

Effects of dietary intervention and quadriceps strengthening exercises on pain and function in overweight people with knee pain: randomised controlled trial

Claire M Jenkinson, research associate,¹ Michael Doherty, professor of rheumatology,² Anthony J Avery, professor of primary care,³ Anna Read, senior dietitian,⁴ Moira A Taylor, associate professor of human nutrition,⁵ Tracey H Sach, senior lecturer in health economics,⁶ Paul Silcocks, clinical senior lecturer,⁷ Kenneth R Muir, professor of epidemiology¹

¹Division of Epidemiology and Public Health, School of Community Health Sciences, University of Nottingham, Queen's Medical Centre, Nottingham NG7 2UH

²Academic Rheumatology, University of Nottingham, Clinical Sciences Building, City Hospital, Nottingham NG5 1PB

³Division of Primary Care, School of Community Health Sciences, University of Nottingham, Queen's Medical Centre, Nottingham NG7 2UH

⁴Department of Nutrition and Dietetics, Queen's Medical Campus, Nottingham University NHS Trust, Queen's Medical Centre, Nottingham NG7 2UH

⁵School of Biomedical Sciences, University of Nottingham, Queen's Medical Centre, Nottingham NG7 2UH

⁶School of Chemical Sciences and Pharmacy, University of East Anglia, Earlham Road, Norwich NR4 7TJ

⁷Nottingham Clinical Trials Unit, School of Community Health Sciences, University of Nottingham, Queen's Medical Centre, Nottingham NG7 2UH

Correspondence to: C M Jenkinson claire.jenkinson@nottingham.ac.uk

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ABSTRACT

Objective To determine whether dietary intervention or knee strengthening exercise, or both, can reduce knee pain and improve knee function in overweight and obese adults in the community.

Design Pragmatic factorial randomised controlled trial.

Setting Five general practices in Nottingham.

Participants 389 men and women aged 45 and over with a body mass index (BMI) of ≥ 28.0 and self reported knee pain.

Interventions Participants were randomised to dietary intervention plus quadriceps strengthening exercises; dietary intervention alone; quadriceps strengthening exercises alone; advice leaflet only (control group). Dietary intervention consisted of individualised healthy eating advice that would reduce normal intake by 2.5 MJ (600 kcal) a day. Interventions were delivered at home visits over a two year period.

Main outcome measures The primary outcome was severity of knee pain scored with the Western Ontario McMaster (WOMAC) osteoarthritis index at 6, 12, and 24 months. Secondary outcomes (all at 24 months) included WOMAC knee physical function and stiffness scores and selected domains on the SF-36 and the hospital anxiety and depression index.

Results 289 (74%) participants completed the trial. There was a significant reduction in knee pain in the knee exercise groups compared with those in the non-exercise groups at 24 months (percentage risk difference 11.61, 95% confidence interval 1.81% to 21.41%). The absolute effect size (0.25) was moderate. The number needed to treat to benefit from a $\geq 30\%$ improvement in knee pain at 24 months was 9 (5 to 55). In those randomised to knee exercise improvement in function was evident at 24 months (mean difference -3.64 , -6.01 to -1.27). The mean difference in weight loss at 24 months in the dietary intervention group compared with no dietary intervention was 2.95 kg (1.44 to 4.46); for exercise versus no exercise the difference was 0.43 kg (-0.82 to 1.68). This difference in weight loss was not associated with improvement in

knee pain or function but was associated with a reduction in depression (absolute effect size 0.19).

Conclusions A home based, self managed programme of simple knee strengthening exercises over a two year period can significantly reduce knee pain and improve knee function in overweight and obese people with knee pain. A moderate sustained weight loss is achievable with dietary intervention and is associated with reduced depression but is without apparent influence on pain or function.

Trial registration Current Controlled Trials ISRCTN 93206785.

INTRODUCTION

Knee pain is a major cause of disability and is especially prevalent in those aged over 50. Much of this knee pain is caused by osteoarthritis, the most common form of joint disease and a leading cause of lower limb disability in older people.¹ A systematic review of knee pain in older adults reported that during a one year period, a quarter of people aged over 55 have an episode of persistent knee pain, around half of whom report associated disability.¹ About 4.5 million people aged over 50 in the United Kingdom are estimated to have severe problems from knee pain, and this figure is likely to rise dramatically as the proportion of the population aged 50 or over increases. Because of its considerable health impact, regional knee pain has been described as the "new back pain."²

Obesity is an established risk factor for the development and progression of both structural knee osteoarthritis³⁻⁶ and knee pain.⁷ It usually predates the development of knee osteoarthritis, supporting cause rather than consequence.⁸ The burden of knee pain is expected to increase with the increasing prevalence of obesity, projected to be about 35% in the UK by 2015.⁹ An estimated quarter to half of all knee osteoarthritis might be prevented by eliminating obesity.¹⁰ Knee osteoarthritis is therefore an increasingly important public health problem with respect to time lost from

employment, worsening health status, and greater prevalence of clinically severe osteoarthritis.¹¹

All international recommendations emphasise the central role of non-pharmacological management of knee pain and osteoarthritis.¹²⁻¹⁵ There is sufficient evidence to recommend weight reduction as an intervention for knee osteoarthritis^{16,17} and convincing evidence, including a recent systematic review, that exercise (both aerobic and muscle strengthening) reduces pain and disability from knee osteoarthritis.¹⁸⁻²¹ Weight loss can also reduce the risk of knee osteoarthritis²² and, together with an exercise programme, improve knee function.²³ Only one randomised trial (in the United States) has assessed the effect of weight loss and exercise specifically in overweight and obese people with knee osteoarthritis.²⁴ That trial reported that the combination of modest weight loss plus moderate exercise provides better overall improvements in self reported measures of function and pain in older overweight and obese adults with knee osteoarthritis compared with either intervention alone.

We used a pragmatic, open, factorial randomised controlled trial to determine whether individualised interventions of diet and quadriceps strengthening exercise reduce knee pain in community derived overweight and obese adults aged 45 and over. We also examined the effects of these interventions on knee stiffness, physical function, and quality of life. A secondary objective was to determine whether it was possible to identify at baseline those individuals most likely to comply and therefore benefit from the interventions by using two simple questions that assess “willingness to change,” lifestyle, and dietary behaviour.

METHODS

Recruitment of participants

All men and women aged 45 and over with a body mass index (BMI) of ≥ 28.0 and knee pain who were registered at one of five general practices in Nottingham were eligible for inclusion. In addition, a small number of people were recruited after publicity in local media. Exclusion criteria were rheumatoid arthritis, cardiac pacemaker, intra-articular injection of steroid into either knee within past three months, lower limb amputation, total knee replacement, unable to complete recruitment questionnaire, unable to undertake either intervention, unwilling to take part.

To ascertain eligible people in the community, each general practice sent a postal questionnaire to all registered patients aged 45 and older. There was no upper age limit. Questionnaires were not sent to terminally ill patients or those with psychiatric illness, dementia, or other incapacitating disease deemed by their general practitioner to make them unsuitable for participation. The questionnaire was designed to assess demographic details, general health, frequency of knee pain, use of analgesics, physical activity, and attitudes to dietary and lifestyle changes. It incorporated the SF-36,²⁵ the hospital anxiety and depression rating scale,²⁶ and two

questions on how willing they were to change their lifestyle and diet.²⁷ People with knee pain were defined as those who reported having knee pain on most days of the past month. We did not include those with recent onset acute pain related to obvious trauma. Completed questionnaires were returned in pre-paid envelopes to the trial centre at the University of Nottingham. The trial coordinator telephoned respondents with knee pain who were overweight or obese and who indicated willingness to receive further information. During this call the trial was explained, any queries were answered, and the coordinator checked that the person met the eligibility criteria (stated above) and that they were interested in taking part. An information pack including a preliminary consent form and reply envelope was then sent out. The study was also publicised via local media (press and radio).

Randomisation procedure

Participants aged 45 or more with a measured BMI ≥ 28.0 and knee pain were randomised to one of four groups: dietary intervention plus quadriceps strengthening exercises; dietary intervention alone; quadriceps strengthening exercises alone; and advice leaflet only (control group). Random allocation to one of the four treatment groups was based on the 2×2 factorial design with a computer generated list, in permuted blocks of 10, stratified by sex, age (<65 , ≥ 65), and BMI (<40 , ≥ 40). Because we expected that more people would withdraw from the dietary intervention groups than the exercise groups, randomisation favoured the dietary intervention groups by a ratio of 3:2 to allow for future planned exploratory analyses. A trial researcher prepared the allocation sequence lists, which were kept in a locked drawer. The trial coordinator carried out the allocation. On receipt of a signed preliminary consent form, the coordinator consulted the appropriate allocation sequence list and assigned the participant to the next treatment group number on that list according to the participant's sex, age, and BMI. The participant was then telephoned to notify them of their group and the first visit booked. All participants were allocated to a treatment group before their first visit. Informed consent was obtained at the first visit. This was an open trial; by necessity the participants and those delivering the interventions were not blind to allocation.

Interventions

All participants in the dietary groups completed the EPIC seven day food diary²⁸ before the first home visit by the trial dietitian. The dietary intervention consisted of individualised dietary advice that would help to create a deficit of 2.5 MJ (600 kcal) a day, in line with healthy eating recommendations (reducing fat and sugar intake, eating more fruit and vegetables, and reducing portion size) and achieve a weight loss of 0.5-1.0 kg a week. The dietitian, the dietetic assistant, or a research interviewer carried out follow-up home visits. If there were questions that could not be addressed by the researcher at the visit, the dietitian

was consulted and the appropriate advice given by telephone as soon as possible after the visit. Newsletters from the dietitian containing recipe ideas and advice for eating healthily when eating out or at holiday times were sent every few months. Occasionally, the EPIC seven day food diary was used again to ascertain participants' eating habits before a visit.

For participants randomised to the diet and exercise group the trial dietitian also taught the programme of exercises at the initial home visit. The exercise programme comprised a series of simple exercises in five sections, primarily designed to strengthen the quadriceps muscle, as used in our previous trials.^{20,21} Although participants received initial instruction in performing the exercises, exercises were subsequently undertaken at home, unsupervised, and with minimal contact with the research visitor and therefore were predominantly self managed. Section A comprised simple flexibility exercises such as extension and flexion of the ankle while the person was seated on the floor or bed. Section B comprised gentle (unresisted) strengthening exercises to start building up the knee muscles—for example, sitting on the floor with both legs out in front, toes pointed towards the ceiling, with a towel roll beneath one knee to bend it slightly. The knee is pushed into the floor so that the thigh muscle tightens. Section C comprised resisted exercises incorporating graded elastic bands, designed to give the thigh muscles more work. After two months, section D exercises were introduced. These were functional exercises, such as rising from the sitting position, designed to help with everyday tasks. After about six months into the programme, participants were asked to attempt section E (aerobic) exercises such as walking and stepping up and down a step. Participants were asked to work through the sections one at a time, at their own pace, doing at least two of the exercises each day. They were asked to repeat the exercises five times, building up to a maximum of 20 for each leg and to record the number and type of exercises carried out each day in their exercise diary. The advice leaflet was based on the Arthritis Research Campaign (UK) leaflet for osteoarthritis of the knee, but we removed information related to the intervention regimens.

Participants in the dietary groups were visited at home once a month for the first six months and then every other month for the duration of the 24 months of follow-up. Those in the exercise only or control groups were visited every four months throughout the 24 months but received a support telephone call in between their visits. These calls were not used to reinforce the exercise programme. At each visit, participants were asked about their knee pain, their general health, their medications, and their levels of physical activity. All participants were weighed at each visit. We endeavoured to arrange that the same researcher visited a participant throughout the trial, although this was not always possible. Visits were conducted in the evening if necessary.

X ray characterisation

All participants underwent knee radiography within the first few months of starting the trial. Posterior-anterior weight bearing knee radiographs were taken with the SynaFlex x ray positioning frame (Synarc, San Francisco, CA²⁹), with feet externally rotated 10° and knees and thighs touching the vertical platform anteriorly and the x ray beam angled 10° caudally. Skyline 30° views of both patellofemoral compartments were taken with the participant in the seated position and the beam angled from feet to knees. A single trained observer (MD), who was blinded to the intervention group, read the radiographs. Severity of tibiofemoral osteoarthritis was scored (0-4) with the Kellgren-Lawrence grading scale.³⁰ Severity of individual features (narrowing -1-3, osteophyte 0-3) in each of the three compartments (medial and lateral tibiofemoral, patellofemoral) of each knee were graded with the Nottingham logically derived line drawing atlas (LDLDA),³¹ which uses different narrowing scales for men and women to allow for normally thicker cartilage width in men. Using this scale, we classified tibiofemoral osteoarthritis as grade 2 narrowing plus grade 2 osteophyte in either tibiofemoral compartment of at least one knee, and patellofemoral osteoarthritis as grade 2 narrowing plus grade 2 osteophyte in at least one patellofemoral joint. Because of the advantages of the line drawing atlas over the Kellgren-Lawrence scale, we used this system to classify definitive radiographic osteoarthritis.

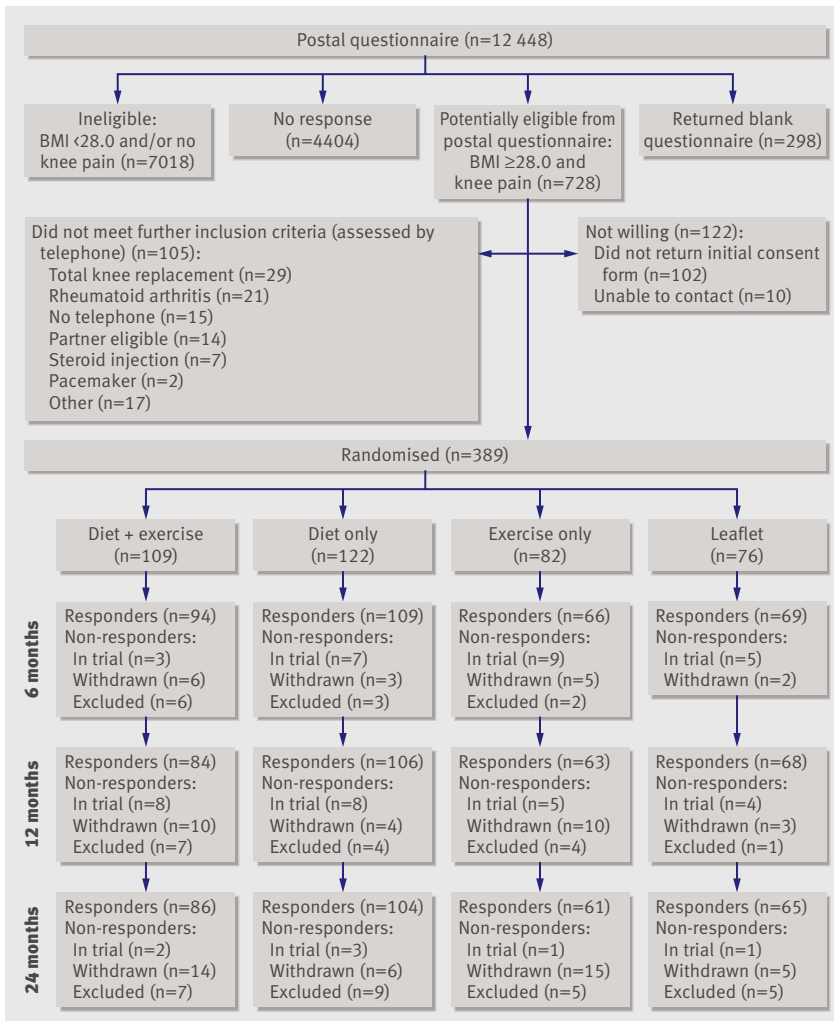
Outcomes

The primary outcome was a "response" defined as a reduction in pain score from baseline of $\geq 30\%$ at 24 months with knee pain severity scored with the pain subscale of the Western Ontario and McMaster Universities (WOMAC) osteoarthritis index.³² We compared mean knee pain scores at 6, 12, and 24 months between treatment arms as a secondary outcome. Additional secondary outcome measures, analysed at 24 months only, comprised mean change in WOMAC stiffness subscale, WOMAC physical function subscale, hospital anxiety and depression rating scale, and mean change in the bodily pain and physical function domains of the SF-36. All outcome questionnaires were posted to participants and were self completed. They were either given to the researcher at the next visit or returned in pre-paid envelopes. Wherever possible, participants who had missed questions were telephoned.

We also asked participants to complete a brief questionnaire at the end of the trial to ascertain their use and dose of analgesics during the trial compared with before the trial.

Statistical analysis

A factorial design allowed examination of two interventions. We had four treatment groups: (1) dietary intervention + quadriceps strengthening exercises; (2) dietary intervention only; (3) quadriceps strengthening exercises only; and (4) advice leaflet. We were



Flow of participants through trial. All those randomised contribute to multiple imputation to follow intention to treat principle. Responders are those returning an outcome. Responders at 24 months contribute to complete case analysis. In each treatment group, categories at each time point are not mutually exclusive as some people who withdrew, returned an outcome

interested primarily in the main effects of diet (1 + 2 v 3 + 4) and exercise (1 + 3 v 2 + 4) with respect to the mean change in WOMAC primary and secondary outcomes, hence we analysed the data collected using an at-the-margins approach (a main effects approach). At the outset of the trial, we did not anticipate an interaction between diet and exercise.

We aimed to recruit 400 participants. A reduction in pain score of 50% or more from baseline to 24 months was defined as a successful outcome, and success rates in the control and intervention arms were assumed to be 20% and 40%, respectively. At a trial steering committee meeting (and before recruitment ended), however, we decided to change the definition to 30% or more to reflect a more appropriate outcome for a community derived population with self reported knee pain (without changing the assumed event rates).

In contrast with usual practice we inflated the sample size to permit adequate power for two exploratory analyses: an assessment of the success of the dietary intervention on knee pain in those prospectively identified

as “willing to change” and comply with the intervention, which, based on our previous work, would be 50%-70% of participants, and an assessment of the effect of dietary intervention in those with radiographic evidence of disease (estimated to be present in about half of overweight people). Furthermore, to allow for potentially greater withdrawal in the dietary intervention group, we aimed to randomise 160 to receive the advice leaflet and 240 to receive the dietary intervention but equal numbers to exercise and no exercise. This resulted in the unusually high power of >98% for both primary comparisons.

Analyses adopted the intention to treat principle, with all participants analysed “as randomised” after multiple imputation for missing data.^{33,34} Multiple imputation was performed with the method of chained equations and five sets of imputations, as implemented in the Stata *ice* add-on.³⁵ The sets of predictor variables for the missing values were determined in an objective manner with the *pred_eq* add-on.³⁶ Imputations were performed separately for each treatment arm with the common set of predictor variables, which permitted inclusion of the response itself. Within each imputed dataset, we dichotomised the imputed pain at 24 months in accordance with the definition of a response (final pain score <70% of baseline). A sensitivity analysis, in which we assumed that missing outcome data were not missing at random, was performed for the primary outcome. For different fractions of those participants for whom the outcome was imputed, the imputed value was replaced by one in the less favourable direction. This was repeated five times and the treatment effect and 95% confidence intervals averaged.

Each analysis of the primary and secondary outcomes included the stratification variables of age, sex, BMI, and baseline outcome as covariates as well as indicators for each intervention (diet and knee strengthening exercise) to calculate estimates of the risk difference and change in mean outcome values. The primary analysis also tested the diet by exercise interaction (at a 10% significance level).

The risk differences were estimated by a generalised linear model with the binomial family, identity link, and robust standard error. We combined the resulting estimates with Rubin’s rule by the *mim* prefix,³⁷ and obtained a covariate adjusted number needed to treat for benefit and approximate 95% confidence limits as the reciprocal of the risk difference and its confidence limits.

The time course of treatment effects was estimated by a linear model incorporating time × treatment interactions and presented as fitted differences in mean WOMAC pain score, with 95% confidence intervals, at 6, 12, and 24 months. Secondary outcomes at 24 months are presented as differences in mean WOMAC stiffness, WOMAC physical function, hospital anxiety and depression, and SF-36 subscales of bodily pain and physical function, with 95% confidence intervals.

We tested for four a priori subgroup-treatment effect interactions, using the baseline thirds of age, BMI, WOMAC pain, and Kellgren-Lawrence osteoarthritis grade. The treatment effect in the top third was compared with that in the lower two thirds in each interaction test. These subgroup analyses were limited to the primary outcome at 24 months.

External validity was assessed by comparing the demographic characteristics of participants with those of the eligible people who were not randomised (that is, those who did not return the initial consent form after receiving the information pack). Summary descriptive statistics, analysis of compliance, “willingness to change,” and analgesic use was performed with SPSS, while all of the above analyses were performed with Stata (version 10.0), and carried out according to a

predefined analysis plan. An independent steering committee and a data monitoring committee monitored the trial. No interim analyses were performed during the study period. Service use and cost implications were examined in an economic evaluation carried out as part of this trial, the results of which are in an accompanying paper (*BMJ* doi:10.1136/bmj.b2273).

RESULTS

Recruitment began in May 2003 and ended in March 2005. The last participant completed the trial in February 2007. The figure shows a summary of recruitment. Of the 728 men and women who had knee pain and a BMI ≥ 28.0 , 122 (17%) were not willing to take part, 105 (14%) did not meet the further inclusion criteria when telephoned, and 10 (1%) could not be contacted. Information packs were sent to 491 people (67%), of whom 389 returned an initial consent form and were randomised: 109 to dietary intervention and quadriceps strengthening exercises, 122 to dietary intervention only, 82 to quadriceps strengthening exercises only, and 76 to advice leaflet (control group). Of these participants, 69 (18%) were recruited via local media and not directly from a general practice. Participants who returned outcome questionnaires at the different time points and the status of those with unknown outcome (non-responders) are depicted in the flow chart (figure). There was no significant difference with respect to age or BMI between participants and eligible non-participants (the 102 people who received information packs but did not return a consent form). There were, however, significantly more women in the participant group (66% *v* 57%). Two hundred and eighty four (73%) completed the trial. Over 3700 home visits took place.

Table 1 shows the baseline characteristics of participants, which were similar between the groups (mean age 61, median BMI 33.6, 66% women). Most participants (351, 90%) had knee radiography within the first few weeks, 47% of which showed signs of osteoarthritis (Kellgren-Lawrence scale ≥ 2). According to the Nottingham logically derived line drawing atlas, 57 (16%) had isolated tibiofemoral osteoarthritis, 35 (10%) had isolated patellofemoral osteoarthritis, and 14 (4%) had both.

Over the course of the trial, 74 participants (19%) withdrew (table 2), most because of personal or medical problems, family commitments, and lack of time. Thirteen of these did not receive the allocation because they cancelled their first visit. Withdrawals occurred more often in the first six months and were significantly greater from the exercise groups, 52 (27%) than from the non-exercise groups, 21 (11%). We excluded 26 (7%) participants (table 2) because they had a total knee replacement ($n=13$), could not be contacted for further visits ($n=7$), exhibited inappropriate behaviour at a home visit ($n=2$), were considered too frail at first visit to undertake intervention ($n=2$), needed steroid injections ($n=1$), or had died ($n=1$). Four of those excluded did not receive the allocation.

Table 1 | Baseline characteristics of participants by treatment group. Figures are numbers (percentages) of participants unless stated otherwise

Characteristics	Diet + exercise (n=109)	Diet only (n=122)	Exercise only (n=82)	Leaflet only (n=76)
Mean (SD) age (years)	61.1 (9.2)	61.7 (9.2)	61.1 (9.8)	61.5 (9.2)
Women	73 (67)	79 (65)	56 (68)	49 (65)
Median (IQR) weight (kg)	91.4 (17.8)	93.4 (17.3)	92.2 (21.8)	94.2 (20.2)
Mean (SD) height (m)	1.65 (0.09)	1.65 (0.09)	1.64 (0.10)	1.66 (0.10)
Median (IQR) BMI	33.0 (5.9)	33.6 (4.6)	34.8 (6.6)	33.0 (6.5)
Kellgren-Lawrence score*:				
0	41 (45)	56 (50)	35 (47)	27 (37)
1	7 (8)	5 (4)	6 (8)	9 (12)
2	16 (18)	13 (12)	8 (11)	9 (12)
3	13 (14)	20 (18)	8 (11)	12 (16)
4	14 (15)	19 (17)	17 (23)	16 (22)
Nottingham LDLDA*:				
Isolated tibiofemoral OA	13 (14)	19 (17)	13 (18)	12 (16)
Isolated patellofemoral OA	8 (9)	9 (8)	10 (14)	8 (11)
Tibiofemoral + patellofemoral OA	3 (3)	3 (3)	4 (5)	4 (6)
No definitive OA	67 (74)	82 (73)	47 (64)	49 (67)
Use of painkillers:				
Never/occasionally	54 (50)	53 (44)	39 (48)	38 (50)
Regularly	53 (50)	68 (56)	43 (52)	38 (50)
Comorbidities:				
Heart disease	12 (11)	23 (19)	9 (11)	10 (13)
Asthma	12 (11)	19 (16)	9 (11)	13 (17)
Cancer	5 (5)	7 (6)	1 (1)	5 (7)
Diabetes	10 (9)	12 (10)	7 (9)	6 (8)
Osteoarthritis (self reported)	50 (46)	50 (41)	26 (32)	25 (33)
BMI category†:				
Overweight	17 (17)	15 (13)	10 (13)	14 (19)
Obese class I	51 (50)	62 (52)	33 (42)	30 (41)
Obese class II	23 (22)	32 (27)	25 (32)	21 (29)
Morbidly obese	12 (12)	11 (9)	10 (13)	8 (11)
Mean (SD) WOMAC‡:				
Pain (range 0-20)	8.03 (3.25)	8.07 (4.03)	7.61 (3.14)	7.32 (3.41)
Stiffness (range 0-8)	3.99 (1.55)	4.03 (1.59)	3.78 (1.53)	3.79 (1.62)
Physical function (range 0-68)	28.46 (12.85)	29.01 (13.90)	27.09 (11.24)	26.26 (12.33)

IQR=interquartile range; BMI=body mass index; LDLDA=logically derived line drawing atlas; OA=osteoarthritis; WOMAC=Western Ontario McMaster osteoarthritis index.

*351/389 attended for x ray investigation.

†Weight at first visit, some participants withdrew before first visit, some were excluded before or at first visit.

‡Highest score=greatest pain, stiffness, dysfunction.

Table 2 | Reasons for withdrawal and exclusion by treatment group. Figures are numbers (percentages of group)

	Diet + exercise	Diet only	Exercise only	Leaflet
Reason for withdrawal:				
Changed mind	5 (5)	7 (6)	7 (9)	2 (3)
Too busy	9 (8)	5 (4)	5 (6)	0
Personal	8 (7)	0	6 (7)	1 (1)
Medical	4 (4)	1 (1)	6 (7)	3 (4)
Other	1 (1)	1 (1)	2 (2)	1 (1)
Total	27 (25)	14 (11)	26 (32)	7 (9)
Reason for exclusion*:				
TKR	2 (2)	6 (5)	2 (2)	3 (4)
Unable to contact	2 (2)	3 (2)	0	2 (3)
Unsuitable for treatment	2 (2)	0	0	0
Inappropriate behaviour	1 (1)	0	1 (1)	0
Steroid injection	0	0	1 (1)	0
Died	0	0	1 (1)	0
Total	7 (6)	9 (7)	5 (6)	5 (7)

TKR=total knee replacement.
*Only excluded for per protocol analysis.

Response to outcome questionnaires at 6, 12, and 24 months was 94, 84, and 86 (86%, 77%, and 79%) for the diet and exercise group; 109, 106, and 104 (89%, 87%, and 85%) for the diet only group; 66, 63, and 61 (81%, 77%, and 74%) for the exercise only group; and 69, 68, and 65 (91%, 90%, and 86%) for the advice leaflet group. In a main effects analysis, we compared those randomised to knee strengthening exercise with those not randomised to exercise (all exercise *v* all non-exercise), likewise, we compared those randomised to the dietary intervention with those not randomised to it (all diet *v* all non-diet). There was no evidence of an interaction between diet and exercise (estimated coefficient = -0.084, 95% confidence interval -0.28 to 0.12; $P=0.407$).

Primary outcome

At 24 months, 38 (47%) of the exercise only group achieved $\geq 30\%$ reduction in pain from baseline compared with 23 (30%) of the advice leaflet group. Mean pain scores were 5.70 and 7.04, respectively (estimates numbers of successes include values based on multiple imputation) (table 3).

Table 4 shows the estimates of risk difference for improvement in WOMAC pain score at 24 months. The risk difference corresponds to a good response,

Table 3 | Percentage with successful outcome and mean WOMAC pain score at 24 months by treatment group

Treatment	No of participants*	No (%) with successful outcome†	Mean (SD) pain score‡
Advice leaflet	76	23 (30)	7.04 (4.21)
Diet only	122	42 (35)	6.96 (4.33)
Exercise only	82	38 (47)	5.70 (3.96)
Diet + exercise	109	46 (43)	6.39 (4.15)

*As randomised.

† $\geq 30\%$ reduction in pain score. Numbers with successful outcome include those derived from imputation.

‡Unadjusted for covariates, but allowing for multiple imputation.

defined as a $\geq 30\%$ reduction in pain from baseline. After multiple imputation, there was a significant reduction in knee pain in the knee exercise groups compared with the the non-exercise groups at 24 months (percentage risk difference 11.61, 95% confidence interval 1.81% to 21.41%). This represents an absolute benefit of 11.6 percentage points and corresponds to the number needed to treat with knee exercise for such a benefit (at 24 months) of 9 (5 to 55), adjusted for dietary intervention, age, BMI, sex, and baseline pain score. Those exposed to knee exercise were more likely to experience a $\geq 30\%$ reduction in pain (relative risk 1.36, 1.05 to 1.76; $P=0.022$). The absolute effect size (0.25) is only just within the moderate range. There was no evidence of an effect of dietary intervention on pain. Table 4 also shows the similarity of the risk differences (for exercise) when we used complete case and per protocol analysis. In this trial “per protocol” refers to analysis of outcome assessments of all those who completed the trial and who were not excluded or did not withdraw. Table 5 summarises the time course of treatment effects. Improvement in the mean WOMAC pain score was evident in the exercise group at 6 months, not evident at 12 months, and significant at 24 months, with a net treatment effect (all exercise minus all non-exercise) of -0.91 (-1.66 to -0.17; $P=0.016$). There was no evidence of an effect of dietary intervention over time on the WOMAC pain score (table 5). The sensitivity analysis for the missing at random assumption showed that using linear interpolation, the 95% lower confidence limit for exercise would just be zero if 34% of the imputed responses for pain at 24 months were in fact in the less favourable direction. We regard this as being moderately sensitive to the missing at random assumption.

Secondary outcomes

Table 6 shows the mean changes in WOMAC physical function and knee stiffness scores at 24 months. There was a main treatment effect of knee strengthening exercise with a significant net reduction in the mean change in WOMAC physical function score (-3.64, -6.01 to -1.27; $P=0.003$) and stiffness (-0.35, -0.66 to -0.03; $P=0.030$). The absolute effect sizes were 0.24 and 0.19, respectively. There was no evidence of an effect of dietary intervention on these WOMAC outcomes.

Analysis of the quality of life outcome data at 24 months (table 6) showed a significant effect of exercise, with improvements in the SF-36 subscales of bodily pain and physical function (absolute effect size for each is 0.22). There was no evidence of an effect of dietary intervention on these secondary outcomes, but there was a reduction in the depression score (absolute effect size=0.19).

Analysis of the pre-specified binary subgroups (age, BMI, WOMAC pain, and Kellgren-Lawrence osteoarthritis grade), with a test for interaction and a significance level of $P<0.10$, did not show any differences in intervention effect across these subgroups (table 7), except for exercise and BMI ($P=0.061$). We also examined mean weight loss at 24 months. The difference in

Table 4 | Risk difference estimates for WOMAC pain at 24 months

Treatment	Risk difference* (%)		P value
	Mean (SE)	95% CI	
Multiple imputation (n=389):			
Exercise v no exercise	11.61 (4.99)	1.81 to 21.41	0.020
Diet v no diet	-0.08 (5.70)	-11.44 to 11.27	0.988
Complete case (n=316):			
Exercise v no exercise	13.18 (5.51)	2.37 to 23.98	0.017
Diet v no diet	-0.24 (5.59)	-11.20 to 10.72	0.966
Per protocol (n=284):			
Exercise v no exercise	12.93 (5.88)	1.41 to 24.45	0.028
Diet v no diet	1.68 (5.90)	-13.25 to 9.89	0.776

*Adjusted for age, sex, body mass index (BMI), baseline pain, and indicators for each intervention.

mean weight loss (initial minus final) at 24 months between the dietary and non-dietary groups was 2.95 kg (1.44 to 4.46; $P=0.000$). There was a non-significant difference in mean weight loss of only 0.43 kg (-0.82 to 1.68; $P=0.501$) between the exercise group and those not exposed to this intervention. These data are adjusted for treatment, age, BMI, sex, and baseline weight. Per protocol analysis with SPSS showed that the dietary intervention was successful; those in the dietary groups (diet + exercise and diet only) being twice as likely to experience moderate weight loss (5% of initial weight) compared with non-dietary groups (exercise only + advice leaflet only) at 24 months (unadjusted relative risk 2.3, 1.42 to 3.74; $P<0.001$). Knee strengthening exercise was not associated with moderate weight loss (results not shown).

Compliance

We were not able to measure direct compliance with the dietary intervention but all participants were weighed at each visit. Compliance with exercise was graded as high or low according to how well the exercise diaries had been completed. They were categorised by a single observer who made a global judgment of all exercise diaries with some adjustment for pattern of regularity. In the diet + exercise group and the exercise only group, 49 (45%) and 37 (45%), respectively, complied highly with the exercise programme for 24 months. Those with high compliance

Table 5 | Differences in mean WOMAC pain scores by time

Time (months)	Difference*		P value
	Mean (SE)	95% CI	
Exercise v no exercise			
6	-0.76 (0.39)	-1.53 to 0.01	0.052
12	-0.52 (0.41)	-1.33 to 0.28	0.202
24	-0.91 (0.38)	-1.66 to -0.17	0.016
Diet v no diet			
6	0.06 (0.40)	-0.75 to 0.86	0.887
12	0.14 (0.38)	-0.60 to 0.89	0.705
24	-0.08 (0.41)	-0.91 to 0.75	0.849

*Analysis after multiple imputation and adjusted for other intervention plus exercise × time, diet × time, BMI band, age band, baseline pain, and sex.

were more likely to have a baseline WOMAC pain score above the top third (>9.0) and were more likely to be women.

Compared with before starting the trial, self reported use of analgesics (for knee pain) and dose during the trial were both significantly lower in the exercise group than in the non-exercise group. Significantly fewer people in the exercise group reported having had knee pain on most days of the past month of the trial. There were no significant differences in the distribution of responses to these questions when we compared the dietary group with the non-dietary group (results not shown). A participant's willingness to change their lifestyle or their diet, categorised from responses in the ascertainment questionnaire (and thus before the start of the trial), was not associated with exercise compliance, pain improvement of $\geq 30\%$, or with loss of $\geq 5\%$ of initial body weight.

DISCUSSION

In overweight and obese adults aged 45 and over, a simple home based knee strengthening exercise programme reduced knee pain, improved the function of the knee, and reduced knee stiffness over a two year period. These effects were not apparent in people allocated to a dietary intervention alone, even though weight loss was achieved, but levels of depression were reduced.

Comparison with other studies

Our results add to the substantial evidence, summarised in a recent overview of nine systematic reviews,³⁸ that exercise interventions for patients with knee osteoarthritis reduce pain and improve physical function but that effect sizes are considered small. Another systematic review and meta-analysis of four randomised controlled trials of weight reduction in obese patients with knee osteoarthritis concluded that there is robust evidence that weight reduction improves self reported disability and reduces pain, though only self reported disability and not pain could be predicted by weight loss.³⁹ Comparison with other studies is difficult because of the diversity in treatment regimens and follow-up periods. We found no evidence of an effect of dietary intervention on knee pain or function. In the review by Christensen et al,³⁹ three of the four trials reporting pain as an explicit outcome showed a significant weight loss in the intervention group, but the pooled mean weight loss (6.1 kg) was higher than that experienced by our dietary participants (2.9 kg at 24 months). The follow-up in these three studies was shorter (8 weeks, 6 months, 18 months) and participants had a higher mean baseline BMI. Post hoc calculations from data from one of the trials in this review also showed that clinical efficacy could be shown only when weight loss is added to an exercise treatment. The weighted pooled effect size from these three studies was small (0.20) so it is possible that the moderate long term weight loss in our trial was not sufficient to affect pain.

It is reassuring that exercise intervention significantly improved the quality of life outcomes of SF-36 physical function and bodily pain. SF-36 measurements sometimes produce different results from those of the primary efficacy outcomes but rarely modify the overall interpretation of randomised trials.⁴⁰ This concordance strengthens our WOMAC primary and secondary outcome conclusions. Dietary intervention was not associated with these quality of life outcomes but did seem to reduce the depression score, which suggests that obesity is associated with a lower health related quality of life, a result also found in an analysis of 1865 patients registered at one general practice who completed the ascertainment questionnaire used in this trial.⁴¹ That paper reported that relative to a normal BMI, obesity was associated with a lower health related quality of life after adjustment for patients' characteristics and comorbidities.⁴¹ A positive association between BMI and depression was recently reported in a large cohort of primary care patients with osteoarthritis,⁴² and a recent review of the impact of obesity on the musculoskeletal system concluded that obesity was responsible for impaired quality of life.⁴³

Strengths and limitations

This was a pragmatic trial and the factors that improve external validity—for example, no upper age or weight limit and ascertainment based on knee pain and not radiographic change—might have reduced the effect size. A relatively long follow-up period might have reduced efficacy. Also, contact time with the researcher was limited to a visit once every four months for those in the exercise only group (a maximum of only seven support visits) and exercise

Table 6 | Differences in mean change in secondary outcome scores at 24 months

	Difference*		P value
	Mean (SE)	95% CI	
WOMAC physical function			
Exercise	-3.64 (1.21)	-6.01 to -1.27	0.003
Diet	-2.84 (1.48)	-5.88 to 0.19	0.065
WOMAC stiffness			
Exercise	-0.35 (0.16)	-0.66 to -0.03	0.030
Diet	-0.16 (0.17)	-0.50 to 0.19	0.365
HADS anxiety			
Exercise	-0.26 (0.37)	-1.02 to 0.51	0.496
Diet	0.09 (0.35)	-0.62 to 0.79	0.807
HADS depression			
Exercise	0.15 (0.37)	-0.62 to 0.92	0.693
Diet	-0.67 (0.32)	-1.30 to -0.04	0.037
SF-36: bodily pain†			
Exercise	5.62 (2.35)	0.99 to 10.25	0.018
Diet	0.94 (2.83)	-4.89 to 6.78	0.742
SF-36: physical function†			
Exercise	5.32 (2.04)	1.30 to 9.33	0.010
Diet	3.93 (2.68)	-1.64 to 9.49	0.157

*Analyses included age, sex, BMI, and baseline outcome of interest as covariates plus indicators for each intervention.

†Positive values reflect improvement.

Table 7 | Subgroup treatment effect interactions

Interaction term	Coefficient* (SE)	95% CI	P value
Diet × age	0.085 (0.11)	-0.13 to 0.30	0.448
Exercise × age	-0.002 (0.11)	-0.22 to 0.22	0.986
Diet × BMI	-0.032 (0.11)	-0.24 to 0.18	0.762
Exercise × BMI	-0.206 (0.11)	-0.42 to 0.01	0.061
Diet × pain	0.081 (0.13)	-0.17 to 0.33	0.518
Exercise × pain	-0.042 (0.11)	-0.27 to 0.18	0.716
Diet × KL	-0.052 (0.11)	-0.27 to 0.17	0.639
Exercise × KL	-0.097 (0.12)	-0.34 to 0.15	0.432

BMI=body mass index, KL=Kellgren-Lawrence osteoarthritis score.

*Analyses included age band, sex, BMI category, and outcome of interest as covariates plus indicators for each intervention.

participants were responsible for the management of their exercise programme, factors that will not have enhanced adherence. Withdrawals were higher from the exercise groups than the dietary intervention group, and the potential selective loss might have resulted in some bias. We attempted to address this in our sensitivity analysis. The most common reasons given for exercise withdrawal were “too busy” and “personal.” Because only 45% of the exercise participants complied highly with their programme, our effects might be underestimated. We could not produce a more finely graded measure of compliance because of the wide range in age and weight and ability to perform the exercises. Thus someone in their late 70s who did only a few exercises every other day was deemed equivalent (with respect to compliance) to a younger more active participant performing more exercises more often.

The fact that the complete case, per protocol, and multiple imputation analyses all give reasonably similar results for the primary outcome must at least partly reflect the low fraction of missing information and is reassuring. This reassurance, however, cannot be predicted a priori and neither can the fraction of missing information, so in general, multiple imputation should become routine practice. Given that it is rare for a sensitivity analysis to be done at all, our procedure is admittedly ad hoc. Both the choice of criterion for assessing sensitivity to “missing at random” and its interpretation are clearly subjective. We chose as a criterion whether the declaration of significance would have been affected, but an alternative might be the extent to which the point estimate of the parameter was altered by changing assumptions. Rather than perform a sensitivity analysis it is also possible to explicitly model the process by which missing data arise in a selection model, but we chose not to do this because this is problematic when covariates have missing values; the regression coefficients for the response might be seriously biased if the model is incorrect, and it is not possible to test such models formally in any case.

We did not ask participants to stop taking painkillers during this relatively long trial, a factor that has the potential to confound the pain outcomes, but we

WHAT IS ALREADY KNOWN ON THIS TOPIC

Knee pain is highly prevalent in the community and is often associated with knee osteoarthritis in middle aged and older people

Exercise (both aerobic and strengthening) can reduce pain and improve physical function and mobility in people with knee osteoarthritis

Current osteoarthritis guidelines also support weight loss for overweight and obese people with knee osteoarthritis, despite the paucity of clinical trials

WHAT THIS STUDY ADDS

A simple home based programme of knee strengthening exercise significantly reduces knee pain and improves mobility in overweight and obese adults with knee pain, with a number needed to treat of nine

Long term improvement is confirmed over 24 months

Dietary intervention did not have an effect on knee symptoms or function but was associated with an improvement in depression

thought that this would have been unacceptable and would have hindered recruitment. There were no differences between the four randomisation groups with respect to self reported use of analgesics at the start of the trial, but those exposed to exercise reported less use and lower doses during the trial than those in the dietary group, facts that support the result of a beneficial effect from exercise but not from dietary intervention on pain.

We were interested in seeing whether we could predict at baseline those who were willing to change their behaviour, information that might perhaps aid recruitment in future studies. With the two questions we used, however, we were not able to do this. Reasons might have been respondents' varying interpretations of the word "lifestyle" and not connecting this to exercise or dietary behaviour (these questions were asked before potential participants knew anything about the trial).

It is clear that regular exercise that strengthens the thigh (quadriceps) muscles can reduce pain and disability from knee pain and osteoarthritis. Such exercise might act by reducing the muscle weakness and impaired balance that occurs with knee pain and osteoarthritis, thus directly improving the stability and health of the affected knee. This allows people to do more with their knee and to experience less pain.

Conclusions and policy implications

This large randomised controlled clinical trial investigated the contribution of quadriceps strengthening exercise and weight loss on knee pain and function specifically in an overweight and obese population with knee pain. A special feature is the use of multiple imputation to address the issue of missing data and the inclusion of a sensitivity analysis. These data also show that long term weight loss through caloric restriction can be achieved in such a population. Our results give strong support to published recommendations,¹²⁻¹⁷ including from NICE,¹⁵ for the management of people with knee osteoarthritis and suggest that clinicians can prescribe knee strengthening exercises and diet for their overweight and obese patients with knee pain. It also

underlines the need for breaking the vicious circle of increase in body weight-decrease in physical activity-increase in osteoarthritis related pain and depression. Treating comorbidity such as depression might have a beneficial effect on pain and disability from osteoarthritis.⁴⁴ Interestingly, in our study, although dietary intervention was associated with a reduction in depression score, there was no significant improvement in knee pain and disability. Our study might have been underpowered to show benefit from non-pharmacological treatment of comorbidity, but clearly there is sufficient justification to treat comorbidity such as obesity and depression, even without secondary gain with respect to osteoarthritis.

Our findings support the long term effectiveness of quadriceps strengthening exercise as an intervention for knee pain in overweight and obese adults aged 45 and over. Although the effect size is moderate, it compares favourably with drug based approaches to the long term management of osteoarthritis. We have also shown that lifestyle interventions have an impact on the psychological wellbeing and quality of life of participants and that these outcomes are as meaningful as the clinical ones. Further work is needed to establish factors that might indicate which participants are most likely to benefit from these interventions and the best way to deliver them in primary care and in a way that overweight and obese people will adhere to, as it is the general practitioner who is the usual care provider for such patients with knee osteoarthritis or knee pain.

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- 1 Peat G, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. *Ann Rheum Dis* 2001;60:91-7.
- 2 Underwood MR. Community management of knee pain in older people: is knee pain the new back pain? *Rheumatology* 2004;43:2-3.
- 3 Felson DT, Zhang Y, Hannan MT, Naimark A, Weismann B, Aliabadi P, et al. Risk factors for incident radiographic knee osteoarthritis in the elderly. The Framingham study. *Arthritis Rheum* 1997;40:728-33.
- 4 Spector TD, Hart DJ, Doyle DV. Incidence and progression of osteoarthritis in women with unilateral knee disease in the general population: the effect of obesity. *Ann Rheum Dis* 1994;53:565-8.

- 5 Reijman M, Pols HAP, Bergink AP, Hazes JMW, Belo JN, Lieveense AM, et al. Body mass index associated with onset and progression of osteoarthritis of the knee but not of the hip: the Rotterdam study. *Ann Rheum Dis* 2007;66:158-62.
- 6 Felson DT. Epidemiology of hip and knee osteoarthritis. *Epidemiol Rev* 1988;10:1-28.
- 7 Jinks C, Jordan K, Croft P. Disabling knee pain—another consequence of obesity: results from a prospective cohort study. *BMC Public Health* 2006;6:258-65.
- 8 Felson DT, Anderson JJ, Naimark A, Walker AM, Meenan RF. Obesity and knee osteoarthritis. The Framingham study. *Ann Intern Med* 1988;109:18-24.
- 9 Ono T, Guthold R, Strong K. *WHO Global comparable estimates infobase*. Geneva: World Health Organization, 2005. <http://infobase.who.int>
- 10 Felson DT, Zhang Y. An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. *Arthritis Rheum* 1998;41:1343-55.
- 11 Gupta S, Hawker GA, Laporte A, Croxford R, Coyte PC. The economic burden of disabling hip and knee osteoarthritis (OA) from the perspective of individuals living with this condition. *Rheumatology* 2005;44:1531-7.
- 12 Roddy E, Zhang W, Doherty M, Arden NK, Barlow J, Birrell F, et al. Evidence-based recommendations for the role of exercise in the management of osteoarthritis of the hip or knee—the MOVE consensus. *Rheumatology* 2005;44:67-73.
- 13 Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JWJ, Dieppe P, et al. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a task force of the standing committee for international clinical studies including therapeutic trials (ESCSIT). *Ann Rheum Dis* 2003;62:1145-55.
- 14 Altman RD, Hochberg MC, Moskowitz RW, Schnitzer TJ. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee. 2000 update. *Arthritis Rheum* 2000;43:1905-15.
- 15 National Institute for Health and Clinical Excellence. *Osteoarthritis: the care and management of osteoarthritis in adults*. London: NICE, 2008 (Clinical Guideline 59). www.nice.org.uk/CG059
- 16 Woolf A, Akesson K, Compston J, Thorngren K-G, van Riel P. *European Bone and Joint Health Strategies Project. European action towards better musculoskeletal health: the bone and joint decade*. Lund, Sweden; 2004.
- 17 Pendleton A, Arden N, Dougados M, Doherty M, Bannwarth B, Bijlsma JWJ, et al. EULAR recommendations for the management of knee osteoarthritis: a report of a task force of the standing committee for international clinical studies including therapeutic trials (ESCSIT). *Ann Rheum Dis* 2000;59:936-44.
- 18 Roddy E, Zhang W, Doherty M. Aerobic walking or strengthening exercise for osteoarthritis of the knee? A systematic review. *Ann Rheum Dis* 2006;64:544-8.
- 19 Fransen M, McConnell S, Bell M. Exercise for osteoarthritis of the hip or knee. *Cochrane Database Syst Rev* 2003;(3):CD004376.
- 20 Thomas KS, Muir KR, Doherty M, Jones AC, O'Reilly SC, Bassey EJ. Home based exercise programme for knee pain and knee osteoarthritis: a randomised controlled trial. *BMJ* 2002;325:752-5.
- 21 O'Reilly SC, Muir KR, Doherty M. Effectiveness of home exercise on pain and disability from osteoarthritis of the knee: a randomised controlled trial. *Ann Rheum Dis* 1999;58:15-9.
- 22 Felson DT, Zhang Y, Anthony JM, Naimark A, Anderson JJ. Weight loss reduces the risk for symptomatic knee osteoarthritis in women. The Framingham study. *Ann Intern Med* 1992;116:535-9.
- 23 Miller GD, Niklas BJ, Davis C, Loeser RF, Lenchik L, Messier SP. Intensive weight loss program improves physical function in older obese adults with knee osteoarthritis. *Obesity* 2006;14:1219-30.
- 24 Messier SP, Loeser RF, Miller GD, Morgan TM, Rejeski WJ, Sevick MA, et al. Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the arthritis, diet, and activity promotion trial. *Arthritis Rheum* 2004;50:1501-10.
- 25 Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36) I. Conceptual framework and item selection. *Med Care* 1992;30:473-83.
- 26 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361-70.
- 27 Prochaska JO, DiClemente CC, Norcross JC. In search of how people change: applications to addictive behaviours. *Am Psychol* 1992;47:1102-14.
- 28 Day N, Oakes S, Luben R, Khaw KT, Bingham S, Welch A, Wareham N. EPIC-Norfolk: study design and characteristics of the cohort. European prospective investigation of cancer. *Br J Cancer* 1999;80(suppl 1):95-103.
- 29 Peterfy C, Li J, Saim S, Duryea J, Lynch J, Miaux Y, et al. Comparison of fixed-flexion positioning with fluoroscopic semi-flexed positioning for quantifying radiographic joint-space width in the knee: test-retest reproducibility. *Skeletal Radiol* 2003;32:128-32.
- 30 Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis* 1957;16:494-502.
- 31 Nagaosa Y, Mateus M, Hassan B, Lanyon P, Doherty M. Development of a logically devised line drawing atlas for grading of knee osteoarthritis. *Ann Rheum Dis* 2000;59:587-95.
- 32 Bellamy N. Outcome measurement in osteoarthritis clinical trials. *J Rheumatol* 1995;22(suppl 43):49-51.
- 33 Allison PD. *Missing data*. Thousand Oaks, CA: Sage, 2001.
- 34 Carpenter JR, Kenward MG. *Missing data in randomised controlled trials—a practical guide*. www.missingdata.org.uk
- 35 Royston P. 2005b. Multiple imputation of missing values: update of ice. *Stata J* 2005b;5:527-36.
- 36 Medeiros R. *Pred_eq: program to create and test imputation models (equations) for ice*. UCLA: Academic Technology Services, Statistical Consulting Group. www.ats.ucla.edu/stat/stata/ado/analysis
- 37 Rubin DB. *Multiple imputation for nonresponse in surveys*. New York: John Wiley, 1987.
- 38 Jantvedt G, Dahm KT, Christie A, Moe RH, Haavardsholm E, Holm I, et al. Physical therapy interventions for patients with osteoarthritis of the knee: an overview of systematic reviews. *Physical Therapy* 2008;88:123-36.
- 39 Christensen R, Bartels EM, Astrup A, Bliddal H. Effect of weight reduction in obese patients diagnosed with knee osteoarthritis: a systematic review and meta-analysis. *Ann Rheum Dis* 2007;66:433-39.
- 40 Contopoulos-loannidis DG, Karvouni A, Kouri I, Ioannidis JPA. Reporting and interpretation of SF-36 outcomes in randomised trials: systematic review. *BMJ* 2009;338:a3006.
- 41 Sach TH, Barton GR, Doherty M, Muir KR, Jenkinson C, Avery AJ. The relationship between body mass index and health-related quality of life: comparing the EQ-5D, EuroQol VAS and SF-6D. *Int J Obes* 2007;31:189-96.
- 42 Rosemann T, Grol R, Herman K, Wensing M, Szecsenyi J. Association between obesity, quality of life, physical activity and health service utilisation in primary care patients with osteoarthritis. *Int J Behav Nutr Phys Act* 2008;5:4.
- 43 Anandacoomarasamy A, Caterson I, Sambrook P, Fransen M, March L. The impact of obesity on the musculoskeletal system. *Int J Obes* 2008;32:211-22.
- 44 Lin EHB, Katon W, Von Korff M, Tang L, Williams Jr JW, Kroenke K, et al. Effect of improving depression care on pain and functional outcomes among older adults with arthritis: a randomized controlled trial. *JAMA* 2003;290:2428-34.

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