Official Title: Linking Biomechanical and Imaging Outcomes to Better Understand the Effects of Running on Knee Joint Health

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Study Protocol

Study design

This research will comprise two complementary studies to obtain direct and indirect measures of the effects of running on knee cartilage in people with and without TFOA. Biomechanical outcomes will be collected *during* running, while cartilage outcomes will be assessed *before and after* running on a separate day. Comparisons between groups will be made prior to starting a 12-week running intervention (baseline), as well as upon completion (follow-up).

Participants

Two distinct groups will be recruited. All eligible participants will be: (i) aged greater than 40 years; (ii) recreational runners who run at least twice per week for a total of at least 10km, and have done so for a minimum of 12 months; and (iii) be comfortable running on a treadmill for 30 minutes. Participants in the TFOA Group will: (i) exhibit radiographic evidence of mild or moderate TFOA according to the Kellgren and Lawrence (KL) OA classification scale (presence of osteophytes and joint space narrowing on X-ray; grades 2 and 3); and (ii) report knee pain on most days of the previous three months (not just during running). Runners in the Control Group will: (i) be free of any radiographic signs of TFOA according to the KL scale (an absence of definitive osteophytes and joint space narrowing; grade 0 – note that we will not be recruiting KL grade 1 individuals due to the potential for early osteoarthritic changes in these individuals); and (ii) be pain-free in both knees for the 12 months prior to recruitment.

Exclusion criteria for both groups will be: (i) any history of traumatic knee injury (defined as one that required surgical intervention or continuous treatment for more than one month); (ii) presence of an inflammatory arthritic condition; (iii) presence of any health condition (other than OA in the TFOA group) affecting normal movement or that precludes engaging in moderate to high impact activities such as running; (iv) use of any oral or injected corticosteroids or viscosupplementation in the previous six months; and (v) any history of surgery in either knee. Furthermore, standard contra-indications to MRI will be assessed for safety purposes.

A total of 80 individuals will be recruited for this study: 40 in each group. Groups will be matched for sex, age (+/- 2 years), body mass (+/- 5 kg), and running experience (+/- 1 year). We are unaware of any studies directly relevant to our proposal that would appropriately inform a sample size calculation. Instead, four similar studies have quantified T2 and T1ρ under loading conditions: Mosher *et al.* 2010, Subburaj *et al.* 2012, and Gatti *et al.* 2017 employed running protocols, but in 37, 20, and 15 young, healthy individuals only; Souza *et al.* 2014 used a lower limb weighting paradigm in a supine position enrolling 44 individuals with knee OA. Thus, our proposed sample of 40 individuals per group is consistent with – and in most cases, exceeds – these studies, and reflects a feasible number within the 5-year timeline proposed for this research.

Procedures

Recruitment and screening

Volunteers will be recruited via print and social media, as well as advertisements in local running clinics. We will also contact individuals from our database of previous study participants and screening individuals who have expressed interest in future studies and provided explicit consent to be contacted again. Interested volunteers will be screened via phone, email, or our lab website by the study coordinator to assess inclusion and exclusion criteria. Individuals passing initial screening will sign a detailed consent form. They will then receive a copy of the MRI Screening Form to assess MRI safety criteria. Those who pass will then be referred to have standing, semi-flexed postero-anterior radiographs of both of their knees taken. A trained assessor will grade all radiographs based on the KL criteria. Those who pass all screening for their respective group will be enrolled.

Data collection

Two separate time points will be included for both biomechanics and MRI testing: baseline and follow-up, with identical protocols at all time points.

a) Biomechanics testing – This will be conducted using high-speed motion analysis cameras and an instrumented treadmill. A total of 42 reflective markers (31 lower limb, 11 upper limb) will be affixed to the skin bilaterally over key anatomical landmarks as is standard in our laboratory. Participants will run on the treadmill for 30 minutes at a self-selected speed. We will collect synchronized kinematic (sampled at 200 Hz) and kinetic (2000 Hz) data for 15 seconds at the start of the run, as well as after 10, 20, and 30 minutes of running. Participant averages for each outcome will be calculated across these time points, as is commonly done in the biomechanics literature. For safety reasons, we will assess knee pain at these time points as well, and will cease the run if pain exceeds 7/10 on a numerical rating scale – common for running studies in the presence of pain. In the event of a stopped run, another assessment will be scheduled and MRI testing will be postponed.

b) MRI testing –Baseline MRI data collection will occur one week following biomechanics testing. Upon arriving at the centre, participants will complete activity questionnaires to assess physical activity levels, as well as the Knee Osteoarthritis Outcome Score (KOOS) to characterize knee symptoms. When combined with study instruction briefing, this will ensure that participants remain seated and inactive for 30 minutes prior to scanning.

Next, participants will undergo the first MRI of the **study knee** [defined as the arthritic knee (unilateral OA) or the most symptomatic knee (in cases of bilateral OA) in the TFOA group; randomly chosen in the Control group] on a research-dedicated Philips 3.0 Tesla MRI scanner. The protocol will include T2 and T1ρ mapping sequences, as well as anatomical scans to assess joint orientation and cartilage integrity. Including participant preparation, each full block of scans lasts approximately 30 minutes in duration.

Following the pre-run MRI, participants will complete a single bout of treadmill running for 30 minutes in their own shoes. To control for the potential effect of running speed on results, participants will choose a comfortable speed between 6 and 10 km/h.

After running for 30 minutes, participants will run back to the MRI scanner for an immediate post-run MRI assessment.

Running intervention

Participants will receive a 12-week running program under the model of building up to a 10 km race. Three weekly training sessions will be planned, and mileage will gradually increase by an average of 10% per week as we have done in our recent running studies. For the purpose of this study, participants will run using their habitual technique – i.e. no specific instructions on 'how' to run will be provided at this stage; rather, they will simply be instructed on 'how much' to run. A Study Trainer not involved in any aspect of data collection or analysis will oversee the implementation of the intervention via weekly phone conversations with participants to ensure proper adherence and to prescribe appropriate weekly mileage increases. Participants will be provided with a GPS-enabled wrist watch to record their running distance throughout the intervention, which will be supplemented with weekly self-report logs completed online.

Data processing and analysis

MR images will be segmented and analyzed by a collaborator who has previous experience working with our group. This collaborator will be blinded to group and to whether the scan was performed before or after the 12-week running program.

Motion analysis data will be processed and analyzed by a trained student. Though data will be collected bilaterally, analysis of biomechanics data for the purposes of this study will be constrained to the study

limb, consistent with all other outcomes.