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Effectiveness and cost-effectiveness of a combined lifestyle intervention compared with usual care for patients with early-stage knee osteoarthritis who are overweight (LITE): protocol for a randomised controlled trial

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ABSTRACT

Introduction Obesity is the most important modifiable risk factor for knee osteoarthritis (KOA). Especially in an early stage of the disease, weight loss is important to prevent further clinical and structural progression. Since 2019, general practitioners (GPs) in the Netherlands can refer eligible patients to a combined lifestyle intervention (GLI) to promote physical activity, healthy nutrition and behavioural change. However, GPs scarcely refer patients with KOA to the GLI potentially due to a lack of evidence about the (cost-)effectiveness. The aim of this study is to determine the (cost-)effectiveness of the GLI for patients with early-stage KOA in primary care.

Methods and analysis For this pragmatic, multi-centre randomised controlled trial, 234 participants (aged 45–70 years) with National Institute for Health and Care Excellence (NICE) guideline diagnosis of clinical KOA and a body mass index above 25 kg/m^2 will be recruited using a range of online and offline strategies and from general practices in the Netherlands. Participants will receive nine 3-monthly questionnaires. In addition, participants will be invited for a physical examination, MRI assessment and blood collection at baseline and at 24-month follow-up. After the baseline assessment, participants are randomised to receive either the 24-month GLI programme in addition to usual care or usual care only. Primary outcomes are self-reported knee pain over 24 months, structural progression on MRI at 24 months, weight loss at 24 months, as well as societal costs and Quality-Adjusted Life-Years over 24-month follow-up. Analyses will be performed following the intention-to-treat principle using linear mixed-effects regression models.

Ethics and dissemination Ethical approval was obtained through the Medical Ethical Committee of the Erasmus MC University Medical Center Rotterdam, The Netherlands (MEC-2020-0943). All participants will provide written informed consent. The results will be disseminated through publications in peer-reviewed journals, presentations at international conferences and among study participants and healthcare professionals.

Strengths and limitations of this study

- ► The trial is pragmatic in design and will be performed in multiple centres, enabling better generalisability.
- ► The combined lifestyle intervention (GLI) is individualised based on the patient's personal goals but also relies on the input of the healthcare professionals involved in the GLI, which may introduce clinical heterogeneity.
- ► Further follow-up is required to assess long-term benefits after the end of the intervention.
- ► A mixed-methods approach using quantitative and qualitative methods will support future implementation.

Trial registration number Netherlands Trial Registry (NL9355).

INTRODUCTION

In almost all the countries, the prevalence of individuals who are overweight is rising.[1] Having a body mass index (BMI) greater than 25 increases the risk of many chronic diseases, including cardiovascular disease, diabetes mellitus (DM), chronic kidney disease, multiple cancers, depression and musculoskeletal disorders such as osteoarthritis (OA).[2] OA is a joint disorder, most frequently affecting the knee, hand, hip and foot joints.[3] The prevalence of OA in the Netherlands is expected to increase from 7% in 2015 to 12% in 2040, which is mainly attributed to rising overweight rates.[4] Patients with knee OA (KOA) experience pain and impaired physical functioning, which may affect their quality of life. KOA is associated with many

risk factors, but most strongly with older age, female sex, high BMI, previous knee injury, knee malalignment and genetic predisposition.[5–8] Although a high BMI is considered the most modifiable risk factor, management of KOA is mainly restricted to diminishing pain and disability with pain medication and exercise therapy.[9] If conservative management is unsuccessful, total knee arthroplasty (TKA) is the last treatment option for patients with advanced KOA suffering from severe pain.[10] Due to the progressive nature of the disease and the absence of a disease-modifying osteoarthritis drug, the average costs for a patient with KOA remain high throughout the course of the disease.[11] In 2017, the medical costs of KOA have been estimated at 488 million Euros, accounting for 1.4% of all healthcare costs in the Netherlands.[12]

Several trials showed that body weight loss has a positive effect on knee pain and function[13–16] and was found to reduce the risk for the onset of radiographic KOA.[17] Therefore, guidelines recommend 5%–10% wt loss for patients with KOA who are overweight.[18] So far, all studies assessing the effects of weight-loss have been performed in patients with established KOA. Although studies have recognised the importance of early identification and treatment of KOA,[19 20] the effectiveness of weight loss in patients with early-stage KOA is unknown up until now. Early intervention increases the chance to prevent or slow progression towards end-stage KOA, when a costly TKA is required.

Since 2019, general practitioners (GPs) in the Netherlands can refer eligible patients to a combined lifestyle intervention (GLI). The general aim of the GLI is to lose at least 5% of body weight by promoting physical activity (PA), healthy nutrition and behavioural change. The GLI is available for patients who are overweight and with DM type 2, cardiovascular disease, sleep apnoea or OA. GPs, as the first point of contact, play an essential role in early case finding and diagnosis, which enables GPs to intervene in an early stage of KOA. Although GPs can refer patients with KOA to the GLI, it is not frequently done in routine clinical practice, potentially due to a lack of evidence about the clinical effectiveness. A longitudinal study showed that the GLI leads to a positive change in behavioural lifestyle factors and a reduction in body weight in patients who are obese.[21] However, it is unclear whether the GLI is effective for patients with early-stage KOA. There are several barriers to weight loss that may pose a challenge for both healthcare professionals (HCPs) and patients, including a desire for high-calorie or high-fat food,[22] low self-efficacy,[23] fear of movement,[24] pain experienced during activities and decreased physical functioning.[25] To date, there have been no studies examining the (cost-)effectiveness of the GLI in the early-stage KOA population.

Objectives

The primary objective of this study is to evaluate the effectiveness of the GLI added to usual care in a primary care setting for patients with early-stage KOA who are overweight compared with usual care alone on (1) self-reported knee pain over 24 months, (2) structural OA progression on MRI over 24 months, (3) weight loss at 24 months and for the cost-effectiveness from a societal perspective (4) Quality-Adjusted Life-Years (QALYs) over 24 months.

Secondary objectives are to determine the effect of the GLI on (1) performance-based physical functioning (Timed Up and Go, quadriceps strength) at 24 months, (2) other disease-specific Patient Reported Outcome Measures (PROMs) over 24 months, (3) general health and inflammation-related outcomes at 24 months including blood pressure, waist circumference, biomarkers (glycosylated haemoglobin (HbA1c), total cholesterol, triglycerides, C reactive protein (CRP), interleukin 6 (IL-6), creatinine) and microbiome composition.

METHODS AND ANALYSIS

The Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines were used in the development of this study protocol (online supplemental additional file 1).[26]

Trial design and setting

The Lifestyle Intervention Trial for Early-stage KOA (LITE) study is a pragmatic, multi-centre, two-arm, superiority randomised controlled trial (RCT). Patients with early-stage KOA who are overweight (ie, BMI≥25 kg/m^2) will be equally randomised to (1) the GLI in addition to usual care or (2) usual care only (figure 1). Multiple GLI programmes are available in the Netherlands ('Slimmer', 'Cool', 'Samen Sportief in Beweging', 'X-Fittt GLI').[27] For the current trial, the 'Beweegkuur-gecombineerde leefstijlinterventie' was chosen as the intervention programme.[28] This decision was based on the greater accessibility of the intervention in the region of Rotterdam and because we expect it to be the best fit for this target population (ie, patients with early-stage KOA who are overweight). Recruitment for the trial began in July 2021 and the aim is to include the last participant by July 2022. With a 2-year follow-up for all participants, the trial is anticipated to be completed by June 2024.

Participants

Two recruitment strategies will be used. Participating GPs can invite eligible patients to participate in the trial. Simultaneously, participants will be recruited with offline and online recruitment strategies (eg, advertisements in newspapers or on social media). Potential participants will be screened by the researchers using the inclusion and exclusion criteria listed in box 1. Eligible participants will be provided with an information package and consent form (online supplemental additional file 2) and will have the opportunity to ask questions. Researchers will obtain written consent from participants willing to participate in the trial before data collection. GPs of participants who signed up via the online and offline

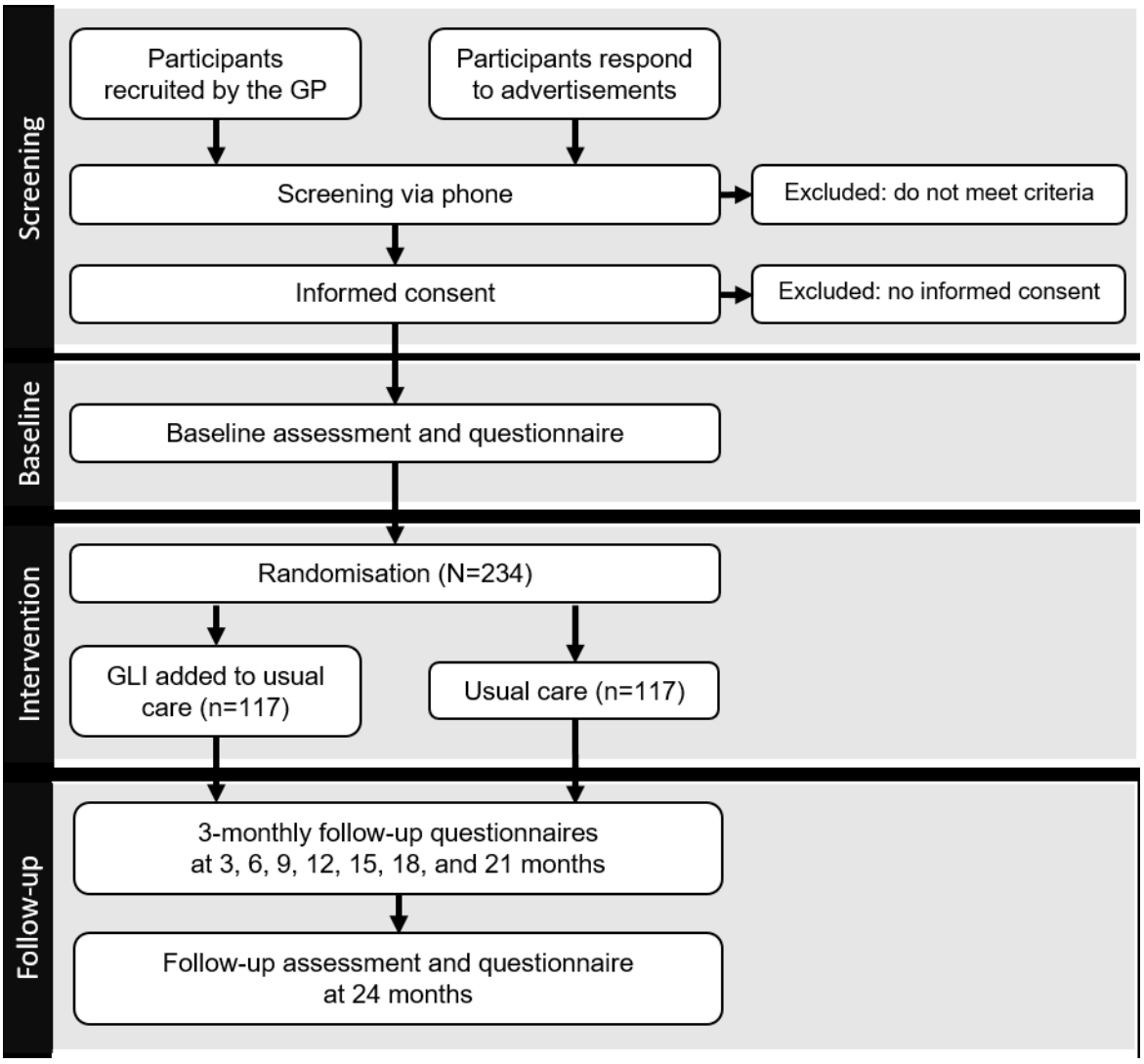

Figure 1 Schematic design of the Lifestyle Intervention Trial for Early-stage KOA trial. GLI, combined lifestyle intervention; GP, general practitioner; KOA, knee osteoarthritis.

recruitment strategies will be informed of trial participation. During the screening, participants will be asked about their most symptomatic knee, which will be considered the index knee for the duration of the trial. If both knees are equally affected, the right knee will be chosen as the index knee.

Allocation and blinding

After the baseline assessment, participants are randomised with an allocation ratio of 1:1 to the intervention or control group. Block randomisation (random size 4 or 6) stratified by BMI (BMI≥25 kg/m^2/BMI≥30 kg/m^2) will be employed using the electronic data capture (EDC) system Castor (Ciwit BV, Amsterdam, The Netherlands). Blinding of participants, researchers and HCPs is not possible due to the nature of the intervention. Researchers will inform participants and their GPs of their treatment allocation and will inform the GP about participants who have been allocated to the intervention group to request a referral to the GLI.

Interventions

Combined lifestyle intervention

Participants allocated to the intervention group will receive the GLI in addition to usual care. The 24-month GLI is a multicomponent intervention addressing PA, nutrition and behavioural skills. The content of the GLI is not designed specifically for the target population. The participants will follow the original programme that is individualised based on the participant's personal goals. The general aim of the GLI is to lose at least 5% of body weight during the first year and to maintain this weight loss in the second year. Participants will be supported by a team of accredited HCPs, including the lifestyle coach (LSC), a physical therapist (PT) and a dietician. The programme consists of individual and group sessions guided by the HCPs (table 1).

Lifestyle coaching

The LSC is trained in motivational interviewing, a method for autonomy-supportive coaching, which is an essential

Box 1 Inclusion and exclusion criteria in the Lifestyle Intervention Trial for Early-stage KOA trial

Inclusion criteria

1. First presentation at the GP with knee complaints within the previous 24 months.
2. Aged ≥45 and <70 years.
3. NICE guideline diagnosis of clinical KOA.
   - Aged 45 or over.
   - Activity-related joint pain.
   - Either no morning joint-related stiffness or morning stiffness that lasts no longer than 30 min min.
4. Presence of overweight (BMI* ≥25 kg/m^2).
5. Able to give written informed consent.

Exclusion criteria

1. Other pathological conditions that could explain the joint complaints, including traumatic onset knee complaints or the presence of other forms of arthritis (eg, rheumatoid arthritis, psoriatic arthritis), prepatellar bursitis or patellar tendinitis.
2. Any lower extremity condition other than KOA resulting in physical impairment that will limit GLI participation.
3. Contraindications for MRI.
4. Previously participated in a GLI.
5. Not being able to speak, read or write Dutch.

BMI, body mass index; GLI, combined lifestyle intervention; GP, general practice; KOA, knee osteoarthritis; NICE, National Institute for Health and Care Excellence.
*BMI is calculated as body weight in kilograms divided by the squared height in metres.

part of the GLI.[29 30] The participant is supported by the LSC to become intrinsically motivated to change their behaviour concerning PA and healthy dietary behaviour. The intake with the LSC is aimed at setting personal goals and identifying barriers and facilitators to a healthy lifestyle. Following the intake, the participant will have five individual sessions with the LSC to evaluate their behavioural change.

Exercise component

The exercise component aims to reach a minimum of 1200 kcal/week of energy expended by PA. The participants will then gradually increase their energy expenditure to 2000 kcal/week by adjusting the frequency, duration and/or intensity of the PA. During the intake with the PT, an exercise programme is formed based on personal goals and the participant's ability to exercise. The PT will support the participant to overcome barriers to exercise and enable the participant to exercise in local facilities. After two sessions with the PT, the participant is introduced to a sports coach to continue with the exercise programme in year 2.

Nutritional component

The sessions with the dietician are aimed to improve the nutritional knowledge and skills to structurally adapt the participant's dietary habits. The nutritional advice is based on evidence-based dietary guidelines.[31–33] A nutritional plan will be formulated during the intake with the dietician. After the intake, the dietician will plan two individual sessions to monitor the participant's eating behaviour and seven group sessions to provide nutritional recommendations, tips to cope with high-risk situations, strategies to prevent relapse and to facilitate interaction between participants.

Usual care

All participants will receive usual care by their GP following the Nederlands Huisartsen Genootschap guideline for non-traumatic knee complaints.[34] This includes patient education, promoting weight loss and advising regular PA (≥30 min/day), prescribing analgesics or intra-articular corticosteroid injections, or referring patients for specialist treatment (eg, exercise therapy).

Use of co-interventions

Any care that participants receive concerning weight loss, PA and use of cointerventions (eg, non-steroidal anti-inflammatory drugs, other analgesic drugs, intra-articular injections, knee braces or inlays) will be documented through self-report. Referral for joint replacement or bariatric surgery is allowed. Participants allocated to the control group cannot be referred to the GLI.

Data collection

Participants will be assessed at nine-time points in the 24-month study period. After providing consent, participants are asked to complete the baseline (T0) questionnaire, prior to the baseline appointment. Thereafter, participants will receive eight 3-monthly (T3–T24) follow-up questionnaires. Questionnaires are sent digitally by Castor EDC and reminders will automatically be sent. The content of the questionnaire per time-point is shown in table 2. Participants will be invited for a clinical examination, 1 hour each, at baseline (T0) and at 24-month follow-up (T24). The examination will be performed by two trained researchers. Adherence to the GLI will be recorded by the HCPs.

Clinical visit

Physical examination

Body weight (kg), height (m), BMI (calculated) and waist circumference (mm) at the midpoint between the iliac crest and the lowest rib will be measured using standardised techniques. Brachial blood pressure will be measured two times in a seated position on the left arm with 3 min rest between consecutive measurements with an oscillometric device (Omron HBP-1320, Omron Health Care Inc., Illinois, USA). Systolic and diastolic blood pressure is automatically calculated.

Knee function will be examined by assessing joint line tenderness, palpable warmth,[35] crepitus with active loaded movement of the joint, bony enlargement, painful and restricted passive range of motion measured by goniometry of knee extension and flexion with the participant in a supine position, effusion using the hydrops test[36] and knee joint alignment (hyperextension, varus or

Table 1 Combined lifestyle intervention programme with the individual and group sessions per healthcare professional

	Lifestyle coach	Physical therapist	Dietician
First-year			
1	Intake		
2		Intake: set up an exercise programme	
3			Intake: set up a nutritional programme
4	Individual session		
5			1st group session
6		1st group session	
7	1st group session		
8			2nd group session
9		2nd group session and the introduction to a local sport coach	
10	Individual session		
11	2nd group session		
12			3rd group session
13	Individual session		
Second-year			
1		Continued coaching of the local sports coach or physical therapist	1st group session
2	Individual session		
3	1st group session		
4			2nd group session
5	Individual session		
6			third group session
7	second group session		

valgus).[37] The hands will be examined for signs of hand OA (Heberden's and Bouchard's nodes).

Physical function will be assessed with the Timed Up and Go (TUG) and by measuring quadriceps strength. The TUG measures the time (s) needed by participants to stand up from a chair, walk 3 m as quickly and safely as possible, walk around a cone, return and sit down in the chair.[38] Participants are allowed to have one practice trial, followed by an actual test.

Maximal voluntary isometric contraction in knee extension (Newton) will be measured with a hand-held dynamometer (HHD) (MicroFET2, Hoggan Health Industries Inc., West Jordan, Utah, USA). Participants will be seated at the examination table with their lower limbs bent over the edge and their arms crossed in front of the body. Participants are instructed to maintain the trunk in the upright position. The HHD will be fixed to the table leg using a fixation belt to allow a maximum of 60° of knee flexion during the muscle contraction. The test will be performed two times per leg, starting with the side of the index knee, with a rest period of 60 s between measurements. The HHD will be placed on the anterior and proximal aspect of the tibia at the level of the malleoli. The fixation belt will counter all resistance to knee extension but the researcher will stabilise the HHD to prevent movement. Participants are verbally encouraged to exert maximum muscle power for 3 s.

Mechanical sensitivity to pain will be assessed with the Pressure Pain Threshold (PPT) test using an HHD with a probe size of 1 cm^2. Two recordings will be taken at three test sites with the participants lying in a supine position, including the (1) medial joint line of the index knee, (2) medial joint line of the contralateral knee and (3) at the mid-point between the wrist and elbow of the volar aspect of the forearm contralateral to the index knee. Pressure was applied at a constant rate of 5 kPa/s until the participants felt pain or 70 kPA is reached. The participants will be instructed to say 'stop' when the pressure sensation changes to the first sensation of pain and asked to rate the intensity of pain on an 11-point Numeric Rating Scale (NRS) with 0 representing 'no pain' and 10 representing 'worst pain possible'. The pressure (Newton) corresponding to the PPT will be recorded.

Blood sampling

Non-fasting venous blood samples will be collected. Serum or plasma concentrations of HbA1c, total cholesterol, triglycerides, CRP, IL-6 and creatinine will be determined by using a standard protocol. The remaining plasma samples will be aliquoted and stored at −80°C for future analyses of relevant biomarkers. Plasma samples will be used to assess targeted proteomics using Olink-technology (Olink Biosciences, Uppsala, Sweden).[39] Cell pellets will be kept frozen at −20°C and DNA will be

Table 2 Summary of primary and secondary data collected by questionnaires

Domain	Measure	Content	Ref	Time
Descriptive variables				
Demographics		Body weight and height.		All
		Sex, menopausal status, education level and ethnicity.		T0
Lifestyle and nutrition	Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH)	The SQUASH assesses perceived PA during a normal week over the past few months over five domains, including activities at work, commuting, household activities, leisure time and sports activities.	48	T0
	Factor Occupational Rating System Scale (FORSS)	The FORSS assesses PA during work and leisure.	49	T0
	Sport participation	Type, duration and intensity of past and current sports.		T0
		Smoking and alcohol consumption.		T0, T24
	3-day food diary	Dietary intake will be assessed with a 24-hour food diary filled in for three consecutive days (2 weekdays and 1 weekend day).		T0, T6, T12, T18, T24
Knee complaints	History of knee complaints	Duration of symptoms, specific patellofemoral pain features, previous knee injuries (type, year of injury, onset and treatment) and medication use related to knee complaints.		T0
	Knee complaints	Flares, the feeling of a swollen knee and the duration of morning stiffness.		All
Comorbidities	Self-Administered Comorbidity Questionnaire (SCQ)	The SCQ addresses 10 medical conditions and three not prespecified problems, regarding the occurrence of the problem, received treatment or medication and experienced limitations in everyday life activities.	50	T0
Primary outcomes				
Knee pain at rest and during activity	11-point Numeric Rating Scale (NRS)	An 11-point NRS with 0 representing 'no pain' and 10 representing 'worst pain possible' assesses self-reported overall average knee pain at rest and during activity over the past month.	51 52	All
Quality-Adjusted Life-Years	Five-level version of the EuroQol (EQ-5D-5L)	The EQ-5D-5L assesses QOL over five domains, including mobility, self-care, usual activities, pain/discomfort and anxiety/depression, scored on a 5-point Likert scale (1='no problems'; 5='extreme problems').	53 54	All
Societal costs	iMTA Medical Consumption Questionnaire (iMCQ) and iMTA Productivity Cost Questionnaire (iPCQ)	The iMCQ assesses the healthcare use (eg, hospital care, surgical interventions, general practitioner visits, medication use) and the patient and family costs (eg, informal care, home care). The iPCQ is focused on the productivity losses from paid work (eg, absence from work). Both questionnaires have a recall period of 3 months.	55	All
Secondary outcomes				
Knee complaints	Knee injury and Osteoarthritis Outcome Score (KOOS)	The KOOS assesses symptoms and functional limitations. It consists of five subscales that are scored on a 5-point Likert scale on pain, other symptoms, ADL, sport and recreation, and QOL in the previous 7 days. All the subscales will be included separately.	56	All
	Intermittent and Constant OsteoArthritis Pain (ICOAP)	The ICOAP is comprised 5-items assessing constant knee pain and 6-items assessing intermittent knee pain in the previous week scored on a 6-point Likert scale.	57 58	T0, T6, T12, T18, T24
	Global Rating of Change (GRoC)	The GRoC assesses the overall perceived change in KOA complaints on a 7-point Likert scale ranging from 'much worse' to 'much better'.	59	T0, T6, T12, T18, T24
	Patient Acceptable Symptom State (PASS)	The PASS assesses whether the current state (eg, consequences of KOA in the past week) would be acceptable or unacceptable if that remained during the rest of their life.	60	All

Continued

Table 2 Continued

Domain	Measure	Content	Ref	Time
Psychosocial factors	Tampa Scale of Kinesiophobia (TSK)	The TSK assesses fear of (re-)injury due to movement with 17-items that is scored on a 4-point Likert scale ranging from 'strongly agree' to 'strongly disagree'.	61	T0, T24
	Self-Efficacy for Exercise (SEE)	The SEE assesses the confidence in performing PA three times a week for 20 min under specified circumstances (eg, lack of time, experience pain during activity, experience stress).	62	T0, T12, T24

KOA, knee osteoarthritis; PA, physical activity; QOL, quality of life.

isolated. Genetic profiles will be determined using DNA-variant microarray analysis.

Microbiome

Faecal samples will be collected at baseline and 24-month follow-up and stored frozen. The intestinal microbiome composition will be assessed using 16S-sequencing.[40] Previously identified microbiome composition that was found to be linked to joint pain and inflammation will be analysed.[40]

MRI

MRI of the index knee will be performed on a 1.5 Tesla MR unit (MAGNETOM Sola, Siemens Medical Solutions, Erlangen, Germany) with a dedicated 18-channel knee coil. The protocol comprises a sagittal, axial and coronal fast spin-echo proton density-weighted sequence with fat suppression, a sagittal and axial proton density-weighted Dixon sequence with fat suppression, as well as a fast spin-echo T2-weighted water excitation 3D sequence. A screening form will be completed by all participants to ensure there is no contraindication for MRI. Semi-quantitative scoring will be conducted using the MRI Osteoarthritis Knee Score (MOAKS) to evaluate multi-feature joint changes.[41] The MOAKS evaluates the presence of articular cartilage loss in conjunction with surrounding bony and soft tissue abnormalities, including bone marrow lesions, osteophytes, lesions of the menisci, ligaments and tendons, joint effusion and synovitis, as well as periarticular features. The change of individual features per subregion (1='progression'; −1='improvement'; 0='no change') and the summed change per feature will be assessed.[42] The summed change scores per feature will be dichotomised into progression versus no progression (change score≥1='progression'; change score<1='no progression').

Outcome measures

Primary outcome measures

The study will include several primary outcomes.

- Clinical outcome: change in average knee pain at rest and during activity (NRS) over 24 months.
- Structural outcome: structural progression of KOA (MOAKS) on MRI at 24 months.
- Mechanistic outcome: change in body weight at 24 months.

For the cost-effectiveness:

- Societal costs (iMTA Medical Consumption Questionnaire, iMTA Productivity Cost Questionnaire) over 24 months.
- QALYs based on quality of life (Five-level version of the EuroQol (EQ-5D-5L)) over 24 months.

Secondary outcome measures

- Change in physical functioning (TUG, quadriceps strength) at 24 months.
- Change in disease-specific PROMs (Knee injury and Osteoarthritis Outcome Score, Intermittent and Constant OsteoArthritis Pain, Global Rating of Change, Patient Acceptable Symptom State) over 24 months.
- Change in general health and inflammation-related outcomes (blood pressure, waist circumference, biomarkers (HbA1c, total cholesterol, triglycerides, CRP, IL-6, creatinine) and microbiome composition) at 24 months.

Other variables of interest:

- General and OA-specific characteristics will be collected at baseline including age, sex, menopausal status, employment status, educational level, ethnicity, knee complaints, history of knee injuries, comorbidities (Self-Administered Comorbidity Questionnaire), plasma biomarkers (Olink proteomics) and genetic profiles.
- Lifestyle data will be collected at baseline including PA level (Short QUestionnaire to ASsess Health-enhancing physical activity), past and current sports participation, PA during work and leisure (Factor Occupational Rating System Scale), and smoking and alcohol consumption.
- Change in psychosocial factors (Tampa Scale of Kinesiophobia, Self- Efficacy for Exercise) at 24 months.
- Change in self-reported body weight over 24 months.
- Change in self-reported diet over 24 months.
- Change in knee function at 24 months.
- Change in pain sensitisation (PPT) at 24 months.

Qualitative interviews

Following the 2-year intervention, semi-structured interviews will be conducted to receive feedback on perceived barriers and facilitators of both participants and HCPs from the GLI. It is anticipated that approximately 15 participants and 10 HCPs will be needed to reach data

saturation, though data collection will continue until data saturation is reached. The interviews will be conducted by a member of the research team and the interviews will be audiotaped and transcribed verbatim. The topic guides for participants and HCPs will be developed from existing literature based on the study aims of measuring barriers and facilitators for the implementation of the GLI. Transcripts will be analysed using thematic analysis. The primary outcome will be to identify barriers and facilitators of patients and HCPs for the implementation of the GLI for patients with KOA.

Sample size

A 5 kg or 5% wt loss was used as the intermediate primary outcome to estimate the sample size. In our previously conducted trial, 17% of the participants in the intervention group who received a diet and exercise programme fulfilled this criterion.[17] For the sample size calculation of the LITE trial, a similar fulfilment for the intervention group was assumed. It was estimated that 5% of the participants in the control group will fulfil this criterion. Based on a power of 80%, an alpha of 5% and a dropout rate of 10% (loss-to-follow-up and missing data) a sample size of 117 participants in each treatment arm is needed. The sample size also provides at least 95% power to detect a minimal clinically important difference of 2-points in mean pain (11-point NRS) in our primary symptomatic outcome.[43]

Statistical analysis

The analysis will be performed using an intention-to-treat approach. Descriptive statistics will be applied to describe the participant's characteristics. The analyses will be adjusted for potential baseline confounders (at least age, sex, comorbidities, BMI and PA). Analysis will be performed using RStudio (R Foundation for Statistical Computing, Vienna, Austria) with statistical significance set at $p<0.05$.

Primary and secondary outcome measures

Repeated measures analysis using linear mixed-effect models (LMMs) will be conducted to analyse the effect on clinical and structural outcomes. Variables will be described as mean with accompanying SD and categorical data as percentages. Time is categorised as baseline and follow-up for the analysis of mechanistic and structural outcomes. For self-reported outcomes on pain and activity limitations 3-monthly or 6-monthly intervals will be considered. An estimator of prediction error (Akaike information criterion, Bayesian information criterion) will be used to select the most appropriate model. The random-effect part of the LMM will include a subject-specific intercept to account for within-subject correlations. The fixed-effect part of the LMMs consists of the predictors of interest: intervention, time and a treatment×time interaction. For each model, the estimated fixed effects with the accompanying 95% CI and p value will be reported.

Logistic regression analysis will be conducted to analyse the effects on weight loss at 24 months. The change scores of body weight will be dichotomised into weight reduction (<5% or <5 kg) and no weight reduction (>5% or >5 kg). ORs and corresponding 95% CI will be calculated.

Cost-effectiveness analysis

The cost-effectiveness and cost–utility analyses will be performed from a societal perspective. For the cost–utility analyses, the EQ-5D-5L health utilities will be used to calculate QALYs. Missing data will be imputed using Multiple Imputation by Chained Equations.[44] The differences in mean QALYs and total societal costs between the intervention and control group will be assessed using a linear regression model. Incremental cost-effectiveness ratios (ICERs) will be calculated by dividing the difference in costs between the groups by the difference in effects. Statistical uncertainty surrounding costs and effects will be estimated using bias-corrected accelerated bootstrapping with 5000 replications and will be presented using cost-effectiveness planes to show the uncertainty surrounding the ICER.[45] Cost-effectiveness acceptability curves will also be estimated showing the probability that the GLI is cost-effective compared with usual care alone for different ceiling ratios (ie, the amount of money that society is willing to pay for a unit of gained effect).[46]

Supplementary analysis

Causal mediation analysis will be conducted to estimate the effects of the GLI on clinical and structural outcomes at 24-month follow-up. The primary mediator, body weight and alternative mediators including PA and diet will be measured at 18 months. The analysis will be adjusted for possible confounders of the mediator-outcome effect. In addition, a per-protocol analysis will be performed according to attendance at the GLI sessions.

Data monitoring and harms

The GLI is an existing lifestyle programme that is recommended as part of standard care, hence, a data monitoring committee was not deemed to be necessary. Data monitoring will be carried out by an independent monitor once a year. Participants in the intervention group who experience adverse outcomes are instructed to discuss these with their GP and LSC. Serious adverse events will be reported to the Medical Research and Ethics Committee (METC).

Patient and public involvement

Patient representatives from the platform Artrose Gezond are involved at several stages of the trial.[47] Patient representatives were involved in the development of the research question and the design of this trial. Patients will be actively involved in the recruitment of participants and dissemination of the final results by advising on appropriate strategies to reach our population and by providing comments on all participant information. For instance, a patient panel discussion was held to share ideas and offer opinions on how to optimise the recruitment. In

addition, patient representatives will provide feedback on the topic guides that will be used during the semi-structured interviews.

ETHICS AND DISSEMINATION

The trial received ethical approval from the METC of Erasmus MC University Medical Center Rotterdam (MEC 2020-0943). The protocol complies with the principles of Good Clinical Practice and the Declaration of Helsinki. Substantial modification must be approved by the METC before being implemented. All participants will provide written informed consent prior to participation in the trial. A unique numeric code will be assigned to every participant that bears no relation to personal data. Trial data will be stored in a locked place for a maximum of 15 years and will be available on reasonable request.

The results of the study will be disseminated in peer-reviewed journals, national and international conferences and to participants, HCPs and the general population through presentations, websites and our patient platform.

DISCUSSION

This is the first RCT to evaluate the (cost-)effectiveness of the GLI in the treatment of patients with early-stage KOA. Given the health economic burden and the social impact of KOA for patients in daily living an effective lifestyle intervention must be identified that is tailored to the OA population.

Although prior research showed that weight loss is beneficial for improving pain and physical function in patients with established KOA,[13–16] it remains unclear what the effect is in patients with early-stage KOA and whether this specific lifestyle intervention can lead to the 5%–10% wt loss recommended in the guidelines. Also, there is still uncertainty whether weight loss can prevent or delay the structural progression of early-stage KOA.[8] Besides, the potential working mechanisms by which the observed improvements in pain and physical function through a lifestyle intervention may be achieved are still not fully understood. In contrast to end-stage KOA, structural alterations in joint tissues at an earlier stage may be more susceptible to disease-modifying interventions, potentially slowing or preventing progressive change. Regardless of structural changes, patient-reported outcomes must be evaluated to better reflect clinically meaningful changes that are relevant to the target population and HCPs. Therefore, multiple primary outcomes are selected to fully capture the important effects of the GLI, in which a change in any primary outcome is clinically or scientifically meaningful, even in the absence of change in any other primary outcome.

With regard to the trial protocol, some strengths and limitations need to be addressed. First, the trial is pragmatic in design and will be performed in multiple centres enabling better generalisability and direct applicability to routine primary care settings. Additionally, the application of a mixed-methods approach will contribute to a potential successful implementation of the intervention. A possible limitation is that the GLI is individualised based on the participant's personal goals but also relies on the input of the healthcare professionals involved in the GLI. This may introduce clinical heterogeneity. Finally, an extended follow-up is required to assess long-term benefits after the end of the intervention.

A positive study outcome, thereby proving evidence of the effectiveness and cost-effectiveness of the GLI, is an important step to improve patient care and reduce the socioeconomic burden of KOA. A less positive outcome is indicative that the GLI in its present form is not suitable for patients with early-stage KOA. In either case, factors that may have influenced the outcome of the intervention will be evaluated in a qualitative study to further refine the intervention.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Section
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Abstract
	2b	All items from the World Health Organization Trial Registration Data Set	Abstract
Protocol version	3	Date and version identifier	n/a
Funding	4	Sources and types of financial, material, and other support	Funding
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Author contributions
	5b	Name and contact information for the trial sponsor	n/a
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Funders
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Introduction
	6b	Explanation for choice of comparators	Introduction
Objectives	7	Specific objectives or hypotheses	Objectives
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Methods and analysis

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Trial design and setting
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Participants, Table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Interventions, subsection ‘GLI’ and ‘Usual care’
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Data monitoring and harms
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Data collection

	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Interventions, subsection 'Use of co-interventions'
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Outcome measures
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Trial design and setting, figure 1 and Interventions, table 2.
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Sample size
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Participants
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Allocation and blinding
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Allocation and blinding
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Allocation and blinding

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Allocation and blinding
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Data collection and Clinical visit
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Data collection and Ethics and dissemination
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Statistical analysis, subsection 'Primary and secondary outcome measures and Cost-effectiveness analysis'
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Statistical analysis, subsection 'Supplementary analysis'

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Statistical analysis
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Data monitoring and harms
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Data monitoring and harms
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Data monitoring and harms
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Ethics and dissemination
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Ethics and dissemination
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Participants
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Ethics and dissemination
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Competing interests
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Ethics and dissemination
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Patient and public involvement
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Ethics and dissemination
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary file 2
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Clinical visit, subsection ‘Blood sampling’ and ‘Microbiome’

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons “Attribution-NonCommercial-NoDerivs 3.0 Unported” license.

Bijlage C: toestemmingsformulier proefpersoon

Behorende bij

Leefstijl en knieartrose

- Ik heb de informatiebrief gelezen. Ook kon ik vragen stellen. Mijn vragen zijn goed genoeg beantwoord. Ik had genoeg tijd om te beslissen of ik meedoe.
- Ik weet dat meedoen vrijwillig is. Ook weet ik dat ik op ieder moment kan beslissen om toch niet mee te doen met het onderzoek. Of om ermee te stoppen. Ik hoef dan niet te zeggen waarom ik wil stoppen.
- Ik geef de onderzoeker toestemming om mijn huisarts te laten weten dat ik meedoe aan dit onderzoek.
- Ik geef de onderzoeker toestemming om mijn huisarts of specialist informatie te geven over onverwachte bevindingen uit het onderzoek die van belang zijn voor mijn gezondheid.
- Ik geef de onderzoekers toestemming om mijn onderzoeksgegevens en lichaamsmateriaal te verzamelen en gebruiken.
- Ik weet dat mijn gecodeerde gegevens naar landen buiten de EU worden gestuurd. Hier gelden niet de privacyregels van de EU en kan niet precies hetzelfde beschermingsniveau worden bereikt als binnen de EU.
- Ik weet dat voor de controle van het onderzoek sommige mensen al mijn gegevens kunnen inzien. Die mensen staan in deze informatiebrief. Ik geef deze mensen toestemming om mijn gegevens in te zien voor deze controle.

- Wilt u in de tabel hieronder ja of nee aankruisen?

Ik geef toestemming om mijn gegevens maximaal 15 jaar te bewaren om dit te gebruiken voor ander wettenschappelijk onderzoek in binnen- en buitenland, zoals in de informatiebrief staat vermeld.	Ja ☐	Nee☐
Ik geef toestemming om mijn (overgebleven) lichaamsmateriaal te bewaren om dit te gebruiken voor ander wetenschappelijk onderzoek in binnen- en buitenland, zoals in de informatiebrief staat vermeld. Het lichaamsmateriaal wordt daarvoor nog 15 jaar bewaard.	Ja ☐	Nee☐
Ik geef toestemming om mij eventueel na dit onderzoek te vragen of ik wil meedoen met een vervolgonderzoek.	Ja ☐	Nee☐
Ik geef toestemming voor bloedafname voor DNA.	Ja ☐	Nee☐

- Ik wil meedoen aan dit onderzoek.

Mijn naam is (proefpersoon): ……..

Handtekening: …… Datum : __ / __ / __

Ik verklaar dat ik deze proefpersoon volledig heb geïnformeerd over het genoemde onderzoek.

Wordt er tijdens het onderzoek informatie bekend die die de toestemming van de proefpersoon kan beïnvloeden? Dan laat ik dit op tijd weten aan deze proefpersoon.

Naam onderzoeker (of diens vertegenwoordiger):…….

Handtekening:…… Datum: __ / __ / __

De proefpersoon krijgt een volledige informatiebrief mee, samen met een getekende versie van het toestemmingsformulier.