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Trajectory of knee health in runners with and without heightened osteoarthritis risk: the TRAIL prospective cohort study protocol

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ABSTRACT

Introduction Running is one of the most popular recreational activities worldwide, due to its low cost and accessibility. However, little is known about the impact of running on knee joint health in runners with and without a history of knee surgery. The primary aim of this longitudinal cohort study is to compare knee joint structural features on MRI and knee symptoms at baseline and 4-year follow-up in runners with and without a history of knee surgery. Secondary aims are to explore the relationships between training load exposures (volume and/or intensity) and changes in knee joint structure and symptoms over 4 years; explore the relationship between baseline running biomechanics, and changes in knee joint structure and symptoms over 4 years. In addition, we will explore whether additional variables confound, modify or mediate these associations, including sex, baseline lower-limb functional performance, knee muscle strength, psychological and sociodemographic factors.

Methods and analysis A convenience sample of at least 200 runners (sex/gender balanced) with (n=100) and without (n=100) a history of knee surgery will be recruited. Primary outcomes will be knee joint health (MRI) and knee symptoms (baseline; 4 years). Exposure variables for secondary outcomes include training load exposure, obtained daily throughout the study from wearable devices and three-dimensional running biomechanics (baseline). Additional variables include lower limb functional performance, knee extensor and flexor muscle strength, biomarkers, psychological and sociodemographic factors (baseline). Knowledge and beliefs about osteoarthritis will be obtained through predefined questions and semi-structured interviews with a subset of participants. Multivariable logistic and linear regression models, adjusting for potential confounding factors, will explore changes in knee joint structural features and symptoms, and the influence of potential modifiers and mediators.

Ethics and dissemination Approved by the La Trobe University Ethics Committee (HEC-19524). Findings will be disseminated to stakeholders, peer-review journals and conferences.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ First longitudinal cohort study to explore the changes in knee joint structure and symptoms in runners with and without a history of knee surgery (and heightened osteoarthritis risk) over 4 years.
⇒ Participants will use wearable devices throughout the study, synchronised with a smartphone app, enabling accurate running training load data monitoring over 4 years.
⇒ Retention of participants to the study may be impacted by potential further restrictions due to the COVID-19 pandemic.

BACKGROUND

Running is one of the most popular recreational activities worldwide, with participation growing 58% in the past decade.[1] The health benefits of running (eg, 25%–40% reduced risk of premature mortality),[2] combined with its low cost and easy accessibility, contribute to its popularity. Although running has many positive health effects, it is also accompanied by an increased risk of lower-limb overuse injuries and pain.[3]

Repetitive joint loads from running might lead to damaged knee articular cartilage, precipitating knee osteoarthritis (OA) development.[4–7] Preclinical animal studies and observational cohorts identified potential detrimental effects of running on knee cartilage,[8 9] yet systematic reviews and meta-analyses[10–12] have not established a causal relationship between running and knee OA risk.[13–15] Uninjured joints appear to tolerate the high joint load associated with running,[12] but the impact of running on the knee joints of individuals with, or at heightened risk of, OA remains unknown.[5] One of the most potent risk factors for OA is a traumatic knee injury and subsequent surgical intervention.[16] The impact of running on joint health in those who have undergone knee surgery (eg, anterior cruciate ligament reconstruction (ACLR) and meniscal surgery[16–19]), who have a particularly high risk of cartilage loss and early-onset OA,[17–20] requires exploration. MRI enables the assessment of early knee OA features, and changes over time that may be observed early in the disease trajectory.[21–25] For example, there is evidence of MRI-detected knee OA from one up to 10 years following ACLR in physically active young adults (18–50 years old).[21–25] Furthermore, MRI (particularly qMRI techniques such as T2 mapping) is sensitive to the accelerated progression of early OA features on MRI (eg, cartilage and meniscal defects) that occur in the short to medium term (1–5 years) after knee surgery.[23 26]

The longitudinal trajectory of symptomatic features (eg, pain, function, quality of life) in regular running athletes with a history of knee surgery has not been prospectively explored.[3] In older adults (45–65 years) with early knee OA, those with bilateral lower-limb pain, associated comorbidities or psychological impairments tended to have a worse trajectory of structural and symptomatic features over 5 years.[27–29] While in a younger population (18–55 years) with a history of ACLR, those with patellofemoral cartilage defects and associated injuries (eg, meniscal lesions) tend to have worse quality of life and symptoms at 5 years after surgery.[26 30] But none of these studies investigated the role of regular running loads on the symptomatic or structural OA (knee health) trajectory. Exploring the longitudinal trajectory of symptoms in regular running athletes with a history of surgery and heightened risk of knee OA, could generate insights on specific knee OA prevention and management strategies.

Exposure to running loads (duration, distance, frequency and intensity)[31] may influence knee health trajectory.[32] However, the relationship of device-measured running training load with changes in knee joint structure and symptoms over-time is unknown.[13 33] Running biomechanics are altered following knee injury and not fully restored with surgery.[21 34–37] Understanding whether running biomechanics are associated with knee OA onset and progression could help healthcare professionals to optimise the management of people who wish to run with knee OA and/or following knee surgery.[13 24 34 38] Other prognostic variables that may relate to future knee joint health and symptoms in running athletes with and without a history of knee surgery include sex, baseline lower-limb functional performance, knee muscle strength, psychological and sociodemographic factors.[13 33]

Objectives

Primary objectives

To compare knee joint (ie, patellofemoral and tibiofemoral) structural features on MRI and knee symptoms at baseline and 4-year follow-up in runners with and without a history of knee surgery.

Secondary objectives

In runners with and without a history of knee surgery, to (i) explore the relationships between training load exposures (running volume and/or intensity) and changes in knee joint structure and symptoms over a 4-year period; (ii) explore the relationship between baseline running biomechanics, and changes in knee joint structure and symptoms over a 4-year period.

We will also explore whether additional variables confound, modify or mediate these associations, including sex, baseline lower-limb functional performance, knee muscle strength, biomarkers, psychological and sociodemographic factors.

Tertiary objectives

We propose to (i) explore baseline and longitudinal associations between knee joint structure, patient-reported outcomes, training load exposures and biopsychosocial factors in runners with and without a history of knee surgery; (ii) evaluate the knowledge and beliefs of runners regarding running and the risk of knee OA.

METHODS

Study design

The TRAIL (TRAjectory of knee heaLth in runners) prospective cohort study will recruit a population of runners with and without a history of knee surgery. The project is approved by the La Trobe University Ethics Committee (HEC-19524) and conducted according to the Declaration of Helsinki. The development of this protocol was guided by the PROGnosis RESearch Strategy (PROGRESS 1 and 2) framework.[39 40] Participants who wish to drop out of the study will have their data analysed unless they request their data to be withdrawn.

Setting

Participants will undergo knee MRIs at a private imaging centre. Clinical examination, functional performance tests, three-dimensional (3D) running biomechanics and muscle strength tests will be completed at the University Gait Laboratory. Patient-reported outcome measures will be completed digitally in a customised electronic platform (Smartabase, Fusion Sport Pty Ltd, Australia). Daily session running load exposure data will be obtained through a wearable device (figure 1). Primary and secondary outcomes will be obtained in the following order: (i) patient-reported outcomes, (ii) knee MRI, (iii) biomechanics, performance-based measures and strength tests. Participants will be asked to refrain from taking any analgesic medications and participating in

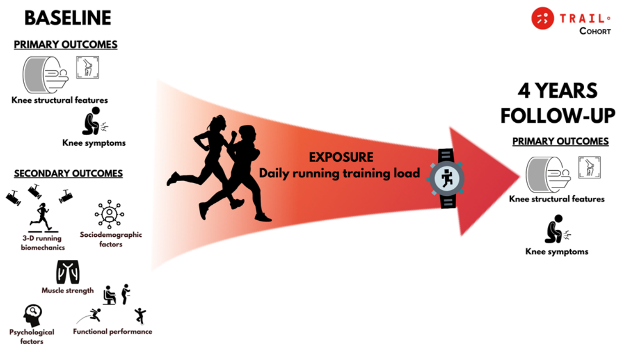

Figure 1 Schematic representation of the design and outcomes of the study. This was created by the authors and are free to use if acknowledgement of the source is provided.

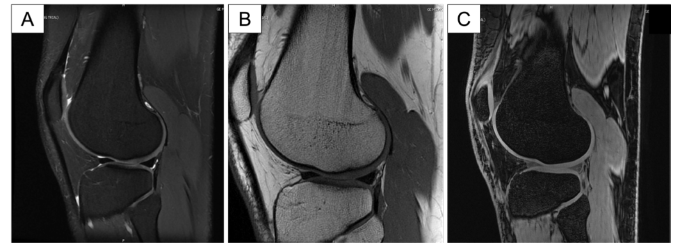

Figure 2 (A) Sagittal proton density fat suppressed; (B) multi-echo-spin-echo (T2 relaxation time); (C) sagittal fast spoiled gradient echo (thickness and bone shape). This image belongs to the authors and are not free to use.

strenuous physical efforts the day prior to data collection or activities they were unaccustomed to.

Recruitment strategy

We will recruit at least 100 (at least 50 women) runners with a history of knee surgery and at least 100 (at least 50 women) control runners (no knee injury/surgery history) from Australia (table 1).[41] To facilitate recruitment we will advertise the study on running clubs, social media and running podcasts. Interested runners will contact the TRAIL research team using a registration recruitment link available at trail.latrobe.edu.au. On registration, an investigator will complete a telephone-based eligibility screening with potential participants. If eligible, participants will complete an electronic consent form to be enrolled in the study.

Outcomes

Primary outcomes will be measured at baseline and 4-year follow-up. Additional variables will be measured at baseline except for training load (daily). A summary of all outcome measures and their respective timepoints are described in figure 1.

Primary outcome: knee joint structural features (baseline and 4-year follow-up)

Knee MRIs will be acquired at baseline and 4-year follow-up using a 3T scanner (Signa Pioneer, General Electric Healthcare, Milwaukee, USA) and an 18-channel knee coil (online supplemental file 1). Sequences acquired will include proton density-weighted fat suppressed fast spin-echo sequences in the sagittal, axial and coronal planes; a sagittal T2 mapping multi-echo spin-echo sequence; and a sagittal fast spoiled gradient echo sequence (figure 2). Changes in cartilage collagen content and orientation in extracellular matrices reflecting degeneration will be defined by quantitative changes in T2 relaxation times[42–44] at baseline and 4-year follow-up. Knee cartilage thickness and bone shape changes over 4 years will also be assessed.[45–47] A custom-written MATLAB-based code (Mathworks, Natick, MA, USA) incorporating deep learning-based automatic segmentation followed by human quality control will be used for bone shape, both T2 relaxation time and cartilage thickness. Knee OA features (eg, cartilage defects, meniscal tears, bone marrow lesions, osteophytes), in patellofemoral and tibiofemoral joints, will be scored with established scoring systems[48 49] at baseline and 4-year follow-up by a trained reader blinded to clinical outcomes. Individual OA feature worsening will be defined as increase in the size or depth of lesions as previously established in cohorts at risk of knee OA.[26 50]

Primary outcome: knee symptoms (baseline and 4-year follow-up)

Knee injury and Osteoarthritis Outcome Score ($KOOS_4$) is the average score for four of the five KOOS subscales, covering pain, symptoms, difficulty in sports and recreational activities, and quality of life, with scores ranging from 0 (worst) to 100 (best).[51] $KOOS_4$ is valid and reliable

Table 1 Participant eligibility criteria

Participants	Inclusion criteria	Exclusion criteria
All participants	Age 18–50 years	Currently pregnant
	Currently running ≥3 times and ≥10 km per week on average in the past 6 months	Contraindications to MRI
		Unable to understand spoken or written English
Runners with a history of knee surgery	History of knee surgery (anterior or posterior cruciate ligament, meniscal, chondroplasty, collateral ligament or arthroscopy)	History of intra-articular knee fracture, arthroplasty, osteotomy, patellar tenotomy or lateral retinacular release. Other lower-limb surgery (eg, hip/ankle)
Asymptomatic control runners		History of lower limb surgery. Any musculoskeletal traumatic or overuse injury in the last 6 months (requiring period of NWB for >24 hours)[104 105]

NWB, non-weight bearing.

(Intraclass Correlation Coefficient (ICC)>0.96)[52] to assess self-reported knee-related issues from acute knee injury through to the development and progression of OA.[53] In addition to the primary timepoints (baseline and 4-year follow-up), we will collect $KOOS_4$ data six-monthly.[54] Individual KOOS subscales will also be obtained and explored as secondary outcomes, including the activities of daily living subscale and the patellofemoral subscale, which are both valid and demonstrate good reliability (ICC>0.86).[52 55–58]

Exposure outcome: running training load (daily until 4-year follow-up)

External running loads (running volume and intensity): all participants

Over the 4-year study period, all participants will use an electronic wearable device to provide daily session running training load data. The wearable device will allow for data extraction via an app (Smartabase, Fusion Sport Pty Ltd, Australia) to provide daily session running: distance (km); duration (min); pace (average min/km) and cadence (average steps/min).[32 33] The Smartabase was set up to send monthly correspondence to the participants.

Internal running loads (heart rate): subset of participants

Average and maximum heart rates[59] will be extracted from a subset of participants, whose electronic wearable device (Garmin or Apple Watch) captures heart rate data from each recorded running session. Heart rate monitoring will provide data on the participants' physiological stress responses during each running session.[60]

Exposure outcome: running biomechanics (baseline)

Set up

3-D kinematic data will be captured using a 10-camera motion capture system (VICON Motion Systems Ltd, Oxford, UK), sampling at a frequency of 200 Hz. Ground reaction force data will be recorded from two force plates (AMTI, Massachusetts, USA) embedded in the laboratory floor and blinded to participants, sampling at 1000 Hz. Participants will wear their own shoes, shorts and crop top. Forty-eight spherical reflective markers (14 mm) will be attached to various locations on the trunk, upper-limbs and lower-limbs to track trunk and lower extremity motion during the tasks (online supplemental file 2).[61]

Procedures

Prior to performing the dynamic trials, a static trial will be captured with the participant assuming a neutral upright stance pose with all markers in situ.[38 62 63] Participants will then run through a 25 m space at an 'easy pace' running speed (3–3.5 m/s) and then at a faster running pace (5–6 m/s).[64 65] Laser timing gates (Fusion Sport Smart Speed Pty Ltd, Australia) will be set up 5 m apart, on either side of the calibrated measurement field to record running speed.[65] Before commencing the running trials, all participants will complete a warm-up consisting of two repeated easy pace running trials to familiarise themselves with the experimental conditions.[38 65] Participants will complete at least eight successful trials at each running speed (starting with 3.5 m/s). A successful trial is defined as meeting the required running speed and clear foot contact on the force plates. One two-dimensional (2D) Vicon Bonita motion camera will also be used to record the foot strike pattern of each running trial.

Additional variables

For all functional performance and strength tests, both legs will be tested, with the left leg always tested first.

Sociodemographic factors and participant characteristics (baseline)

Sociodemographic factors include address, highest education level, current employment status, current occupation, if participants are from Aboriginal or Torres Strait Islander (Indigenous) background. At baseline, we will also obtain participant's age, sex, height, body mass, knee injury and surgery history, and use of pain medication. Knee injury and surgery type(s) and date(s) will be recorded and classified with the Orchard Sports Injury Classification System.[66] Running behaviour will include previous training experience and running training characteristics (duration, distance, frequency, performance, type of training, shoe preferences and use of other running accessories). We will also obtain data regarding participation in other weight-bearing sports and frequency.

Lower-limb functional performance (baseline)

Hop for distance

Participants will stand on a starting line, weight bearing on a single lower limb with both hands held behind their back, then instructed to hop as far forward as possible landing on the same foot. The distance hopped (cm) will be measured from the toe at take-off to the heel at landing, and the furthest of three trials will be recorded.[67–70] The trial will be considered unsuccessful if the participant loses their balance or needs to support their body mass on the non-tested limb. In the case of an unsuccessful trial, an additional trial will be performed. The single-leg hop for distance demonstrates excellent test–retest reliability (ICC=0.94).[71]

Side hop

Participants will hop side to side between two parallel strips of tape, placed 40 cm apart with their hands on their waist.[72] Participants will be instructed to hop as many times as possible for 30 s. A successful side hop is defined as a hop performed over the two strips of tape without touching the tape. An assessor will record the number of successful and unsuccessful hops. This test demonstrates good test–retest reliability in people following surgery (ICC=0.87).[72]

One leg rise

Participants will be positioned sitting on the edge of an adjustable plinth with the heel of the test leg positioned on a line marked on the floor 10 cm in front of the edge of the plinth. The plinth height will be adjusted so that the angle of the testing knee is 90° for all participants. Participants will keep their arms folded across their chest during the whole test. Participants will be instructed to rise from the sitting position to an upright standing position, until they achieve full knee extension, and to return to sitting in a controlled manner. Cadence of one leg rises will be paced with electronic auditory metronome at 45 bpm and the maximum number of successful repetitions recorded. The repetition will be considered unsuccessful if the participant does not achieve full knee extension or if they do not seat down in a controlled manner. One-leg rise test demonstrates good intra-rater reliability in a post-surgical population (ICC=0.84).[73]

Vertical hop (leg stiffness)

Participants will place both hands on their waist, stand on one leg, then hop vertically for 30 s on a force plate.[74] A metronome will be used (120 bpm) to standardise hop pace. The test will be performed on both legs, 1 min rest will be allowed between each leg.[74] Participants will complete five practice hops on each leg before starting the test. The trials will be recorded by the 2D Vicon Bonita motion camera and participants will wear the reflective markers described in online supplemental file 2. Leg stiffness will be calculated as described by Dalleau *et al*.[74]

Knee extensors and flexors muscle strength (baseline)

Bilateral peak isometric torque and rate of torque development (RTD) will be assessed using an isokinetic dynamometer at 60° of knee flexion (Biodex System 4 Pro, New York, NY, USA) with a sampling frequency of 100 Hz.[75 76] This test is reliable in people following knee surgery (ICC=0.92).[76]

Participants will be instructed to perform a contraction as powerful, and quickly as possible.[75] Standardised verbal encouragement will encourage participants to achieve maximum power and strength. Participants will perform one submaximal familiarisation contraction for knee extensors and flexors (6 s) prior to performing three maximal isometric contractions for both each muscle group (6 s duration with 30 s rest between each contraction).[75] Torque data will be normalised to participant body mass (N m kg^{-1}). RTD will be derived from the slope of the torque/time curve, obtained by dividing the normalised torque variation (N m kg^{-1}, represented as %) by the time variation (ms) from the onset of the contraction.[77 78]

Clinical knee examination (baseline)

Participants will undergo a standardised clinical knee examination by an experienced physiotherapist (>10 years of experience managing running athletes). On both knees, we will assess: (i) passive knee flexion range of motion in supine with a goniometer[79]; (ii) knee extension difference between legs in prone with both knees over the edge of a plinth (record the heel-height difference in cm[80]); (iii) medial and lateral knee joint line tenderness in supine (graded present or absent); (iv) assessor-based knee joint crepitus (graded positive or negative). An assessor will place the palm of their hands on the knee joint and ask participants to perform two consecutive bilateral squats to 90° of knee flexion.[54 81 82] The test will be considered positive for knee crepitus when a grinding, crackling or crunching sensation during knee extension or flexion is detected (one or two clicks or pops will not be considered crepitus).

Biomarkers: subset of participants

Blood samples will be collected from a subset of participants with and without knee surgery. Venous blood (~6 mL) will be collected from the antecubital vein, processed (centrifuge for 10 min at ~1500 rcf) and plasma frozen (−80°C).[83] Flow cytometry-based cytometric bead array assays (BD Biosciences) will be used to analyse plasma samples for cytokine levels (interleukin (IL) 1b, IL-6, IL-8, IL-10, tumor necrosis factor-a). The assays will be performed and analysed on a FACS Canto II (BD Biosciences) using FCAP Array V.3.0.1 software per the manufacturer's instructions.

Health well-being (baseline)

Sleep

The Athlete Sleep Screening Questionnaire (ASSQ) is a 16-item questionnaire validated in athletic populations, to measure both sleep and circadian factors related to sleep (ie, quantity, quality, disturbance).[84 85] Five items are used to generate a 'sleep difficulty score' which classifies athletes into a category of a clinical sleep problem: no problem (score 0–4); mild (score 5–7); moderate (score 8–10) or severe (score 11–17). The ASSQ demonstrates good diagnostic sensitivity (81%), specificity (93%) and positive predictive value (Cohen's kappa=0.84).[85]

Health satisfaction

The Patient Acceptable Symptom State (PASS)[86] asks about participants perception about their own health. The participants will complete yes or no to the following question 'Considering your knee function, do you feel that your current state is satisfactory? With knee function, you should take into account all activities during your daily life, sport and recreational activities, your level of pain and other symptoms, and also your knee-related quality of life'. PASS responses are associated with disease severity in people with OA.[87]

Psychological factors (baseline)

Fear of movement

The Tampa Scale for Kinesiophobia (TSK) was designed to identify fear of movement or activity avoidance in chronic and acute musculoskeletal pain.[88] The TSK consists of 17 items and is scored on a 4-point Likert scale.[88–90] A high score indicates a strong fear of pain-related movement. The TSK has good construct validity and reliability (Cronbach alpha, 0.74–0.87; ICC=0.80).[91 92]

Knee self-efficacy

The Knee-Self Efficacy Scale (K-SES) is designed to assess self-efficacy beliefs related to behaviours after knee surgery.[93] The K-SES consists of 22 items measuring daily activities, sports and leisure activities, physical activity and knee function in the future. The K-SES is valid and demonstrates good reliability (ICC=0.95).[94]

Running and OA beliefs and experiences (subset of participants throughout study period)

Qualitative data

Semi-structured interviews, guided by a prestructured topic guide will explore beliefs and experiences related to running and OA, including perceived benefits and risks of running. Purposive sampling will be used to recruit and interview participants of different sexes and age. Approximately 40 interviews (20 runners with a history of knee surgery; 20 control runners), will be conducted. Interviews will be audio recorded, transcribed, and analysed using Framework Analysis,[95] supported by Nvivo software.

Quantitative data

Participant's beliefs regarding running and knee OA will be collected using a questionnaire developed for people with and without medical background and knowledge.[96 97]

Data analysis plan

Sample size calculation

A sample size of 144 will enable the proportion of participants with structural change over 4 years to be estimated at the hypothesised value of 16%[98] with a precision of 6% (alpha=0.05).[62] Allowing for 28% dropouts and missing data,[99] 200 participants will be recruited.

Statistical analysis of baseline characteristics, and 4-year trajectory of knee joint structural features on MRI and knee symptoms will be performed descriptively and comparatively using parametric or non-parametric statistics depending on the nature of the data, with adjustment for potential confounders by multivariable regression analysis. To explore the relationships between (i) training load (exposure) and (ii) running biomechanics with change in knee OA structural features and symptoms (outcomes) in the knee surgery and control groups, multivariable logistic regression models and linear regression models, respectively, will be constructed adjusting for potential confounding variables (eg, age, time since surgery). The influence of moderating or mediating variables will be explored. Data will be transformed as necessary. Further models will be developed to explore relationships between changes in knee OA structural and symptomatic features and clinical symptoms, biomechanical, functional performance, muscle strength, biomarkers, psychological, social and factors.

Participant retention strategies

We developed engagement activities to maximise response rate and participant retention. These activities include (i) monthly correspondence; (ii) recruitment of two ambassadors to promote the importance of ongoing participation in the study (eg, female Australian Olympic marathon runner and a male runner with a history of knee surgery); (iii) publication of podcasts on a variety of running-related projects targeted to participants on our customised study website and (iv) sharing annual newsletters updating participants with interim outcomes.

Patient and public involvement

Interviews with 27 ACLR participants from a previous trial[100] informed the design and development of the research questions of our prospective cohort study. Their knowledge and beliefs about running and OA risk after knee surgery ('I want to be able to go for a run – but my surgeon told me running was bad for my knees'; 17/27 agree/strongly agree that repetitive joint loading increased the risk of OA) highlighted the need to better understand the relationship between running exposure with knee joint health and symptoms. Running was a common goal after ACLR (12/27 had returned to running and only 5/27 returned to their preinjury sport), and many (44%) re-valuated their goals to aim for return to running instead of sport ('overall very happy with improvements in pain everyday activities, would like to be able to increase running tolerance'). The views of and data from participants following ACLR highlighted the need for this longitudinal prospective study in runners with a history of knee surgery.

We will disseminate the findings in peer-reviewed journals and social media.[101] We expect to publish several articles based on data collected at the baseline and follow-up. All results (negative, positive and inconclusive findings) will be disseminated and published. Participants will be notified of all published studies and receive an infographic with a summary of the findings.

DISCUSSION

Repetitive joint loads associated with running have been hypothesised to be detrimental to knee joint health.[4 8 10] The TRAIL study will be the first prospective cohort study to challenge the belief that 'running is bad for your knees'[96] by evaluating knee joint structural features and knee symptoms at baseline and 4-year follow-up in runners, and comparing the changes in those with and without a history of knee surgery. A strength of our study is the use of MRI techniques, such as T2 mapping, which can detect early signs of knee OA features after knee surgery.[26] Interestingly, a systematic review reported that T2 values would decrease immediately after running, and then return to baseline in the next 24 hours.[102] However, a prospective study with longer-term follow-up is necessary to understand the impact of regular running on knee joint structural features.

We will also quantify the association of device-measured running load exposure and running biomechanics with changes in knee joint structural features and symptoms over time. Previous reports suggest that MRI-based superficial and medial areas of knee cartilage and meniscus seem to be more susceptible to mechanical loading.[102] But no prior study has investigated the role of regular running loads or the knee joint load (eg, knee extension and abduction net external joint torques, tibiofemoral and patellofemoral reaction forces) during running itself on MRI knee joint structural features. Clinically, our study may offer clinicians the ability to identify modifiable factors that could be suitable targets for prevention and intervention strategies such as running retraining and load management.[32 103]

We will redress the gender/sex bias in this research field by including a balanced number of women and men runners. For example, the recent systematic review exploring the association of running with hip and knee OA included 125 810 participants, where approximately 71% were male runners.[10] TRAIL will tackle the under-representation of female runners, producing results that can be applied to all people who run.

Limitations

Our study has some limitations that should be acknowledged. Conducting a 4-year longitudinal cohort study has an inherent risk of follow-up loss; we developed participant retention strategies to mitigate this risk. Capturing 'real-world' running load data through wearables over 4 years will provide valuable insight into the association between load, overuse injury and knee health. However, there is a risk of participants stopping or making inconsistent use of their wearables despite our risk mitigation strategies (ie, monthly correspondence with participants). Participants may change their running behaviour (for a number of reasons, including injury), and drop below the eligibility criteria for inclusion. Different wearable brands (Garmin or Apple Watch) may result in slightly different measures of internal running loads (eg, heart rate).

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Supplementary File 1.

Details of MRI sequences acquired.

	Proton Density weighted fat suppressed fast spin-echo ***Axial***	**Proton Density weighted fat suppressed fast spin-echo** ***Sagittal***	**Proton Density weighted fat suppressed fast spin-echo** ***Coronal***	**Multi-echo spin-echo (MESE) T2 relaxation time mapping** ***Sagittal***	**Fast spoiled gradient echo (FSPGR)** ***Sagittal***
Repetition time (msec)	3725	2300	2325	3225	10.3
Echo time (msec)	36	36	36	10, 20, 30, 40, 50, 60, 70, 80	Minimum (~3.7)
Matrix	340 x 300	360 x 300	340 x 300	320 x 269	512 x 512
Field of view (cm)	16	16	16	12	16
Resolution (mm)	0.5x0.5x3.0	0.4 x0.5x3.0	0.5x0.5x3.0	0.4x0.4x3.0	0.3x0.3x3.0
Slice thickness (mm)	3.0	3.0	3.0	3.0	1.5
Slice gap (mm)	0.3	1.0	0.3	1.0	0
Flip angle (°)	142	142	142	90	12
Number of echoes	10	10	9	8	-
Number of slices	32	31	34	31	80
Number of excitations	1	1	1	0.5	1
Bandwidth	50	35.71	35.71	31.25	31.25
Bandwidth/Pixel	297.1	198.4	210.1	195.3	208.2
Scan time (mins)	2:59	2:55	4:21	7:51	15.08

Criteria for MRI-defined osteoarthritis derived from MOAKS ratings[1]

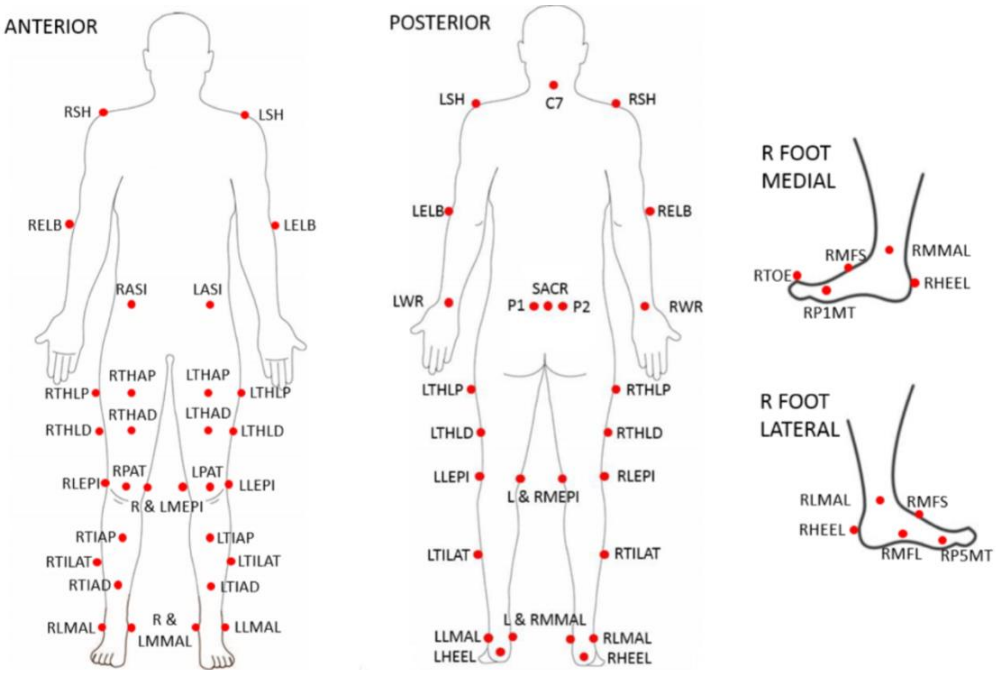
MRI-defined tibiofemoral OA	Meets either of the following criteria in either medial or lateral tibiofemoral compartments: • A definite osteophyte AND full-thickness cartilage loss or • A definite osteophyte OR full-thickness cartilage loss PLUS two of the following: - subchondral BML not associated with meniscal or ligamentous attachments - meniscal subluxation, maceration or degeneration - partial-thickness cartilage loss where full-thickness loss is absent
Mixed MRI-defined tibiofemoral OA	Meets the above criteria by having some OA features in one tibiofemoral compartment and others in a second tibiofemoral compartment
MRI-defined patellofemoral OA	A definite osteophyte AND partial or full-thickness cartilage loss in the patellofemoral compartment

BML, bone marrow lesion; MRI, magnetic resonance imaging; MOAKS, MRI Osteoarthritis Knee Score; OA: osteoarthritis

1. Runhaar J, Schiphof D, van Meer B, Reijman M, Bierma-Zeinstra SMA, Oei EHG. How to define subregional osteoarthritis progression using semi-quantitative MRI osteoarthritis knee score (MOAKS). Osteoarthr Cartil. 2014;22(10):1533-1536. doi:10.1016/J.JOCA.2014.06.022

Supplementary file 2:

Reflective marker placement



For the upper limbs, markers will be placed over the lateral epicondyle on the humerus and the dorsal aspect of the wrist.

For the trunk, markers will be placed on the acromio-clavicular joints and over the spinous process of the 7th cervical vertebra.

For the pelvis, markers will be placed over the left and right anterior superior iliac spines and posterior superior iliac spines, and one marker will be placed on the sacrum (mid distance between the posterior superior iliac spine markers).

For the lower-limbs, markers will be placed over the medial and lateral femoral epicondyles (and the patella) and the medial and lateral malleoli.

Foot markers will be placed over participant's shoes at the heel, the medial and lateral midfoot, the medial aspect of the 1st metatarso-phalangeal joint, the lateral aspect of the 5th metatarso-phalangeal joint, and on the dorsal surface of the 1st toe.

Four tracking markers will be placed over the anterolateral aspect of the thigh and three tracking markers over the middle third of the shank.