computer-generated random number sequence (http://www.randomization.com), created by Dr. Gerard E. Dallal, Tufts University) for the participants who complete the baseline assessments.

Stratification by sex and BMI (≤25-30 kg/m^2 vs. ≤ 30 kg/m^2) is being carried out. Study identification and sequential treatment allocations are enclosed in numbered, opaque sealed envelopes, and distributed to each participant after baseline assessment.

Participants are then designated to one of the five study arms for one year in a balanced ratio. Trainers in each study arm are informed and the outcome, while all assessors are blinded to the allocation.

Interventions

Table 3 provides detailed information of visits required for each study arm.

- ***Gait Retraining***

Several gait modification strategies have been shown to reduce the KAM [15, 36-38]. According to a systematic literature review [18], the following gait modification strategies have demonstrated immediate reductions in the KAM at varying stages of the gait cycle: increased medio-lateral trunk lean, toe-in gait (walking with feet internally rotated), toe-out gait (walking with feet externally rotated) and medial knee thrust gait (a dynamic medialisation of the knee joint during stance). More recent cohort studies also demonstrated effective reductions in the KAM over time, which has been demonstrated with a toe-out gait modification over 10 weeks [19] and toe-in gait modification over 6 weeks [20]. Whilst there is evidence that immediate load-modifying effects of toe-in and toe-out gait may differ throughout the stance [39], both studies reduced the early stance peak KAM over the time and achieved symptomatic relief. Furthermore, there is no consensus on the optimal gait modification to implement or the magnitude of modification required and a single gait modification might not suit all participants, or may produce minimal effects. Accordingly, the combined effect of more than one gait modification may yield superior biomechanical effects with more subtle gait changes [13].

The potential effectiveness of those gait modification strategies for our proposed intervention is supported by Wishart and Lee, [40] who found that older adults in particular benefit from concurrent augmented visual feedback when learning a bimanual task. Similarly, we have shown that concurrent augmented visual feedback significantly improved patterns of work during an exercise task, compared to no augmented feedback [41].

In this study, gait retraining will be conducted in a motion analysis laboratory under the supervision of an exercise physiologist trained in biomechanics. We aim to reduce the peak KAM by 20% over time. For the supervised portion of the gait retraining intervention, participants will attend a one-hour gait retraining session every fortnight during one year. At the first session, they will be educated on the significance of joint loading, the KAM and the main objective of this study arm. A larger peak observed indicates greater loading placed through the medial "inner" compartment of the knee joint. The participants' natural gait pattern and joint kinetics will be assessed at the initial session for target level of 20% load reduction to be set. Participants will undergo three-dimensional gait analysis using a force platform (model 9281, Kistler, Winterter, Switzerland) and 14 camera motion capture system (Eagle cameras, Cortex 5 software, Motion Analysis Corporation, USA). The motion of the affected lower limb will be tracked using 16 passive-reflective markers during habitual gait in order to evaluate the baseline early stance peak KAM, knee abduction moment (KAbM), mid-stance KAM, gait velocity and measure of pain. KAM and KAbM will be available graphically in real time using Kintools (Motion Analysis Corporation,

USA). Participants will be asked to "just walk" along the laboratory walkway with no instructions provided regarding a modified gait. Three trials will be captured. These variables will be used to monitor biomechanical progress throughout the year by the trainer.

As part of the second session, participants will be made aware of the range of gait modification strategies via a PowerPoint presentation and will able to choose the modification to attempt first. Participants will then attempt to practice all gait modification strategies while walking in the laboratory. The trainer will aid skill acquisition by the provision of regular verbal feedback or visual feedback using a mirror. Standardized instructions will be provided to them and each strategy will be systematically tested. Their trials will be recorded and their knee kinematics will be monitored until an optimal benefit is reached based this on peak KAM reduction measured from the real time graphs.

For subsequent sessions, participants will return to the biomechanics laboratory and will be instructed to perform strategies that led to the greatest reduction in their peak KAM from the previous session. Once an optimal gait modification (or combination) is identified, the participant will be instructed to perform this on a regular basis. Each session will provide further feedback about their progress in mastering the gait strategy. Participants will be instructed to perform their modified gait strategy(s) at home using a mirror each day for a minimum of 10 minutes and to use the modified gait strategy(s) during all daily walking. Adherence and pain will be monitored via a

logbook and reviewed by the trainer fortnightly.

- ***Progressive Resistance Training***

Participants assigned to this group will undergo high intensity PRT twice a week over 12 months. Training sessions will average 60 minutes and include the following exercises: leg press, knee extension, bilateral knee flexion, standing hip adduction and abduction, chest press, triceps extension and seated row. Keiser (Keiser Sports Health Ltd., Fresno, CA USA) pneumatic strength training equipment, which allows for low impact and smooth, continuous progressive loading will be used. The specific protocol for the strength training has been successfully used in the Resistive Exercise for Articular Cartilage Health (REACH) study by our team and is supported by a large RCT evidence base for the use of PRT in knee OA [42]. Knee extensors will be trained unilaterally (3 sets of 8 repetitions) to maximise isolation of the muscle groups and training adaptations, as well as to customise loads for asymmetry in strength due to underlying OA.

Initial resistance will be set at 50% of the baseline one repetition maximum (1RM), and will be increased to 80% of the participant's initial 1RM over the first month of training. The 1RM will be reassessed every 3 weeks and the resistance will be increased progressively at each session by approximately 3% of 1RM. The load will be further titrated in order to maintain a training intensity between 15 and 18 on the Borg Rating of Perceived Exertion scale [43], and still allowing participants to achieve a full range of motion (modified as needed for joint pain) for all exercises. To maximise the potential of full body strength and individualise rehabilitation of pre-

existing musculoskeletal concerns, novel free weight or machine-based exercises will be introduced after every 12 sessions, or progressed throughout the training. These exercises may include shoulder lateral raise, shoulder external and internal rotation, shoulder/scapula retraction, ankle cuff exercises, back extension, unilateral leg press, bilateral knee extension, hip extension and hip flexion, ankle dorsiflexion, calf raise, bicep curl. Isometric exercises and ankle cuff exercises for lower extremities will be used to help increase strength if a participant is unable to use the machines correctly.

With each strength training equipment item, the following protocol will be used:

- The participant will be shown how each piece of strength training equipment works, what muscle group it isolates and where this muscle group is located.
- It will be explained and demonstrated to the participants why emphasis is placed on proper breathing technique (exhaling on exertion, avoidance of Valsalva maneuver).
- The participant will be placed on the piece of equipment and the settings recorded to ensure proper biomechanics so that they can be replicated for all training sessions and follow-up assessments.
- The participant will perform 3 sets of 8 repetitions on each machine. Each repetition will be slow for both the concentric and eccentric phase (3-4 seconds), with a 2-3 seconds rest between repetitions and 60-90 seconds rest between sets.

The participants will be encouraged to discuss with the trainer any problems that arose before, during and after each training session regarding muscle soreness, dizziness, light-headedness or any discomfort of any kind. Alternating between upper

and lower body exercises will be implemented in order to limit fatigue in particular muscle groups that may impair performance of subsequent exercises.

Exercise Modification:

A modified version of exercises will be prescribed for patients experiencing pain or discomfort. Table 4 lists the exercises most commonly requiring modification.

- ***High Protein / Low Glycemic Index Energy Restricted Diet***

Participants in this group will be counselled to adopt a HP/ low GI energy restricted diet with the goal to reduce weight by 5-10% over 12 months with a sustainable change in eating patterns, improved food choices and moderate energy restriction. Total daily energy intakes will be prescribed according to participants' energy requirements, as estimated using the Harris-Benedict equation with an appropriate activity factor and 2000kJ (500 calories)/day deficit, to encourage a moderate weight loss amongst participants. Four levels of daily energy will be used in the study (5, 7, 9 or 11MJ/day) and participants will be prescribed a diet energy level closest to their calculated energy intakes. The target macronutrient composition is 45% of energy from carbohydrates, emphasising low glycaemic sources, 25-30% from protein and 30% from fat. This macronutrient distribution is similar to the average Australian diet, [44] but protein is modestly higher (~5% of energy) and the GI index is lower. The diet will aim to be as low in GI as practical and achieved by replacing higher GI carbohydrates (e.g., conventional white or wholemeal bread, breakfast cereals, potatoes) with lower GI carbohydrates (e.g., Burgen® grain breads, oats, pasta, Basmati rice). A GI diet value of <50, and a low glycaemic load (GL) diet with a

value of 77 will be the goal for participants and will be calculated using published data for Australian foods [45]. In addition, the diet will emphasise lean sources of protein, monounsaturated/polyunsaturated fats and restriction of saturated and trans fats.

Individual counselling sessions will be conducted by the study dietitian to identify current dietary patterns, recommend specific changes, identify barriers to dietary changes and provide appropriate strategies to assist changes in behaviour with the participants. Nutrition counselling will incorporate a combination of behavioural theory, cognitive behaviour and trans-theoretical model in modifying dietary patterns, weight and health risks [46-49]. This will be accomplished with individual sessions with the dietitian once per week for the first month, then fortnightly for the next 2 months, then monthly for the final 9 months for a total of 17 sessions. The majority of the nutrition educational materials will be delivered during the first 12 weeks, with information on energy restriction, high protein and low GI addressed within the first 4 weeks and reiterated during sessions thereafter in combination with addressing behaviour modification. The study dietitian will also be available for telephone counselling and email queries outside of scheduled visits for additional support if required. Participants will be provided with a comprehensive written manual explaining all aspects of the diet, including sample meal plans. To further encourage dietary adherence, key foods will be provided in the form of a hamper (sample bag) and food, to give examples of low GI choices available [45].

All participants will have their waist circumference taken and will be weighed at each

diet visit using the same calibrated scale at the laboratory. In addition, participants will be instructed to record their weight at home daily, measure their waist circumference weekly and complete a weekly 24-hour food dairy in a pocket-sized logbook provided at the beginning of the program. Regular self weighing and monitoring has previously been shown to encourage and significantly enhance compliance and weight loss efforts [50, 51]. Participants' logbooks will be reviewed at each visit or phone calls will be made to ensure compliance and to address any problems or concerns encountered by the participant. Additionally, 24-hour dietary recalls will be conducted during diet appointments in conjunction with completion of 3-day food records at baseline, 6 months and 12 months to assess and monitor dietary compliance.

Participants identified to have renal impairment or proteinuria unrelated to urinary infections requiring limitation to protein intake will not be prescribed the higher protein diet. However, they will be advised to follow a low GI, reduced energy diet prescription and a referral to a nephrologist will be recommended.

- ***Combined Group***

Participants assigned to this group will receive a combination of all the components of gait retraining, high intensity PRT and HP/ low GI energy restricted diet interventions. The visits to the campus will be offered in combined sessions to minimise the burden in this group; thus, participants will attend 104 visits (2 days per week during 12 months) with 61 visits for PRT only (60 min approximately), 17 sessions for PRT and diet consultation (120 min approximately) and 26 for gait

retraining plus PRT (120min approximately). Gait retraining will be conducted prior to PRT when they occur on the same visit to minimise fatigue. Adequate rest periods will be provided between all intervention components.

- ***Control Group***

Participants in the Lifestyle Advice Control group will receive standard healthy eating and physical activity advice accompanied by written pamphlets. General lifestyle advice will be given at one education session by a trainer and participants will have the opportunity to ask any questions through their weekly phone calls. Dietary advice will be based on the Australian Guide to Healthy Eating [44], including information on recommended serves of food each day (e.g. breads and cereals, fruit, vegetables, dairy, meat and alternatives) as well as serving sizes and healthier choices for certain foods (e.g. low fat dairy products, lean meats). No specific energy or macronutrient distributions will be set for this group, however the Australian Guide to Healthy Eating reflects macronutrient distributions of 15-21% protein, 52-57% carbohydrate and 27% fat [25]. In addition, there will not be a specific weight loss target set for these participants throughout the study period, though weight loss will not discouraged. Physical activity advice will be based on the Australian Government's National Physical Activity Guidelines of at least 30 minutes of activity on most days of the week. [11] No structured or supervised exercise will be provided.

Adverse Events

Adverse events will be monitored by a weekly questionnaire, provided in person or by

telephone call, and proxy information obtained whenever necessary to minimise missing data. Additionally, participants will be requested to report all changes in medication, health care professional visits, new diagnoses, acute illness or allergies, changes in daily physical activities or any new symptoms. Any musculoskeletal, cardiovascular event or metabolic abnormality attributed to study protocols will considered as adverse events [52]. Case conferences will be held weekly to discuss all study participants in terms of adherence, changes in health status, intervention modifications, adverse events and behavioural issues that were deemed relevant to study participation.

OUTCOME MEASURES

Participants will be assessed at baseline, six months and 12 months (immediately after completion of one-year program) by blinded outcome assessors. Blinding of participants is not possible due to the nature of the interventions.

Primary outcome

Peak KAM during the early stance phase of gait will be obtained in three-dimensional analysis laboratory. Data will be collected using a 14-camera Motion Analysis system (Eagle cameras, Cortex 5 software, Motion Analysis Corporation, USA) synchronised with three force plates (model 9281, Kistler instruments, Switzerland) embedded in the laboratory floor. Spatiotemporal, kinematic and kinetic will be computed from inverse dynamics analysis of an eight-segment body model defined by 30 markers over anatomical landmarks on the trunk, pelvis and lower limbs. The maximum KAM

between heel contact and 50% of stance will be derived and normalised to body weight times height (Bw*Ht). The early stance peak KAM has been shown to be highly reproducible, with a mean difference between test sessions of 0.1%. This biomechanical analysis will be used to assess secondary gait variables, including the KAM impulse, KAM late stance peak, peak knee flexion moment, cadence, velocity, step length, kinematics of the ankle, knee and hip.

Secondary outcomes

Radiographic joint-space width (JSW) has been recommended as primary structural endpoint in clinical trials of knee OA by the 1999 guidance document of the Food and Drug Administration (FDA). JSW represents both, thickness of articular cartilage as well as meniscus extrusion [53]. Some of the variation associated with serial JSW measurements in clinical trials is caused by image positioning; minimizing this source of variation is therefore the key to effective multi-center radiography [54]. In our study, reduction in radiographic JSW will be measured and recorded with the SynaFlexer^{TM} Positioning Frame and Phantom during fixed flexion standing posterior-anterior (PA) knee radiography[32, 55] to determine the change in medial minimum JSW between baseline and 12 months follow-up. The JSW (in millimetres) will be measured using digitised image analysis with Holy's software, UCLB, Lyon, France[56]. In addition, the severity of radiographic disease will be rated at baseline and follow-up using two clinical scoring systems, the Kellgren and Lawrence OA score [33] and the Osteoarthritis Research Society International (OARSI) atlas of radiographic features[34].

Additionally, a number of targeted outcomes will be measured (as shown in Table 5).

DISCUSSION AND CONCLUSIONS:

At the moment, recruitment is 80% complete and it is anticipated to conclude at the end of 2015. The most common reasons for ineligibility have been difficulty to commit time, or being too physically active, rather than medical exclusions, attesting to the potential generalizability of this volunteer sample to typical ageing sedentary adults with multiple stable chronic illnesses. Dropout rate has been lower than expected at 9.7 %, which is considered excellent for a long-term intensive intervention trial in an overweight/obese cohort.

Our primary outcomes are anticipated to be available in early 2017. This information will provide novel and robust evidence for the efficacy of strength training, HP / low GI energy restricted diet and gait retraining for people with knee OA. This study conforms to all CONSORT criteria for the conduct and reporting of RCTs, making it relatively unique in the field to date. Our secondary outcomes will enable the first comprehensive investigation of the relative and combined benefits of strength training, gait training and HP / low GI energy restricted diet on inflammatory markers for disease progression, depressive symptoms, self-efficacy, quality of life, body composition, musculoskeletal strength, pain due to OA and metabolic health. These outcomes will not only provide evidence of the potentially broad benefits of THE LO Study interventions in this cohort, but also clarify the hypothesised mechanisms contributing to any observed physical outcomes. If successful, we will have initiated a paradigm shift in the clinical approach to OA: from simply analgesia and palliative

treatment, to an ability to offer those who suffer from this condition a potent *disease-modifying treatment*.

In summary, THE LO Study will test a novel three component non-pharmacological intervention that targets middle aged and older adults with medial knee OA and is compared to isolated interventions or a usual advice control. By implementing a regime of physical exercise, diet and gait modification we aim to empower the individual, contribute to their physical and psychological health and fitness, slow the progression of the disease and associated co-morbidities, and ultimately improve quality of life and reduce suffering in this growing population.

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AUTHOR'S CONTRIBUTIONS

All authors critically reviewed the manuscript. YG manuscript draft; MFS, HOC, JBM, LM, AA, GW, KS, YD, RS design of study; MFS, HOC, JBM, LM, AA, study conception; NS, JM, participant recruitment, telephone screening and scheduling; MFS, MS, GW, YD YG, JM eligibility screening; YG, JM, NF, KS, GW, YM assessments; MFS, MS, YG, GW, YD, database and protocol management; KB, YD, GW, YG, YM training; MFS, MS, YG, YD data management and analysis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

Figure 1.Flowchart for THE LO Study design.

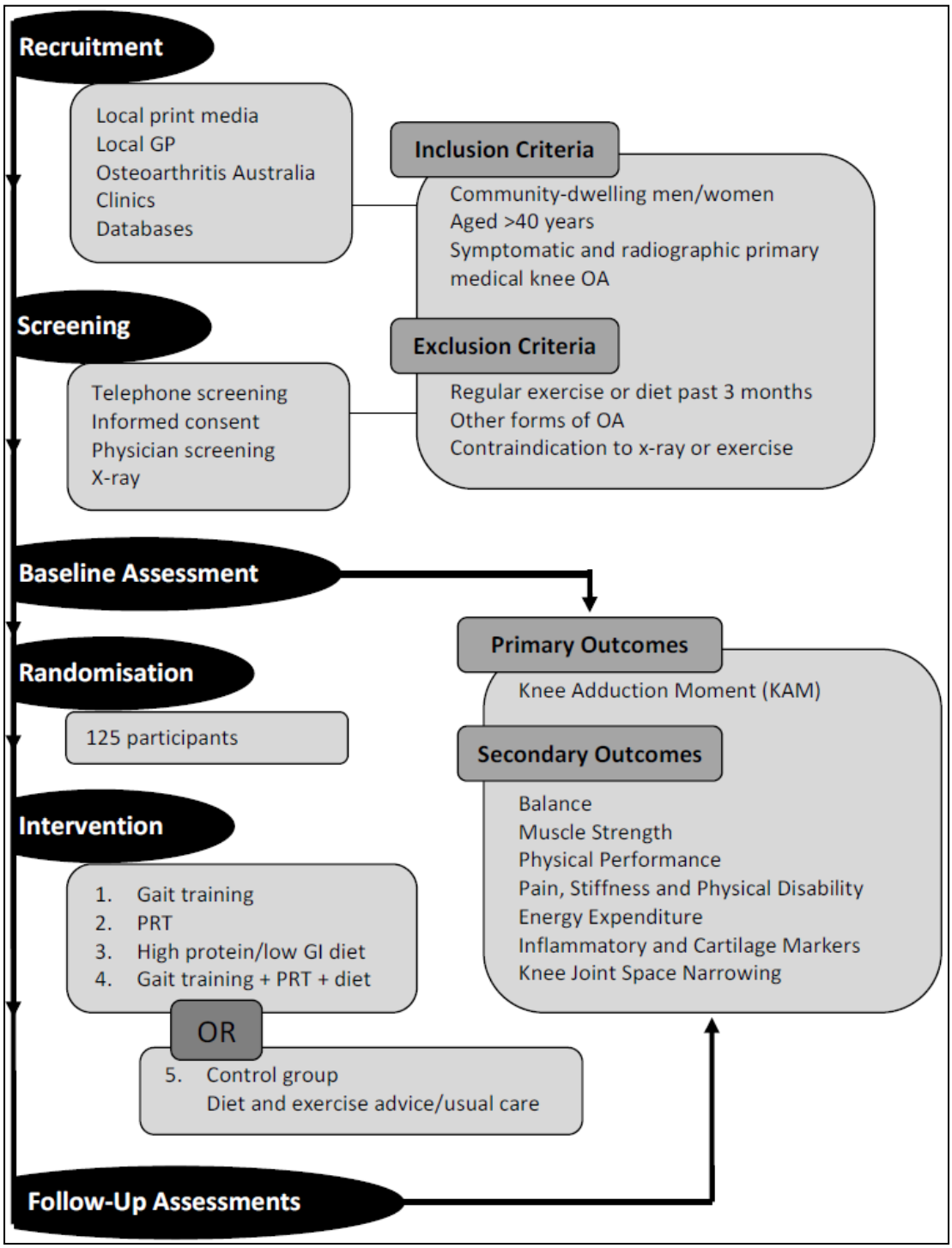

Table 1. Inclusion and Exclusion Criteria for THE LO Study Trial.

Inclusion criteria	Exclusion criteria
• Age ≥ 40 • Competency in English sufficient for assessment and training • Presence of medial Knee OA* • BMI ≥ 25 Kg/m^2 • No unstable disease precluding planned exercise* • Willing to be randomized and able to commit to study • Not planning to have knee replacement during the study • Able to see and hear sufficiently to participate in planned exercise	• Unstable medical conditions* • Participation in regular structured exercise > 1/wk. of moderate to high intensity • Rapidly progressive or terminal illness • Secondary osteoarthritis (traumatic or post-surgical), rheumatic disease, gouty or septic arthritis, Paget's disease, pseudo-gout, major congenital abnormalities, hemochromatosis, Wilson's disease and other rare forms of arthritis) • Amputation above 2nd toe • Fractured lower limb in past 6 months Knee cartilage surgery in INDEX KNEE^ • Diagnosis of depression (DSM-IV) GDS++ >9 or current treatment with antidepressant medications, greater than 3 episodes of depression in the last 5 years ("episode": requiring treatment), > 10 episodes requiring treatment over lifetime, past suicide attempts, current bipolar diagnosis and treatment, > 3 past episodes requiring treatment in last 5 years. • Severe visual impairment • Unrepaired abdominal or other known aneurysm • Myocardial infarction or cardiac surgery within past 6 months • Unstable angina or uncontrolled malignant arrhythmias at rest or on exercise stress testing • Recent retinal haemorrhage or detachment/proliferative retinopathy • Participating in another research study which would interfere with this study • Valgus knee deformity (defined as mechanical knee joint alignment of greater than 5° valgus on radiograph); • Inability to comply with study requirements over the course of one year.

* Examples of unstable conditions include uncontrolled arrhythmias, hypertension, hyperglycaemia, symptomatic enlarging hernia, acute pulmonary embolism, deep venous thrombosis, recent or unstable fracture, inflammatory or traumatic joint injuries, etc. Such individuals may become eligible if medical or surgical treatment stabilizes their condition.

**Criteria used to make OA diagnosis:

- Knee pain
- + At least 1 of 3:
  - Age > 50 years - Stiffness < 30 minutes - Crepitus
- + Osteophytes
- + X-ray diagnosis (or other previous scans)

^ Identified by the study physician as the more affected knee with medical knee OA after reviewing radiographs and doing physical examination.

Table 2. Details on visit for the testing and training sessions

	LIFESTYLE GROUP	DIET GROUP	GAIT GROUP	PRT GROUP	COMBINED GROUP
Assessment sessions (Number of time points)	3 Baseline 6 months 12 months	3 Baseline 6 months 12 months	3 Baseline 6 months 12 months	3 Baseline 6 months 12 months	3 Baseline 6 months 12 months
Training sessions (12 months)	1 visit At the beginning of the study	17visits 1st month: once weekly 2nd & 3rd month: once fortnightly 4th and further: once monthly	26visits One fortnightly session	104 visits Two weekly sessions	104 visits 61 PRT sessions only 17 PRT + diet sessions 26 PRT + Gait sessions
Health Status Check	Weekly: All by telephone call, emailed or posted.	Weekly: During the training period, these will be done in person.	Weekly: During the training period, these will be done in person.	Weekly: During the training period, these will be done in person.	Weekly: During the training period, these will be done in person.

Table 3. Progressive Resistance Training Exercise Modification

Exercise	Difficulty/Symptom	Modification	Instructions And Feedback
Knee Extension	Patello-femoral pain	Isometric contraction against static resistance Hold for 10 seconds (1 repetition) If unable, hold as long as possible Repeat 23 or 15 repetitions If pain is still present: Do sub-Max isometric contractions.	Alternate legs. 10 seconds rest between contraction Observe effort and ask patient to visualize pushing against the bar as hard as they can. Place the participant's hand on their muscle in order for them to ascertain how the muscle feels when they are performing at a maximum effort.
	Shin pain	Extra padding on padded bar	No pain or pressure
	Baker's Cyst (swelling behind the knee joint)	Sit further forward on the seat Minimal contact or pressure behind the knee at the seat Extra pad behind the knee,	
	Pain (during eccentric phase)	Start at 80 degrees and perform the eccentric phase slowly	
Hip Machine	Knee pain	Move roll bar higher up thigh to avoid touching the knee	No pain
	Hip pain	Isometric contraction against static resistance	No pain
	Vertigo	Hold for 10 seconds (1 repetition) Repeat 15 or 23 repetitions Use ankle cuffs Perform the abduction and/or adduction lying prone on a plinth Can perform hip abduction lying on the side	

Table 4. Secondary outcome measured

Outcome Measured	Explanation	Description
Health Status	Medical History	Physician completes medical history record and physical examination.
	Habitual Physical Activity level	Sedentary behaviour, physical activity and sleep quality are measured with two Actigraph accelerometers worn for eight days. Physical activity is measured with the Actigraph worn on the waist and sleep time with the Actigraph allocated on the wrist. The software program ActiLife (Version 6.11.4) is used to initialize (set the start times), download and analyse data from the both monitors.
	Dietary status	Three days food record is completed by the participants to calculate the energy intake and food variety.
Biochemical status	Serum samples for nutritional, biochemical and hormonal factors	After 12 hour fasting, a blood draw is taken to measure adipokines and inflammatory markers (serum leptin, serum adiponectin and serum interleuquin-6, high-sensitivity C-reactive protein levels) and cartilage turnover (serum cartilage oligomeric matrix protein, serum hyaluronic acid, serum N-terminal propertied of collagen type II alpha 1, serum collagen helical peptide). We also are looking at fasting levels of insulin, glucose, liver function test, creatinine and creatinine clearance, total protein, and 25-OH vitamin D level; Genotyping is used to identify genetic OA risk factors.
Cardiovascular health	Blood Pressure (BP)	Blood Pressure Measurement is taken in triplicate and fasted state after lying down on a flat surface for ten minutes in supine position.
	24h Blood Pressure	Twenty-four hour ambulatory BP monitoring awake (every half hour from 5:00AM to 10:00PM) and nocturnal means (every one hour from 10:00 PM to 5:00 AM) circadian rhythm is also obtained utilizing the Ambulatory blood pressure monitor model: TM-2430 (A&D Co., LTD, Abingdon, Oxon, U.K.).

Outcome Measure	Explanation	Description
Body composition	Anthropometry	*Standing height*: Stretch stature is measured only during baseline with a measuring tape and wall mounted Holtain stadiometer (Holtain Limited, Crymmych Pembs. UK) *Body mass (weight):* Naked weight (weight in gown – weight of gown) is measured utilizing electronic scales (AND HW (<100kgs) & SECA Wedderburn (>100 kg) *Waist circumference*: the distance between the iliac crest and lower costal border is palpated and both sites marked to determine the waist mid-way. A flexible tape measure (Graf co®, GRAHAM FIELD, Model # 17-1340-2) is placed around this point. All of them are being obtained in triplicate after 12 hour fasting and body mass index (BMI) is calculated as fasting body weight (kg/height m^2).
	Dual-energy X-ray Absorptiometry (DEXA scan)	Dual-energy X-ray Absorptiometry (DEXA) is obtained in fasting condition to determine whole body and regional muscle, fat and bone mass as well as bone mineral density using the Lunar Prodigy DXA Scanner and the enCORE software. (GE Medical Systems Lunar, Madison, Wisconsin).
Exercise Capacity	Muscle strength and endurance	Maximal strength and endurance muscle measurements are obtained using the digital K400 Keiser pneumatic resistance machines (Keiser Sports health Equipment, Inc. Fresno, CA). Exercises performed includes seated leg press, unilateral knee extension, bilateral knee flexion, standing hip adduction and abduction, chest press, triceps push down and seated rows.

Outcome Measure	Explanation	Description
	6 Minutes walk test (6MWT)	Six minutes walk test is a proxy for overall cardiovascular endurance capacity (aerobic capacity). In addition to cardiovascular efficiency; however, in the elderly subject it may be determined by muscle strength and endurance, balance, orthopaedic or neuralgic abnormalities, and other problems. It works best as an estimate of aerobic capacity in individuals who cannot run, so that variations in walking velocity describe most of the possible range of function. Therefore, it is very appropriate in very frail or elderly volunteers as well as healthy elderly [44].
Physical performance test	Gait speed: Habitual and Maximal Conduction Velocity (CV)	Habitual and maximal conduction velocities are assessed over 2 meters (Ultra-timer: Raymar, Oxfordshire, UK) with the average of two times taken as Habitual (CV = 8.7%) and Maximal (CV = 7.6%) gait velocity respectively.
`	Chair stand	Chair stand test is used as an indicator of lower extremity power, or the ability to generate high forces rapidly, with participants primarily utilizing the hip extensor and knee extensor muscle groups[56].
	Static Balance	Static balance is assessed up to 15 seconds in five different positions (feet apart in parallel stance, feet together in parallel stance, half tandem stance, tandem stance, one legged stance and one legged stance with eyes closed), without the use of assistive. Total static balance is calculated by summing the time recorded for each of the six stances [57].
	Tandem walk	Participants complete a 3 meter forward tandem walk along a marked course with and without a cognitive distracter task (verbal fluency) to assess dynamic balance.
	Stair climb	The purpose of this test is to climb stairs as rapidly as possible to enable the calculation of Leg Power (Watts). Power is calculated from the formula: Power (watts) = $\underline{(M \times D) \times 9.8/t}$ Where: M = Body Mass (NN), D = Vertical Distance (m), t = Time (s) and, D = vertical height of the staircase = height of 1 step in meters × number of steps [58]

Outcome Measure	Explanation	Description
Demographic survey	Demographics	The Demographic survey will provide specific information of the study population including, sex, education level, and economic situation.
Depression and self-efficacy	Geriatric Depression Scale (GDS)	The (GDS) is a 30-item self-report assessment designed specifically to identify depression in the elderly. It has been validated against therapist ratings of depressive symptoms [59]
	Ewart Self-Efficiency Scale (EWART)	Participants are asked to rate on a scale of 0 to 100% (from not confident at all to very confident) how confident they are that they could perform the task mentioned, right now. Tasks include lifting objects, climbing flights of stairs, walking, jogging & performing push-ups [60].
Quality of life, Pain and Physical activity assessment	*Western Ontario and McMaster University Osteoarthritis Index (WOMAC)*	The extensively-validated WOMAC questionnaire will be used to assess pain, stiffness, and physical function in patients with hip and / or knee osteoarthritis (OA) WOMAC consists of 24 items divided into 3 subscales: Pain, Stiffness, Physical Function based in the past 7 days [61].
	Physical Activity Scale for the Elderly (PASE)	PASE is a brief, easy tool for assessment of short-term physical activity in epidemiological studies of the elderly for the past 7 days. It is designed for community-dwelling older adults ages >65 years. This questionnaire addresses the activities commonly engaged in by elderly in addition to sport and recreational activities [62].
	Physical and Mental Health Summary Scales (SF36)®	The SF-36, Version 2 (norm-based) is a multi-purpose, short-form health survey and includes eight generic health concepts and 2 summary scales. The SF-36 has proven useful in surveys of general and specific populations, comparing the relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments[63].