Magnetic resonance imaging of lower limb joints of marathon runners

Laura-Maria Horga

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University College London

Faculty of Medical Sciences
Division of Surgery and Interventional Science

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Declaration

I, Laura-Maria Horga, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature

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Date

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Abstract

Marathon running is extremely popular. The increasing participation of beginner runners, including older ones, in marathon races has been anecdotally associated with an increase in lower limb injuries. Evidence is scarce, yet no previous study showed significant marathon-related damage on joints, but involved small sample size, no beginner runners and injury detection tools of limited sensitivity. Therefore, the impact of marathon running remains unclear.

The aim of this thesis is to better understand how marathon running affects the knee and hip joints of large groups of novice marathoners, and how to minimise risks of injury.

Prevalence of knee joint abnormalities in asymptomatic novice marathoners before the start of their marathon training was morphologically assessed, using high-resolution 3.0 T MRI and validated questionnaires; 97% knees had abnormalities and the patellofemoral compartment was most lesioned ($p<0.0001$).

Changes in the knee MRI results from the pre-marathon scan to short-term post-marathon scan were evaluated, using 3.0 T MRI and questionnaires. For the first time, counterbalanced effects of running were detected: reduction in the extent of pre-existing tibiofemoral bone marrow edema ($p=0.082$), and increase in the prevalence of patellofemoral cartilage lesion ($p=0.0005$), although asymptomatic.

Six months later, the reduction in bone edema was sustained in all cases and there were signs of reversibility of cartilage damage (14%).

Prevalence of hip joint abnormalities in both asymptomatic novice marathoners and experienced marathoners was evaluated, using the same methodology. Prevalences were relatively moderate in both experienced marathoners (63%) and non-experienced marathoners (51%).

Changes in the hip MRI findings of novice marathoners after marathon running were analysed, and no significant changes were detected ($p=0.684$).

Results from this thesis show that first-time marathon running does not damage the knee and hip joints of runners with no pre-existing injuries, and inform on the types of structural changes and potential clinical implications.

Impact statement

Over one million people run marathon races worldwide every year and many are beginner runners, with limited previous running experience. More and more marathon entrants are older individuals who may potentially be at increased risk of developing running-related musculoskeletal injuries or even arthritis. This is of tremendous importance given that musculoskeletal conditions pose a significant global medical and economic burden on patients, their families and the society. In the UK, musculoskeletal conditions cost the NHS over £4.76 billion annually and affect the quality of life of millions of people. The reported prevalence of running injuries varies substantially from 18 to 92%, however the existing scientific evidence is very little and failed to demonstrate any major abnormalities of clinical relevance after running. No study to date evaluated the lower limb joints of novice marathoners and used high-quality imaging equipment.

This thesis presents two independent projects evaluating two of the most commonly reported sites of running injuries – knees and hips, respectively. The study designs are innovative in that each conducts large scale investigations of the joints of first-time marathon runners of all ages, before and after a marathon race, using cutting-edge imaging equipment with excellent resolution and reliability.

Results from the thesis did not reveal significant damage to the knee and hip joints of asymptomatic novice marathoners. These findings provide a better understanding of the types of running-related joint changes, the key internal structures at increased risk of damage and correlations with symptoms. This helps inform running-related decision-making and injury prevention strategies. Physiotherapists and personal trainers could recommend specific muscle strengthening exercises and complementary activities to runners to incorporate in their running routine and race preparation and better protect their joints. This will help improve existing training programmes, for which there are no clear guidelines, and minimise the risk of injuries.

Moreover, for the first time in a research study, potential beneficial effects of running on the joints were demonstrated, suggesting that running may, in fact, delay or prevent the progression of osteoarthritis. This is speculated to occur due to muscle strengthening during training, coupled with gradual increase in running duration. Also, running experience in individuals with no pre-existing lesions appeared to have a protective effect

on hip joints, although further analysis is needed. These findings are extremely promising and encourage closer monitoring by radiologists, clinicians and orthopaedic physicians.

Moreover, the detection of numerous joint lesions in healthy individuals before starting their marathon training, and which would normally require surgery if symptomatic, may guide surgeons in reconsidering their clinical decision-making criteria, while allowing clinicians to identify patients at greatest risk of developing pathologies.

Overall, these projects take an important step forward in helping guide clinical practice and health recommendations for the improvement of quality of life of young and elderly people, by informing injury prevention initiatives and thus helping reduce the healthcare and economic burden of musculoskeletal conditions. This will enable the reallocation of resources to other clinical priority areas. Also, they support the general positive role of exercise on health and wellbeing.

Acknowledgements

First and foremost, I would like to thank my primary supervisor Professor Alister Hart, who expertly guided me through my PhD journey and who shared his passion for running and orthopaedics research. His unwavering enthusiasm kept me constantly engaged with my research, and his commitment to my professional and personal growth gave me access to a wide range of outstanding opportunities, including participation in international conferences, courses, public engagement education and teaching programmes.

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Most of all, I thank God for giving me a purpose to fight for, as well as the strength, knowledge and ability to undertake this PhD project, from the beginning to the end.

I could not have made it without You.

Dedicated to my Grandfather

Cezar Popa

& Great-grandfather

Narciz Popa

Contents

Acronyms and Abbreviations

ACL – anterior cruciate ligament

ACLOAS - Anterior Cruciate Ligament OsteoArthritis Score

AH – anterior horn of the meniscus

B_0 – main magnetic field vector

B_1 – radiofrequency field vector

BLOKS - Boston Leeds Osteoarthritis Knee Score

BME – bone marrow edema

BMI – body mass index

CI – confidence interval

3D - three-dimensional

dGEMRIC - delayed gadolinium-enhanced MR imaging of cartilage

DICOM - digital imaging and communications in medicine

FOV - field of view

FS – fat-suppression

FU – follow-up

GRE - gradient echo

GRF - ground reaction force

HOAMS - Hip Osteoarthritis MRI Scoring System

HOOS - Hip disability and Osteoarthritis Outcome Score

HRA - Health Research Authority

KOOS - Knee injury and Osteoarthritis Outcome Score

IRAS - Integrated Research Application System

IW FSE - intermediate-weighted fast spin-echo

KOSS - Knee Osteoarthritis Scoring System

LCL – lateral collateral ligament

LFC – lateral femoral condyle

LTC – lateral tibial condyle

MCL – medial collateral ligament

MFC – medial femoral condyle

MOAKS - MRI Osteoarthritis Knee Score

MR - magnetic resonance

MRI - magnetic resonance imaging

ms - milliseconds

MTC – medial tibial condyle

MTSS - Medial Tibial Stress Syndrome

NEX - number of excitations

NRES - National Research Ethics Service

OA - osteoarthritis

OR – odds ratio

PACS - picture archiving and communication system

PCL – posterior cruciate ligament

PD - proton density

PFPS - Patellofemoral pain syndrome

PH – posterior horn of the meniscus

Pre-M – pre-marathon

Post-M – post-marathon

RA - Rheumatoid arthritis

RF - radiofrequency

RRMI - Running-related musculoskeletal injury

SD – standard deviation

SE - Spin-echo

SHOMRI - Scoring Hip Osteoarthritis with MRI

T - Tesla

T_1 - longitudinal relaxation time

T_{1rho} - T_1 relaxation time in a 'ro'tating frame

T_2 - transverse relaxation time

T_{2*} - T_2 relaxation time dependent on magnetic field inhomogeneities

TE - echo time

TR - repetition time

TSE - turbo spin-echo

VIBE - volumetric interpolated breath-hold examination

WOMAC - Western Ontario and McMaster Universities Arthritis Index

WORMS - Whole-Organ Magnetic Resonance Imaging Score

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Chapter 1

Introduction

1.1 MOTIVATION

Marathon running has gained tremendous popularity over the last decade. Despite its known health benefits, running has been controversially linked with a high risk of musculoskeletal injuries due to the high impact forces exerted on lower limb joints. Moreover, the increasing participation of older runners, with little to no running experience, in marathon runs has given rise to concerns regarding the risks of developing injuries and joint pathologies such as osteoarthritis. Musculoskeletal conditions are associated with a significant economic burden and have an enormous effect on the quality of lives of millions of people in the UK and worldwide. Serious running injuries may result in high medical costs and lost working days. The knee and hip joints are two of the most commonly reported sites of injury. Therefore, a better understanding of the impact of marathon running on knee and hip joints is crucial for developing strategies for injury prevention and costs reduction to the NHS.

However, the existing literature is limited and there is no reliable evidence to suggest that marathon running induces any clinically significant changes on lower limb joints. So far, no research study has evaluated the impact of a marathon run, including the training in preparation for it, on the knee and hip joints of first-time marathon runners lacking previous running experience. Most previous studies focused on experienced long-distance runners instead of beginner runners or vulnerable populations.

The development of magnetic resonance imaging (MRI) techniques has revolutionised medical healthcare and enabled improved diagnosis of joint pathologies. High-resolution 3.0 Tesla (T) MRI provides unprecedented accuracy in identifying and differentiating between various anatomical structures and soft tissues. Even subtle lesions and early signs of pathologies can be detected in a much greater level of detail than before. This is a promising tool in orthopaedic research.

Moreover, running injuries are multifactorial and a number of participant characteristics, previous injuries and training specifics may increase the risk of injuries. So these factors need to be considered as well apart from impact of the run itself on the joints.

1.2 AIM

To determine the impact of marathon running on the knee joints and hip joints of asymptomatic novice marathon runners.

1.3 OBJECTIVES

- To assess the reported prevalence of running injuries on lower limb joints, potential risk factors, imaging tools for the detection of pathologies, quantification methods and outcome measures, and the existing scientific evidence on the impact of marathon running on lower limb joints
- To morphologically assess the prevalence of knee joint abnormalities on 3.0 T MRI of asymptomatic novice marathon runners before training for/and marathon running
- To do a comparative morphological analysis between the 3.0 T MRI scans of the knees of novice marathon runners before and after marathon running, and thus evaluate the impact of marathon running on their knee joints (short-term and medium-term follow-ups)
- To morphologically assess the prevalence of hip joint abnormalities on 3.0 T MRI of asymptomatic 1) novice marathon runners before training for/and marathon running, and 2) experienced marathoners and ultrarunners
- To do a comparative morphological analysis between the 3.0 T MRI scans of the hips of novice marathon runners before and after marathon running, and thus evaluate the impact of marathon running on their hip joints (short-term follow-up)
- To draw conclusions on the impact of marathon running on knee and hip joints in novice marathon runners

1.4 THESIS OUTLINE

The thesis begins with a literature review of the prevalence of running injuries in lower limb joints, an overview of MRI-based tools of injury evaluation and findings from previous marathon running research, which is followed by 2 experimental projects organised in 6 chapters.

Chapter 3 describes the overall picture of abnormal knee findings in asymptomatic adults, using 3.0 T MRI, before their participation in any running activity.

Chapter 4 reports all knee changes following both the training for the marathon and the marathon race itself, by comparing the 3.0 T MRI scans done 1) before the marathon and 2) shortly after the marathon (short-term changes).

Chapter 5 discusses the post-marathon knee changes within 6 months after finishing the marathon (medium-term changes).

Chapter 6 aims to define the overall picture of abnormal hip findings in asymptomatic adults, both novice and experienced marathoners, using 3.0 T MRI.

Chapter 7 reports all hip changes following both the training for the marathon and the marathon race itself, by comparing the 3.0 T MRI scans done 1) before the marathon and 2) shortly after the marathon (short-term changes).

Chapter 8 summarises conclusions from both the knee and hip studies, and describes future work.

1.5 RESEARCH TEAM ROLES

As a PhD student, my main roles included: 1) conducting literature reviews to inform and facilitate the development of study designs, including desk research on: existing studies on running, medical imaging technologies, imaging-based scoring systems, joint health-related questionnaires; 2) organising the research studies, working closely with radiologists (facilitating MRI interpretation and reporting), liaising with study participants, medical staff and collaborators; 3) undergoing data collection, synthesis and analysis of all the data resulting from studies; 4) writing manuscripts and disseminating the research findings.

The radiologists were responsible for providing guidance and support in selecting appropriate MRI study protocols according to our research purposes, for advising on suitable MRI scoring systems and had a key role in the interpretation and reporting of the MRI scans.

The Chief investigator and the other PhD supervisors were involved in supervising my activity, providing support, training and constant monitoring to ensure the smooth organisation of the studies, as well in the processing and analysis of the data.

1.6 ETHICAL APPROVAL

All investigations were conducted in conformity with ethical principles of research involving human participants.

The first project described in Chapters 3 to 5 (Knee studies) is part of a bigger study organised in collaboration with the Department of Cardiovascular Sciences, at St George's University of London, which submitted the initial ethics application for the investigation of cardiovascular health of marathon runners. The musculoskeletal research group from which the author of this thesis is part of decided to collaborate with this group and include the performance of knee MRI scans, apart from cardiac MRI scans. This required a substantial amendment to existing ethics. The amendment was granted by London - Queen Square Research Ethics Committee and Health Research Authority National Research Ethics Service (HRA NRES), Amendment number 5 on 13/08/16 (15/LO/0086), followed by Amendment number 6 on 20/10/16, with Integrated Research Application System (IRAS) project ID 156948 (see Appendix A.1.1 for ethical approval document). The cardiac MRI investigation is not part of the thesis submitted by the author of the thesis.

The second project described in Chapters 6 and 7 (Hip studies) required a new ethics application, which was prepared entirely by the author of this thesis. The application was approved by UCL Research Ethics Committee on 29/11/2018 (13823/001) (see Appendix A.2.1 for ethical approval document).

Chapter 2

Literature review

2.1 THE KNEE JOINT

The knee is the largest joint in the human body. The knee is composed of 2 joints: 1) the tibiofemoral joint, where the thigh bone (femur) meets the large shin bone (tibia); and 2) the patellofemoral joint, where the kneecap (patella) joins the femur. The tibiofemoral joint is the main weight-bearing knee joint and has an inner (medial) and an outer (lateral) compartment, while the patellofemoral joint protects the front of the knee.

The main role of the knee joint is to enable flexion and extension of the lower legs around a transverse axis in a sagittal plane, but also to rotate from side to side. It has a major role in performing essential activities such as walking, running, jumping and other movements.

The function and stability of the knee relies on a number of connective tissues (that connect and support tissues and organs) and specialised internal structures: menisci, bones, articular cartilage, ligaments, tendons, muscles, synovial fluid within the joint, and other connective tissues (Figure 2.1). The synovial fluid lubricates the soft tissues inside the joint capsule [1].

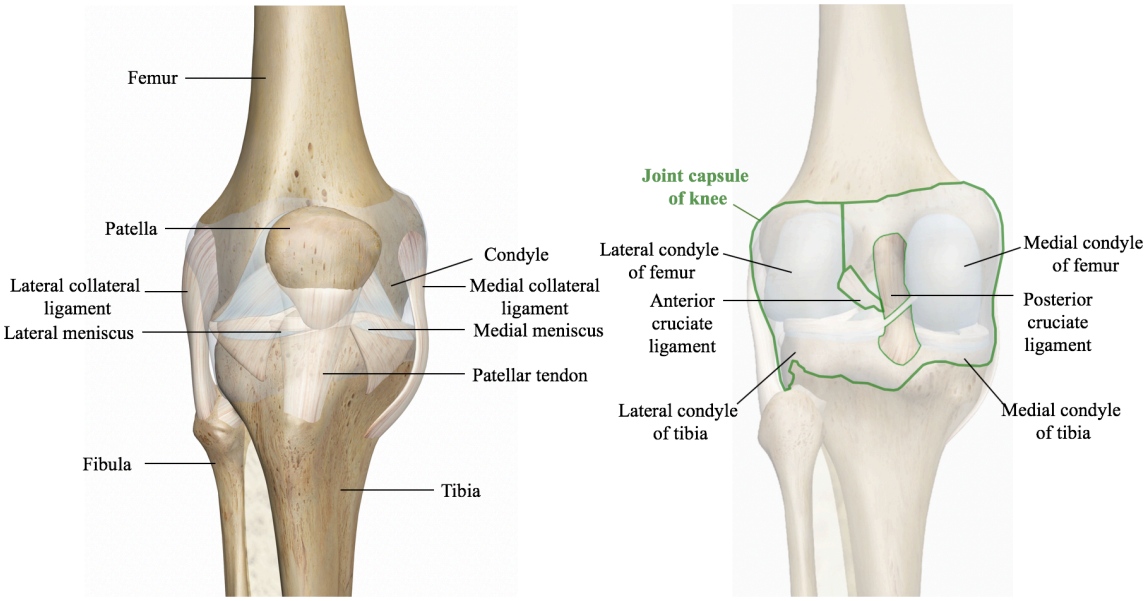


Figure 2.1. Cross-sectional view of the knee joint (adapted from innerbody.com).

2.1.1 Knee joint structures

Meniscus

The meniscus is a C-shaped fibrocartilaginous structure which is found between the femur and the tibia. There are 2 menisci (medial and lateral) that act as shock absorbers, friction reducers and provide structural integrity to the knee.

Bones

There are four bony structures around the knee: femur (distal end), the tibia (proximal end), patella and fibula. The femur is the longest bone in the human body and runs from the hip to the knee. The tibia runs from the knee to the ankle, while the fibula is located on the lateral side of the knee, alongside the tibia. Finally, the patella is a triangular bone which rests in a groove on top of the femur, known as the trochlear groove, and protects the anterior surface of the knee. During bending and straightening of the knee, the patella moves from side to side inside the groove.

Articular cartilage

The ends of the bones have round knobs called condyles. These are covered in hyaline (articular) cartilage. The articular cartilage is flexible and slippery, enabling smooth movement of the bones against each other. This is due to the formation of an oily lubricant called synovial fluid within the joint. If the cartilage damages, the knee movement becomes restricted and painful. Unlike other tissues, the cartilage does not have nerves or blood vessels, so it may be more vulnerable to mechanical stress [2].

Ligaments

Ligaments are strong fibrous tissues which attach to bones and provide stability to the joint. There are 4 key ligaments of the knee: anterior cruciate ligament (ACL), posterior cruciate ligament (PCL), medial collateral ligament (MCL) and lateral collateral ligament (LCL). ACL prevents translation of the tibia on the femur, while PCL prevents the femur from sliding forward on the tibia. The MCL and LCL function to prevent the femur from sliding side to side. Additionally, the patellar ligament joins the patella to the top of the tibial tuberosity (ridge-like prominence) and is a continuation of the quadriceps tendon.

Tendons

Tendons are flexible collagen tissues. They join the knee bones to the leg muscles to help with the joint movement. The patellar tendon attaches the bottom of the patella to the tibia. The quadriceps tendon is important in extension and is located at the front side of the knee, joining the quadriceps muscles to the tibia via the patella and the patellar ligament. Other tendons include: semimembranosus, sartorius, gracilis. Also, the iliotibial band is a long tendon along the femur, spanning between the hip and the knee, and is an extension of the tensor fascia latae and gluteus maximus muscles.

Muscles

The muscles around the knee are responsible for knee stability, alignment and correct movement. The two main muscle groups involved here are: the quadriceps and the hamstrings. The quadriceps comprise of 4 muscles on the front of the thigh and are important for extension: rectus femoris, vastus lateralis, vastus medialis, vastus intermedius; these are assisted by tensor fascia latae. The hamstrings comprise of 3 muscles on the back of the thigh which are involved in flexion: biceps femoris, semitendinosus and semimembranosus, assisted by gracilis and sartorius. Also, other muscles are used in medial rotation: popliteus, semimembranosus and semitendinosus, assisted by gracilis and sartorius; while lateral rotation by biceps femoris.

Bursae

Bursae are synovial fluid-filled sacs and they lubricate the tendons and ligaments. Each type of bursa is named after their specific knee location. The knee has a number of bursae which help in reducing friction between different knee structures: prepatellar (between the patella and the overlying subcutaneous tissue), superficial infrapatellar (between the tibial tubercle and the overlying skin), deep infrapatellar (between the patellar tendon and the tibia), suprapatellar (between the quadriceps tendon and the femur, above the patella), pes anserin (on the anteromedial part of the tibia), popliteal (by the proximal popliteal tendon), iliotibial bursa (on the iliotibial band).

Also, a number of fat pads are present between the knee joint capsule and the synovium. One of them is Hoffa's fat pad which is found posterior to the patellar tendon and anterior to the capsule and helps in distributing the synovial fluid and absorbing the forces targeting the joint [3].

Blood supply and nerves

The knee receives a rich blood supply from several arterial blood vessels with branches from the femoral artery to the popliteal artery. The supply comes from 3 sources: descending branches (of the lateral circumflex femoral artery), ascending branches (posterior tibial artery, anterior tibial artery – anterior and posterior tibial recurrent branches) and branches of the popliteal artery (genicular arteries: lateral superior, lateral inferior, medial superior, medial inferior, middle).
Joint and muscles innervation comes from femoral nerves (flexion) and sciatic nerves (extension) [1].

2.1.2 Knee joint pathologies

Osteoarthritis (OA) of the knee is a leading cause of chronic disability affecting millions of people worldwide. It is the most common form of arthritis in the elderly, whereby the articular cartilage gets damaged over time causing the bones to rub against each other. Also, meniscal degeneration may occur sometimes and extensive synovial fluid may be generated in an attempt to clear the joint from the resulting debris. Symptoms include stiffness, swelling and pain that become worse over time with activity. There are lots of factors leading to varying levels of severity. There are two types of OA: primary and secondary. Diagnosis is often done using clinical examination and imaging modalities. Conservative treatment may involve physical therapy, weight reduction, steroids and nonsteroidal anti-inflammatory drugs. If these are unsuccessful, the next therapy line is knee resurfacing or total knee replacement [4].

Rheumatoid arthritis (RA) is a chronic inflammatory disorder, whereby the body's immune system attacks the joints. It shares similarities with OA, causing pain, swelling and stiffness [5].

A meniscal tear is a frequent knee injury, especially in older patients who suffer from degenerative changes. It is sometimes accompanied by other knee conditions, such as ligament abnormalities. Meniscal tears can develop without the patient noticing any changes, or they can present with pain or symptoms such as knee clicking, locking or catching during physical activities. There are different types of meniscal tears which were named based on their specific pattern of damage (see Figure 2.2): radial, oblique, horizontal, flap, vertical, bucket-handle, complex and degenerative (multiplanar) [6].

Generally, diagnosis involves clinical examinations and MRI analysis as preferred imaging modality. Treatment varies from conservative to surgical treatment [7,8].

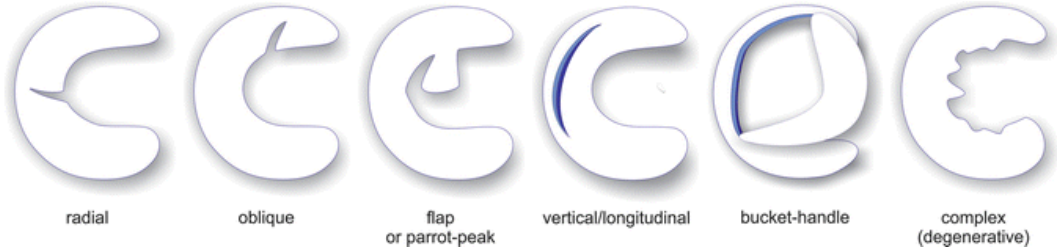


Figure 2.2. Types of meniscal tears (reproduced from Piedade SR *et al* [6]).

Chondromalacia patella (patellofemoral syndrome) is a common cause for knee pain in sports medicine. It is an irritation of the patellar cartilage which can worsen due to bending of the knee during different sports activities. The underlying reasons for this condition are not yet well understood, but it is considered to be linked with muscle imbalance, overuse, improper patellar tracking. Clinical symptoms and imaging are used for its detection, then treatment includes physical therapy, rest, stretching and gradual return to exercise [9].

Bone marrow edema or bone marrow lesion or bone marrow edema-like lesion (BME), sometimes referred to as 'bone bruising', is characterised by build-up of fluid in the marrow (deep tissue inside the bone), which can create pressure within the bone and may lead to future bone erosion and OA. BME may also be the result of direct or indirect trauma, may be symptomatic or asymptomatic and some types are transient i.e. resolve after a certain period of time. MRI analysis and physical examinations are usually used for diagnosis. Additionally, subchondral cysts are fluid-filled sacs which may be spotted in the bone, just underneath the cartilage [10–13].

Ligament tears appear when they are stretched beyond normal capacity. ACL sprain or tear is most common in sports with sudden changes in direction, jumping and landing. The knee's stability may be affected, followed by swelling and pain. Depending on its severity, recovery may involve rest and muscle strength rehabilitation exercises, or even surgical replacement of the torn ligament may be required [14].

Knee strains occur as a result of stretched or torn muscles and/or tendons, due to muscle weaknesses, injuries or overuse. Patellar tendinitis (jumper's knee) is an irritation of the patellar tendon and is commonly found in athletes whose physical activity involves frequent jumping. Physical therapy is usually recommended for treating tendinitis by

strengthening the muscles around the knee [15]. There are different forms of pathologies affecting various tendons: tendinopathy (any abnormal tendon condition), tendinitis or tendonitis (an inflammation of partially torn tendon), tendinosis (intratendinous degeneration, without inflammatory component); although sometimes the terms tendinopathy and tendonitis are used interchangeably [16]. Also iliotibial band friction syndrome is a painful irritation of the iliotibial band tendon as a result of overuse, and can usually be managed by rest, foam rolling and/or physical therapy [17].

Baker's (popliteal) cysts are fluid-filled swellings in the back of the knee. They may develop as a result of excess fluid due to arthritis or other knee conditions. The pain usually worsens during full flexion or extension. Treatment of symptomatic cysts involves treating the underlying cause [18].

Bursitis is an inflammation of the bursa, which may appear as a result of overuse injury, trauma, infection or inflammatory response. It can be clinically diagnosed but most of them heal on their own [19].

Joint effusion is a build-up of fluid in the knee, while Hoffa's synovitis is an inflammation related to Hoffa's fat pad. They usually develop as a result of inflammation, arthritis, or injury. However, small asymptomatic effusion may be found in healthy people [20,21].

2.2 THE HIP JOINT

The hip is the second largest joint in the human body. It is a ball and socket-type of synovial joint, formed between the concave structure of the pelvis (acetabulum or hip's socket) and the head of the femur (hip's ball).

The main function of the hip joint is to support the weight of the body/trunk (weight-bearing), thus maintaining stability. This is achieved through strong ligaments, tendons and muscles surrounding the joint (Figure 2.3). Also, the load transmission is done through the hip joint from the axial skeleton to lower extremities, allowing the thigh to move and rotate smoothly in different directions for walking, running and other physical activities. The hip is regulated by the transport of synovial fluid within the hip joint capsule, which reduces friction and enables hip's range of motion [22].

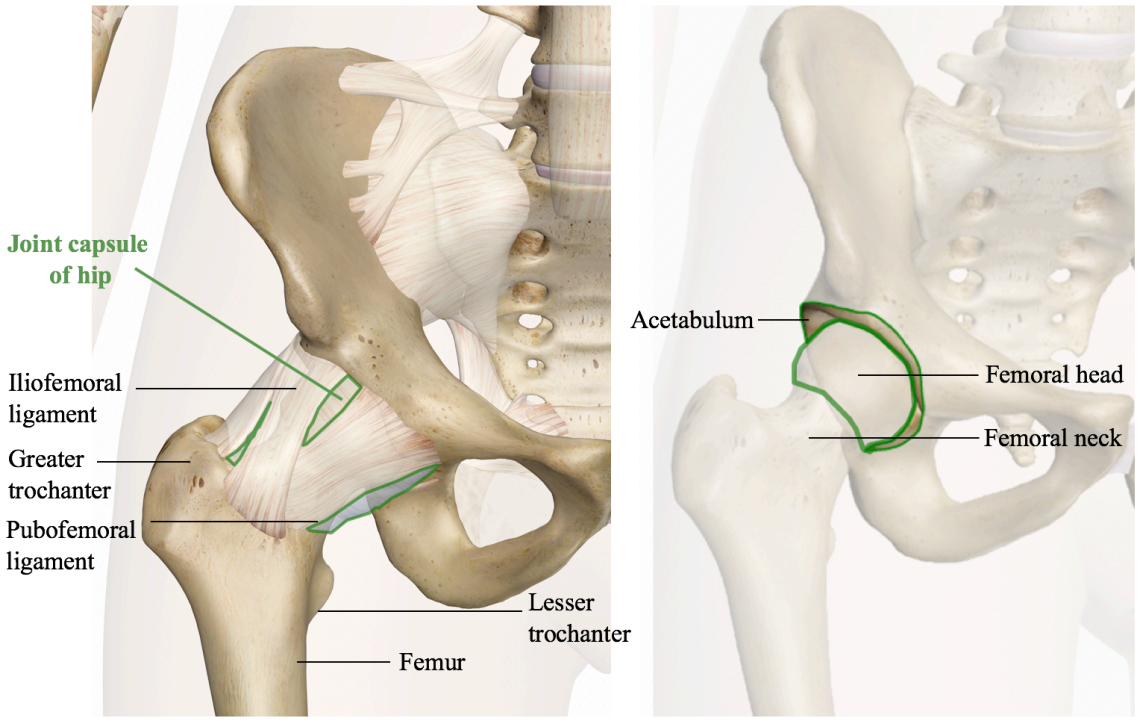


Figure 2.3. Cross-sectional view of the hip joint (adapted from innerbody.com).

2.2.1 Hip joint structures

Labrum

The labrum is a ring of fibrocartilage around the acetabulum. It has an important role in force transmission and regulation of the synovial fluid flow, to maintain hip joint stability and movement.

Articular cartilage

The articular cartilage covers the ends of both the acetabulum and the femoral head, and is thicker at the weight-bearing area. It enables the two components to slide against each other.

Bones

The acetabulum is a cup-shaped opening located on the pelvic girdle which is formed where three hip bones all meet: the ischium, ilium, and pubis.
The head of the femur is of hemispherical shape and fits perfectly into the acetabular cavity. The proximal aspect of the femur is divided into head and neck, and two bony prominences – the greater trochanter and the lesser trochanter. The intertrochanteric line is a bony ridge connecting the two trochanters.

Ligaments

The hip joint ligaments are essential for hip stability. There are one intracapsular ligament (inside the joint capsule) and three extracapsular ligaments (outside the joint capsule). The intracapsular ligament is a small ligament of the femoral head (the ligamentum teres) and runs from the acetabular depression to the femur fovea. The iliofemoral ligament is the strongest extracapsular ligament. It has a Y shape and prevents hip joint hyperextension. The pubofemoral extracapsular ligament prevents hyperabduction of the joint, while the ischiofemoral ligament restricts internal hip rotation, thus impeding excessive extension.

Tendons

Tendons work with muscles to help stabilising the hip joint. These tendons include gluteus medius, gluteus minumus, gluteus maximus, iliopsoas, hamstring.

Muscles

A number of muscles are responsible for different hip joint movements. Flexion is achieved using iliopsoas (joined psoas and the iliacus), and assisted by rectus femoris, sartorius, pectineus. Extension is governed by gluteus maximus and hamstring muscles (semimembranosus, semitendinosus and biceps femoris). Lateral rotation is possible due to the quadratus femoris, the obturator muscles and the gemelli, and assisted by gluteus maximus, piriformis, sartorius. Abduction occurs due to the action of gluteus medius and gluteus minimus, with assistance from sartorius and the tensor fascia latae. Adduction is accomplished by adductor longus, magnus and brevis, and assisted by the gracilis and pectineus. The range of hip movements is controlled by the knee – during knee flexion, the hamstring muscles are relaxed and the degree of hip flexion is increased.

Blood supply and nerves

Blood supply is primarily provided by the medial and lateral circumflex femoral arteries, branches of the femoral artery (which travels posteriorly), as well as the artery to the femoral head, branch of the obturator artery (which travels in the ligament of the femoral head).

Innervations to the joint come from the femoral, obturator, sciatic and gluteal nerves. The same nerves act on the knee, explaining why knee and hip pain are linked to each other [22].

2.2.2 Hip joint pathologies

Hip OA is very common in adults aged 40 or older. This is due to joint cartilage damage, and is accompanied by pain, disability, stiffness - generally in the groin, buttocks and thigh areas. Some patients can develop both hip and knee pain. Diagnosis is based on physical examination and imaging techniques. Similarly to knee OA, non-surgical management as first line of treatment includes lifestyle changes, physical therapy and medications. In severe cases, surgical interventions, such as hip resurfacing or total hip replacement, may be required [22].

Hip RA is an autoimmune disease which affects the hip joint and shares similarities with knee RA [23].

Hip dysplasia is a condition whereby the femoral head is not completely covered by the acetabulum, causing the hip joint to get partially or fully dislocated. It is commonly known as developmental dysplasia of the hip since the majority of patients are born with it. Diagnosis includes physical exam and leg length asymmetry tests. While mild cases may reverse spontaneously, standard treatment involves wearing a harness that keeps the hips in the correct position; this aims to get the acetabulum held firmly in place by the femoral head [24].

Femoroacetabular impingement is characterised by abnormal contact between the femoral head and the acetabular component of the hip joint, which may result in painful damage to the labrum and articular cartilage. Therefore, it may even increase the risk of OA. Diagnosis is based on physical exam, health history and hip and pelvis radiography, while treatment can include a surgical intervention if conservative management fails [25].

Hip labral tears, ligament lesions and tendinitis are also common as a result of trauma or repetitive twisting motions in different sports, such as football and hockey. Hip strains involving muscles and tendons may vary from simple stretches, to partial or complete tears of muscle fibres and/or tendons. These can be symptomatic or asymptomatic and in severe cases may require surgical interventions [22,26–28].

Trochanteric bursitis is an inflammation of the bursa at the location of the greater trochanter. It can be painful and usually occurs as a result of hip injuries, overuse, incorrect posture, or additional stress from conditions such as arthritis. Conventional treatment including rest and physical therapy are primarily recommended. Hip joint effusion may also come up in similar conditions as an accumulation of fluid [29].

Avascular necrosis occurs when blood supply to the femoral head is stopped, leading to bone tissue death. This condition is linked to excessive steroid intake, alcohol abuse, trauma. Necrosis may be symptomatic or asymptomatic and diagnosis is usually done based on imaging tests. Treatment includes medication and therapy or even surgery [30].

Finally, femoral neck fractures and other traumatic injuries can occur as a result of high impact trauma, falls and accidents, and may require hip replacement surgery [31].

2.3 KNEE AND HIP JOINT SURGERIES

Arthroscopy is one of the most commonly performed orthopaedic surgeries. It is a minimally invasive surgical intervention (keyhole surgery) which uses a small video camera (arthroscope) and small incisions for both diagnosis and treatment of a variety of symptomatic knee and hip injuries (Figure 2.4). This technique provides benefits over open surgeries where larger incisions are needed, including: reduced pain and stiffness to the patient, shorter recovery time and return to normal physical activities [32].

During this procedure, the surgeon makes small incisions around the joint area and an injection containing a sterile substance is done to separate the different structures within the joint. A narrow tube having a small camera attached to it is then inserted into one incision to provide a clear view of the internal structures on a video monitor. The surgeon carefully analyses those joint features to understand the underlying cause of the pain during the operation, then the diagnosis is established. The repair of the specific lesioned structure can be performed next using surgical instruments [33].

Since the advent of MRI, patients are usually scanned before undergoing arthroscopy. Neither arthroscopy or MRI can detect pathologies with 100% accuracy, however their use has significantly improved diagnosis and treatment of musculoskeletal injuries [34].

Knee arthroscopy is frequently performed in older patients with a painful knee and suspected torn meniscus or articular cartilage lesions, or OA. Arthroscopic debridement

(removal of loose debris and unhealthy tissue) can be done for OA. Also, meniscal tears are often repaired or removed in the setting of OA, depending on the level of meniscal damage and self-healing abilities, age, health, fitness level. Meniscectomy is the surgical removal of a damaged meniscus (partial or total) [33,35,36]. Other indications for knee surgery include damaged ligaments, patellar malalignment, severe inflammation of the synovial fluid, painful Baker's cysts, certain bone fractures [37–39].

Moreover, hip arthroscopy can be recommended for painful hips, commonly due to: labral tears, articular cartilage defects, early OA, dysplasia, femoroacetabular impingement [40].

In advanced stages of either knee or hip OA, joint replacement surgery (arthroplasty) may be suggested (partial or total) to remove the damaged joint components and replace with an artificial joint [41,42].

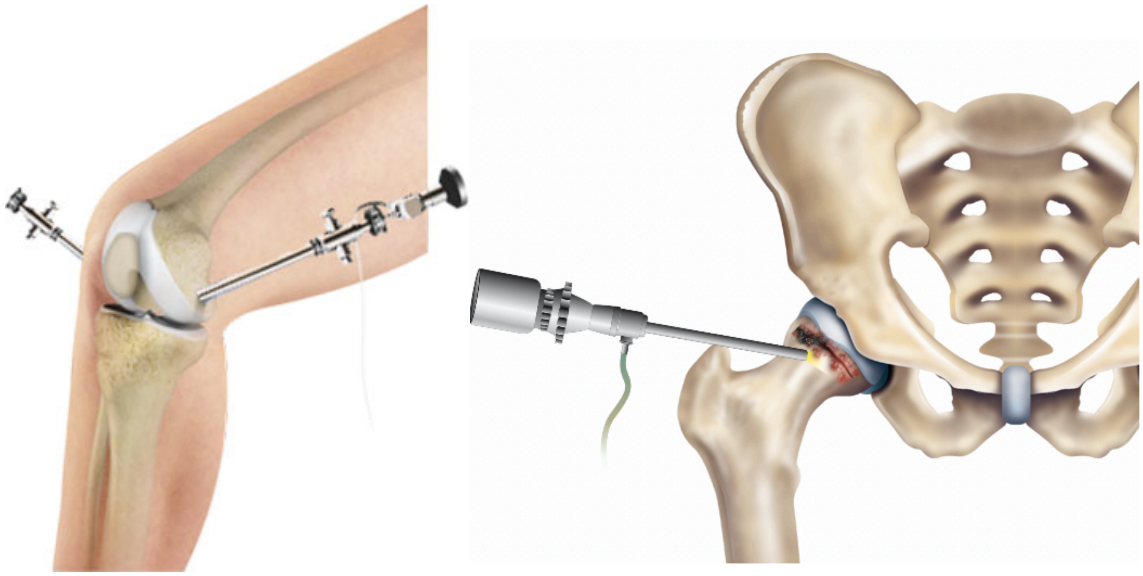


Figure 2.4. Arthroscopic procedure in the knee, on the left-hand side, and hip, on the right-hand side (adapted from davidsapermd.com and holycrossleonecenter.com).

2.4 RUNNING AND LOWER LIMB JOINTS

2.4.1 Running overview: trends, types, concerns

Running popularity and benefits

Running is an extremely popular physical activity nowadays. Worldwide there are over 30 million runners, [43,44] of whom around 10 million train and enter mass running

events every year – this increased by 58% over the last decade and continue to be on the rise [45].

The convenience and low cost of running makes it a highly preferred leisure sport among a significant number of individuals of different ages and fitness levels [46,47].

Running has multiple benefits for overall health and wellbeing. Running has been linked to a reduction in the rates of cardiovascular and respiratory diseases, obesity, diabetes, mental illnesses, and other chronic health conditions [48–53]. Apart from disease prevention, it has been associated with promoting longevity [54]. This explains the rise in the number of people taking up running as a hobby to achieve healthier lifestyles through weight control and aerobic fitness.

Levels of running

Running can be done as a hobby, recreational activity or competitively. There are no standardised definitions of different types of running, but runners can be generally classified as: recreational or amateur runners; and competitive or professional runners. Running can be done at different levels, from short distances (sprints up to 400 m) to middle-distances (longer than sprints, up to 3 km) and long-distances running (> 3 km) [55,56].

Long-distance or endurance running, either practiced recreationally or professionally, includes, in order of level of difficulty: 5 km and 10 km races, half-marathon (21 km), marathon (42 km) and ultramarathon or ultrarun (>42 km). Recreational long-distance running has become one of the most popular types of running, with marathon runs being the ultimate and most desirable challenge while ultramarathons being considered to be more extreme [45].

Marathon races gather over one million participants every year, with the goal of completing a running distance of 26 miles (42 km) [45]. Marathon running has grown in popularity over the last 10 years all around the world by 49.4%. The growth has been seen in both genders, with a higher prevalence in women participation in marathon events (56.8%) than in men's (46.9%) [57]. Many inexperienced runners sign up for a marathon as a personal challenge for the first time and go through a training programme before the race. Also, more and more older runners aged 40 or over have taken up running as a hobby and are participating in marathon runs [58].

Concerns about marathon running

However, the increase in the number of people participating in marathon runs, including novice runners of all ages, has been controversially linked to a rise in related injuries. The main concern is whether repetitive musculoskeletal stress on the joints, which is part of the training for and participating in intense running activities, such as marathon running, may result in potential musculoskeletal damage.

Generally, internal biological structures can adapt to repetitive musculoskeletal stress if the forces are within a dilative limit and if there is adequate rest time between the applied forces. Traumatic injury can occur when the stress exceeds those dilative limits. A general overuse injury is characterised by overloading of the musculoskeletal structures, from excessive repeated stress applied on the joints over a long period of time, and insufficient rest time between forces, which may lead to the development of microtrauma [59,60].

As with any other sport, in excess running can result in musculoskeletal injuries. Nevertheless, the optimal duration of running and the precise runner's threshold above which the amount of loading during running becomes detrimental to the joints are yet unclear. Also, at the moment there is no consensus definition of running-related musculoskeletal injuries, therefore making it hard to estimate the exact number of injuries resulting from marathon running or from either lower or higher duration of running [55,61,62].

2.4.2 Running-related injuries

Epidemiology: Prevalence of running-related injuries

Running-related musculoskeletal injuries (RRMIs) are most frequently the result of overuse (80%). Acute injuries related to running are less frequent and include muscle lesions, sprains, or blistering skin conditions and abrasions [63].

RRMIs prevalence rates vary between 18% and 92% [64–66] or 6.8–59 RRMI per 1000 hours of exposure to running [55,61,67–71]. This wide range may be related to differences in study populations' characteristics and demographics, distinct definitions of RRMIs, diagnostic tools, follow-up periods, different methods of analysis for the RRMI prevalence/incidence rates (e.g. proportion in a sample, or number of injuries per km of running or per hours of running) and other criteria in various studies [65,72]

Despite the relatively high rate of injuries associated with running, the prevalence is 2-6 times lower than in other sports and physical activities [44].

Economic impact and NHS burden

Musculoskeletal conditions are the most common cause of disability and long-term pain in the UK. They affect 54% of all working age disabled people and cost the NHS over £4.76 billion per year. Moreover, over 30 million working days are lost as a consequence of musculoskeletal conditions [73,74].

Specifically for running-related musculoskeletal injuries, medical costs per injured runner at the emergency department can reach around £1200.[75] For runners training for a race, another study estimated that healthcare expenditure accounts for ~£50 per injury. Moreover there are additional ~£100 indirect costs from missing work [76].

Common running-related injury sites

Overuse RRMIs affect lower extremities the most, with more than 80% of them being found from the knee down. Knees and hips are two of the major joints affected by running [77,78].

The most prevalent site of RRMIs is the knee (40%). This is followed by hip and groin (15%), lower leg (20%), foot and ankle (20%), back (5%).[44,79,80] The connective tissues located at these sites are thought to be most vulnerable to overuse RRMIs. Specifically, the cartilage, bones, tendons and ligaments are presumed to be primarily affected since these tissues are poorly perfused and adapt to the mechanical load during running at a much slower rate than muscles. If the length of a run is increased too fast, it is speculated that these soft tissues may not be able to withstand the demands of an increased workload [63].

According to previous clinical studies, the most common complaints among runners were indeed lower extremity soft tissue conditions, including: patellofemoral pain syndrome, stress fractures, medial tibial stress syndrome, Achilles tendinopathy, patellar tendinopathy, iliotibial band friction syndrome; these were followed by muscle injuries, especially the hamstrings and quadriceps [81–83].

Discrepancy in the running-related injury prevalence rates

The large discrepancy in running injury prevalence rates is considered to be due to the following factors: difference in participants' demographics and characteristics, various definitions of RRMIs, different injury classifications and/or diagnosis. As stated in a systematic review [77], this large heterogeneity in studies does not allow researchers to gather the appropriate data for a meta-analysis to provide a useful comparative evaluation of the prevalence rates of RRMIs.

The definition of RRMIs differs among studies and it is one of the main reasons for the large discrepancy in RRMI prevalence rates. For example, one study defined RRMIs as 'injuries sufficiently severe to impair their performance', while another study defined them as 'injuries that markedly hampered running training or competition for at least 1 week' [77]. Since 2007, the need to introduce a standardised RRMI definition has been emphasised by the sports medicine community, however so far there has been no consensus on the best definition of RRMIs. Proposed definitions may need to cover multiple aspects, such as the presence of symptoms, the need to stop training or give up a competition, the need for medical help [77]. However, it is challenging to have a standardised RRMI definition considering the different cultural aspects of each country or health systems and what is considered as 'minor or serious' injury, or what are the patient-specific pain and injury thresholds, which may lead to underestimation or overestimation of injury rates. Therefore, new consensus definitions, potentially local ones for specific countries and cultures, need to be proposed and further research is needed to test the validity of those consensus definitions and their potential accurate translation in other languages.

Running-related injuries in different types of runners

A systematic review by Lopes *et al* [77] evaluated the prevalence of different types of RRMIs. The authors differentiated between 'general RRMIs' (of recreational runners of different levels of experience, from sprinters to long-distance runners up to marathon runners) and 'RRMIs of ultramarathon runners'. The review concluded that the most frequent general RRMIs were medial tibia stress syndrome, Achilles tendinopathy, plantar fasciitis, patellar tendinopathy and iliotibial band syndrome (Table 2.1), while the key findings in ultramarathon runners were Achilles tendinopathy and patellofemoral syndrome (Table 2.2).

Table 2.1. Prevalence of RRMIs during training (pooled n=3276 runners)

General RRMI	Prevalence (%)	No. of articles that reported RRMIs
Medial tibial stress syndrome	9.5	2/2
Achilles tendinopathy	6.2-9.5	2/2
Plantar fascitiis	5.2-17.5	2/2
Patellar tendinopathy	12.5	1/2
Iliotibial band syndrome	10.5	1/2
Ankle sprain	9.5	1/2
Hamstring muscle injury	6.7	1/2
Tibial stress fracture	4.5	1/2
Hamstring tendinopathy	12.5	1/2
Patellofemoral syndrome	5.5	1/2
Meniscal injury	3.5	1/2

*percentages or percentage ranges are included where specified.**number of articles that reported the prevalence (total of prevalence articles=2); RRMI, running-related musculoskeletal injury.

Table 2.2. Prevalence of RRMIs during ultramarathon races (pooled n=126 runners)

RRMI of ultramarathon runners	Prevalence (%)*	No of articles that reported RRMIs**
Achilles tendinopathy	2.0-18.5	3/3
Patellofemoral syndrome	7.4-15.6	3/3
Ankle dorsiflexors tendinopathy	1.0-29.6	2/3
Patellar tendinopathy	6.3-18.5	2/3
Medial tibial stress syndrome	7.8-11.1	2/3
Quadriceps muscle injury	1.0-4.7	2/3
Trochanteric bursitis	3.0-3.1	2/3
Psoas bursitis	11.1	1/3
Extensor digitorum tendinopathy	7.8	1/3
Ankle sprain	5.1	1/3
Iliotibial band syndrome	4.7	1/3
Gastrocnemius muscle injury	3.7	1/3
Extensor hallucis longus tendinopathy	3.1	1/3
Peroneal tendinopathy	3.1	1/3
Tibialis anterior muscle injury	1.0	1/3

*percentages or percentage ranges are included where specified.**number of articles that reported the prevalence (total of prevalence articles conducted in ultramarathon races=3); RRMI, running-related musculoskeletal injury.

The optimal duration of running for the human body is however poorly understood. It is yet unclear from existing literature which types of runners benefit most from running while outbalancing the risk of injuries, and which types of runners are most vulnerable to RRMIs. To date, only one recent systematic review [84] provided evidence from 13 articles on the incidence of RRMIs per 1000 h of running in different types of runners. Participants with little to no running experience were found to have a significantly higher RRMI rate of 17.8 (95 % CI 16.7–19.1) in comparison to regular runners (long-distance runners including marathon runners) who presented with 7.7 (95 % CI 6.9–8.7) RRMIs per 1000 h of running. There was not enough data from ultramarathon runners' studies to make further comparisons between other types of runners. Also, limitations of the review include the heterogeneity in definitions of injury and of different types of runners.

Common running-related conditions of the knee and hip

Patellofemoral pain syndrome

Patellofemoral pain syndrome (PFPS) or runners' knee is one of the most common types of overuse RRMI. It is described as a pathology of the anterior part of the knee, with pain usually being felt under or around the patella. The pain worsens during running, as well as squatting or climbing the stairs [85–87]. PFPS describes a range of pathologies, including patellofemoral instability, tight retinacula (which normally helps in stabilising the tendons), irritations of the medial patellofemoral ligament, infrapatellar or Hoffa's fat pad. Subluxation or misplacement of the patella in the trochlear groove may also occur [86,88,89]. PFPS should not be confused with chondromalacia patellae which is a degenerative abnormality of the patellar cartilage. Diagnosis is made based on imaging tests and clinical evaluation of symptoms, then treatment involves rest, low-impact physical activities and strengthening exercises for the muscles supporting both the patient's knees and hips and for maintaining limb alignment, including the quadriceps, hamstrings and abductor muscles. These will help the patella track correctly in its groove [90,91].

Iliotibial band friction syndrome

Iliotibial band friction syndrome is the second most frequent complaint among runners, known as a common overuse RRMI in the lateral and outer side of the thigh and knee [17,49,92]. The iliotibial band connects the knee and hip joints, running from the pelvis to the tibia. Irritation of the iliotibial band is usually accompanied by pain and tightening on the outside of the knee [92,93]. Treatment includes rest, temporary discontinuation of running, use of foam roller, as well as physical therapy to improve the flexibility and strength of leg muscles [94].

Medial Tibial Stress Syndrome

Running-related stress fractures are common small cracks or bruising in the bone caused by overuse, and they are most commonly found in the tibia. Medial Tibial Stress Syndrome (MTSS), also called Shin Splints, account for up to 16% of all RRMIs, and is considered to be triggered during excessive weightbearing activities. Pain generally appears in the posterior-medial part of the tibia [95]. A number of abnormalities are associated with the onset of MTSS, including: pathologies of the tibialis posterior and

anterior, of soleus muscles, tibial stress lesions (periostitis, tendinopathy, other stress reactions) [96]. Management of this condition includes physical examination and imaging, and treatment is usually conservative through physical therapy and rest [97].

2.4.3 Risk factors for running-related injuries

There are a number of important risk factors that can make a person susceptible to RRMIs. Apart from the potential impact of running itself and overloading on the joints, a variety of individual factors may lead to RRMIs [60,65,75]. RRMIs have complex multifactorial origins. Although evidence from relevant literature is scarce, RRMI risk factors can be divided into 3 groups: 1) personal factors; 2) running/training factors; 3) health and lifestyle related factors.

Personal factors. There has been conflicting evidence as to whether increased *age* is a significant risk factor for developing RRMIs [65]. Some high-quality studies showed that the older the runner, the higher the chances of incurring injuries [71,81,98,99], while other studies reported the opposite, that it can actually have a protective effect on the joints [99,100] while most studies failed to show any significant differences between participants of different ages and RRMI incidence [60].

Gender is another proposed risk factor. In a systematic review, no association between gender and running injuries could be made for most of the included studies [101]. However, few studies showed associations between overall RRMIs of lower extremities and female participants;[100] limited evidence suggested a link between female gender and hip injuries while male participants were more prone to encounter hamstring or calf lesions [99].

Regarding runners' *height*, there is not much evidence in the literature except for one Canadian study showing that male runners with a height of at least 170 cm could be at greater risk of encountering lower extremity RRMIs [102].

Very limited evidence can also be found for *weight* and *BMI* (body mass index, defined as the weight in kilograms divided by the square of their height in metres) as risk factors for incurring injuries. No significant differences were found overall,[75] but Wen *et al* [71] reported that greater weight/BMI can predispose female runners to back injuries, while lower BMI can increase the likelihood of men to develop foot injuries. Another

study indicated that BMI >26 kg/m^2 may have a protective effect against RRMIs in men [81].

Anatomical and biomechanical characteristics of runners could be another risk factor. Some evidence showed that higher leg length difference may be a risk factor for overall lower extremity injuries. Other malalignment issues, including larger left tubercle–sulcus angle (formed between the medial and lateral trochlea) or higher heel valgus (abnormal turning of the bone) with lower right high-arched foot were associated with shin injuries or knee injuries, respectively [71]. Little evidence reported an association between larger heel valgus and better outcomes against knee and foot lesions. Additionally, it has been suggested that static biomechanical alignment of lower limbs is not connected to RRMIs [68].

Genetic factors may also be involved in RRMI susceptibility, such as positive family history of a specific musculoskeletal injury [103,104].

Running/training factors. Few studies evaluated *running experience* as a potential risk factor for incurring RRMIs [71,105–107]. Based on two studies, increased running experience was associated with injuries [71,105], while running with little experience (within one year) had an apparent protective effect against RRMIs [106]. Extensive running experience was deemed to increase the risk of presenting with knee and foot lesions, but these findings were inconclusive due to limited evidence [71,105]. Moreover, a big large survey-based study of 1212 participants [108] showed the opposite, demonstrating that inexperienced long-distance runners are more susceptible to developing lower limb joint injuries than experienced ones [109], and that regular training may lead to the development of adaptive mechanisms in the joints over time, with a protective effect against RRMIs [110–112].

Training - Interval training was found to protect the knees of male runners from lesions [105], while other studies showed that interval training may increase the incidence of shin injuries [71,113]. Also another study found that increasing the amount of hours of running each week may prevent knee and foot injuries [71], while reducing the number of hours may increase the incidence of heel injuries [113]. Limited evidence showed that running more than 6 times/week makes runners more likely to get injured, and also that running up less than 10 miles, up to 1-3 days each week, may actually have a protective effect against RRMIs [106].

Running distance was also linked to the incidence of RRMIs, but the optimal one remains unclear [68,105,107,113]. In one study, a higher number of miles ran per week was associated with greater risk of developing hip injuries, including hamstrings lesions [113], whereas training up to 40 km/week reduced the risk of getting calf issues [105].

No associations between *running pace* and RRMIs were identified [71,114].

Regarding *race participation,* only one study showed a higher risk of developing injuries in male runners who took part in over 6 competitive long-distance races in the previous year [105].

Two studies looked at the relationship between the inclusion of a *warm up* in the running routine and RRMIs, but no correlations could be made [102,115].

No significant associations were found between runners running on specific *surfaces* and lower limbs running injuries. Only for concrete surfaces, limited evidence showed an association between female runners and a beneficial impact of running on these surfaces on preventing back and thigh lesions [113], while another study showed an increased risk of acquiring lower limb injuries in female runners [115]. Running on hills or at different times of the day (morning/night) was not associated with injuries either [115].

Only few studies evaluated the impact of *running shoe use* and RRMIs. Limited proof for associations was found between the frequent change of running shoes and shin injuries and other RRMIs, as well as between the use of 1-2 pairs versus alternating between >2 pairs of running shoes and knee injuries [71,113]. Shoes that had been used for 4-6 months since they were purchased had a protective impact against injuries in men, while for women they were linked to RRMIs [81]. Wearing worn out shoes or the wrong type of shoes which do not match the foot morphology may also be linked to injuries [116]. Moreover, using shoe inserts or orthotics was associated with an increased risk of RRMIs [106,113].

Health and lifestyle related factors

A history of previous injuries was found to be a key risk factor for incurring RRMIs in a number of high quality studies [71,102,105,115,117,118]. There was strong evidence to suggest that having sustained a lower limb injury or exercise-related pain in the past year makes a runner much more susceptible to get a RRMI than a runner with no pre-existing

injuries [71,105,118]. For example, a past lower extremity injury may increase the risk of getting further knee and/or calf injuries [105].

Smoking proved to have a role in preventing people from getting blisters during running in one study, however the evidence is limited [99].

On the contrary, *drinking alcohol* was associated with developing exercise-related blisters or thigh lesions [99].

A possible link between other *health conditions or co-morbidities* and RRMIs was suggested, but existing evidence is limited [99].

However, some of the above mentioned associations are questionable considering that in the cited study [99] a wide range of potential risk factors for RRMIs were assessed. Confounding may be the reason for the resulting associations, especially for those ones with no obvious biological or plausible explanations i.e. smoking and the reduced risk of getting blisters. Therefore, measuring multiple factors and including a set of statistical interferences simultaneously may lead to a multiple comparisons problem with the higher the number of interferences being made, the higher the risk of obtaining erroneous interferences.

2.4.4 Running and arthritis

There is no evidence so far from existing studies to suggest that running in general, including long-distance running, increases the risk of arthritis. However, the lack of evidence does not necessarily guarantee the absence of this condition or of some risks associated with it from running, since arthritis (OA, in its most common form) is very complex and its underlying mechanisms are not completely clear. Therefore, the literature is inconclusive regarding this subject. According to a recent US survey-based study [108], a low prevalence of arthritis (8.8%) was reported in experienced marathoners and this was significantly lower than the prevalence in the matched non-runner population (17.9%, $p < 0.001$). The participants were active long-distance runners who previously completed at least 5 marathons and were training 10 miles/week. No significant associations were found between the risk of arthritis and running duration, intensity, number of miles or marathons completed.

2.4.5 Biomechanics of running

During running, vertical forces of 4 up to 8 times greater than walking are acting on the hip, knee, and ankle joints [119]. The impact forces exerted in a runner are expected to be at least 3 times the body weight [119,120]. For example, a runner weighing 70 kg and participating in a marathon run would sustain extreme forces of around 2,800 N on the lower limb joints [43]. An important role in absorbing these forces have the muscles and their dynamic action, however the joints may still need to withstand a significant burden [43,121]. Moreover, at the end of a race, muscle fatigue occurs and a higher amount of the load acts on the joints. An additional malalignment issue of the lower limbs, which can be found in a number of people, may even increase overloading to extremely abnormal levels [122–124]. Therefore, the lower limb extremities are subjected to a high level of repetitive musculoskeletal stress during running, including long distances, as in a marathon.

The external forces exerted during running are the following: force of gravity (weight), aerodynamic drag force (air resistance) and ground reaction forces [125,126]. They all act on the runner's centre of mass (Figure 2.5). While the force of gravity is constant, the ground reaction forces (GRFs) develop between the foot and the ground during ground contact and are constantly changing during all the phases of the running gait cycle [125–127]. The magnitude of the vertical GRFs depends on running speed and foot strike pattern. The higher the running speed, the higher the peak force amplitude. Shortly after the initial contact, the GRF goes up and then turns to zero when the feet are not in contact with the ground anymore [128]. Therefore, the forces are never balanced during running, even when the speed of running is maintained.

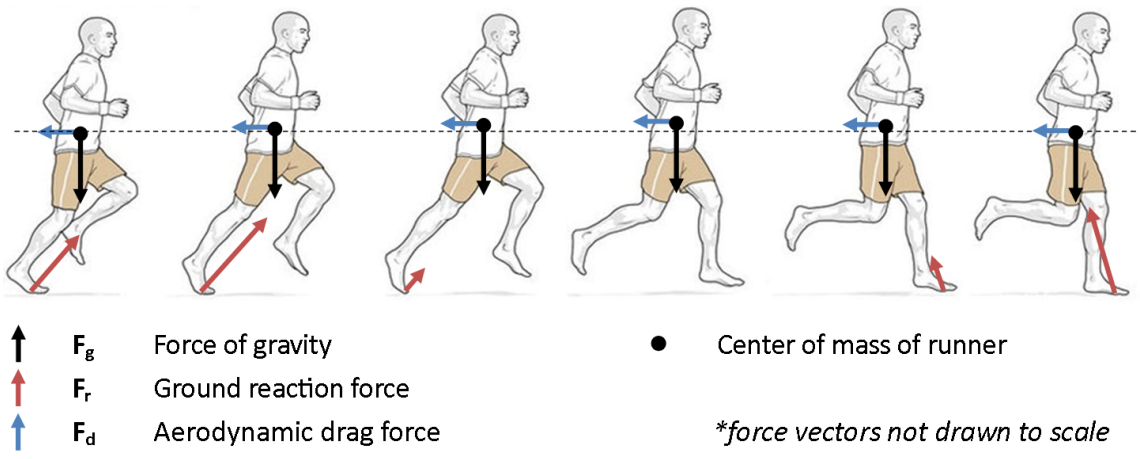


Figure 2.5. External forces acting during running (adapted from codybeals.com).

The rise in forces during running requires appropriate strength and range of motion to reduce the speed of the body and adjust the forces at foot strike. If these capabilities are not present, the body will not be able to withstand the running demands and injury may occur. Therefore a good understanding of running biomechanics, as well as phases of running (gait cycle), may help in preventing injuries.

Running gait cycle

The gait cycle starts when one foot is brought in contact with the ground and ends when the same foot is in the same position. This phase is called initial contact (heel contact). From heel contact to mid-stance, the ankle begins to flex and pronate so the foot arch collapses (inward rotation, essential for shock absorption). In the next phase, the ankle attains maximum level of pronation, followed by a period of supination (opposite of pronation) when the weight tends to be on the outside of the foot. When the foot is no longer touching the ground this marks the end of stance. Then take off (or toe off) is the start point of the swing phase. In the swing phase the quadriceps and hip flexors contract to move the leg forward, while the gluteus muscles help in stabilising the pelvis. Finally, in the terminal swing phase, an extension of the same leg which came in contact with the ground at the start of the gait cycle occurs. All lower limb muscles get activated here to support this extension, whereas the hamstrings and adductor muscles help in slowing down and stabilising the forward moving leg [129,130]. All phases are illustrated in Figure 2.6 below.

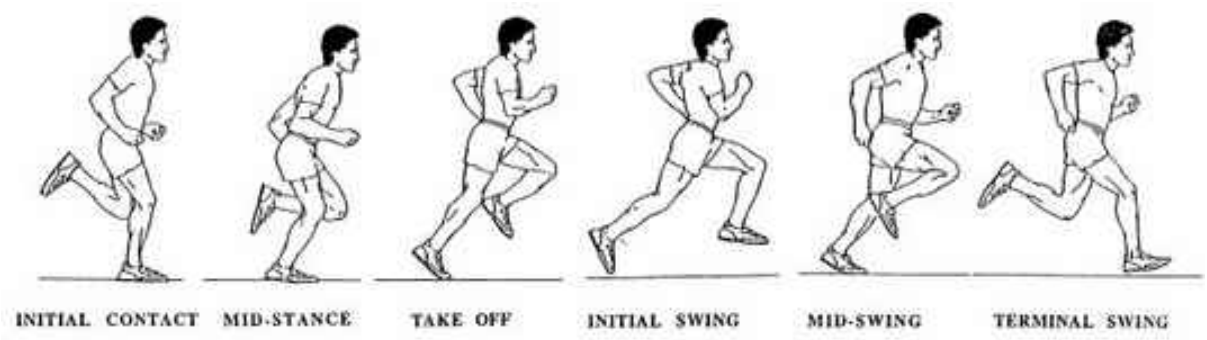


Figure 2.6. Running gait cycle (reproduced from bluestreakst.com).

During walking, the stance phase accounts for more than 40-50% of the gait cycle. Two periods of double-limb support occur when both feet are on the ground. By contrast, no periods of support occur during running since at no time are both feet on the ground. This may happen because the stance phase occupies more than 50% of the gait cycle [44,128].

Instead, the feet are both off the ground two times throughout the gait cycle (double float), at the start and the end of the swing phase [131].

Prevention of injuries

As discussed before, the precise causes of running-related injuries may vary significantly and different risk factors may potentially interact with each other, thus complicating the process of identifying injury prevention strategies [132–134]. The complexity of incurring RRMIs is not fully understood and is given by multiple running-related aspects, including biomechanics, gait cycle, risk factors, vulnerable anatomical structures. To prevent RRMIs, it is important to perform relevant research studies to monitor and analyse changes in behaviour in specific cohorts of runners, in clearly defined conditions. This will guide efforts of promoting health and exercise education, by supporting early detection of the signs of overuse and by optimising training plans or training environment [60].

2.5 CHARACTERISTICS OF MAGNETIC RESONANCE IMAGING (MRI)

2.5.1. Introduction to MRI

MRI is an imaging technology that generates high-resolution three-dimensional (3D) anatomical images in a non-invasive way. It is an excellent tool for visualising and primarily detecting various soft tissues and related pathologies in the human body, for diagnosis and ongoing treatment monitoring [135,136].

An MRI scanner is fundamentally a huge magnet. The field strength of the magnet is measured in Tesla (T).

The human body is made up of over 55% water [137]. Each water molecule is composed of two hydrogen atoms and one oxygen atom. By using magnetic fields and radio waves, MRI scanners can measure the amount of water of various human body tissues, localise the molecules of water in space and, based on this, produce a detailed reconstructed image of the biological structure of interest. Specifically, the hydrogen atoms in water are the

ones being used to measure the signal from biological structures to create the MRI scan [135,138].

The hydrogen atom in every human cell has a central nucleus, with two further components: neutrons (not charged) and protons (positively charged). Each hydrogen proton being positively charged acts as a small magnet which spins around its axis (Figure 2.7). Billions of naturally occurring spinning hydrogen protons are found in random positions in our bodies. The spinning motion results into a magnetic field, which can be redirected into a particular orientation upon the application of a magnetic field (indicated as vector B_0) using MRI scanners, so that their axes align with the more powerful magnetic field induced by the scanner [139].

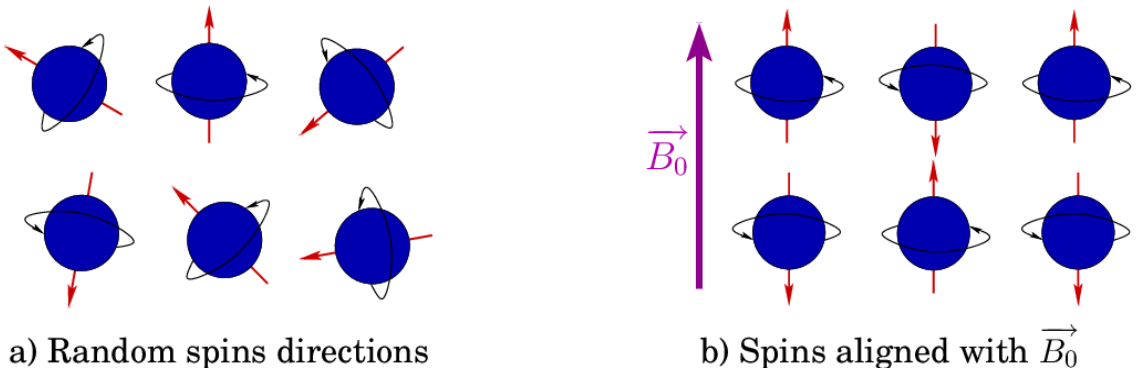


Figure 2.7. Directions of hydrogen proton spins, in a) normal conditions, when no external magnetic field is present (random spins) and b) when an external magnetic field B_0 is present (aligned spins); each spin rotation is within a cone around B_0 (reproduced from Lenglet *et al* [140]).

2.5.2 Types of MRI

MRI allows visualisation of a variety of features, from detailed anatomical structures to chemical processes and distribution of metabolites (spectroscopic imaging), measurements of blood flow (perfusion) or other physiologic properties, including water-molecules diffusion (diffusion weighted MRI), tissue oxygenation or blood vessels (angiography) [141].

The key medical purposes of MRI are: neuroimaging, structural anatomy and functional activity. Neuroimaging or brain imaging specialises in detecting neurological cancer. Structural MRI looks at the detailed anatomy of the musculoskeletal system, particularly to detect joint pathologies and abnormalities of soft tissues. Functional MRI is primarily

used in brain analysis and evaluates the relationship between different brain parts and various stimuli from the external environment [141].

2.5.3 How MRI scanning works

The MRI system has a number of components:1) principal strong magnet generating a constant magnetic field; 2) shim coils - improve homogeneity of the magnetic field for providing equal distribution; 3) gradient coils (including their active shields) – used for imaging to detect signals and localise them in space; 4) radiofrequency (RF) body coil - transmits radio signals into the specific body part which is being scanned; 5) patient (receiver) coil – detects the returning radio signal (MR signal or 'echo'); 6) computer – used for reconstruction of the MR image of the body part of interest, from the signals captured [142]. Additionally, a console is used to coordinate and inter-face all these MRI system components with the user (see Figures 2.8 and 2.9) [141].

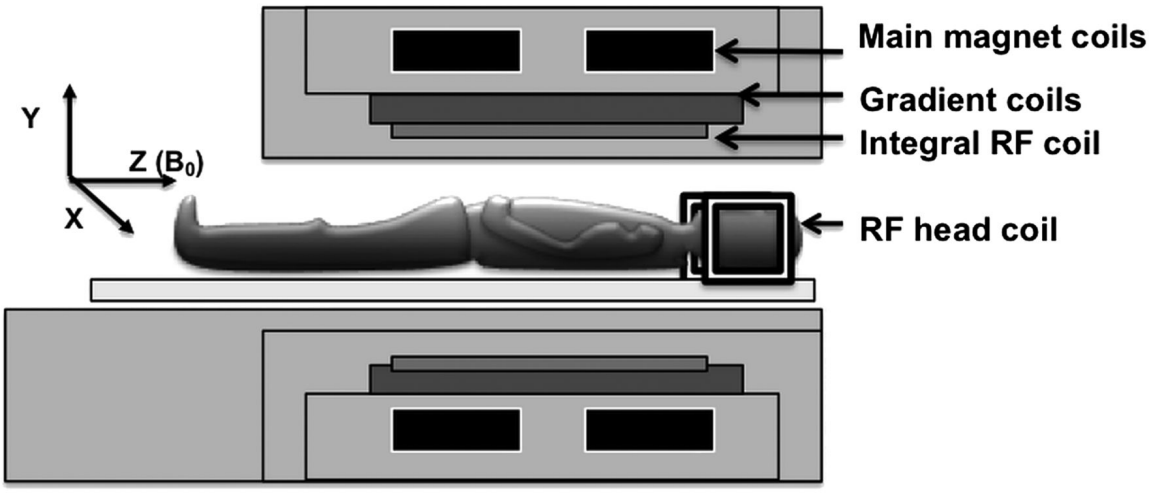


Figure 2.8. Schematic representation of different magnet coils of the MRI machine (reproduced from Currie *et al* [143]). A RF head coil is only used in neuroimaging; RF, radiofrequency; B_0, main magnetic field vector; x, y, z – coordinate axes of the magnetic field.

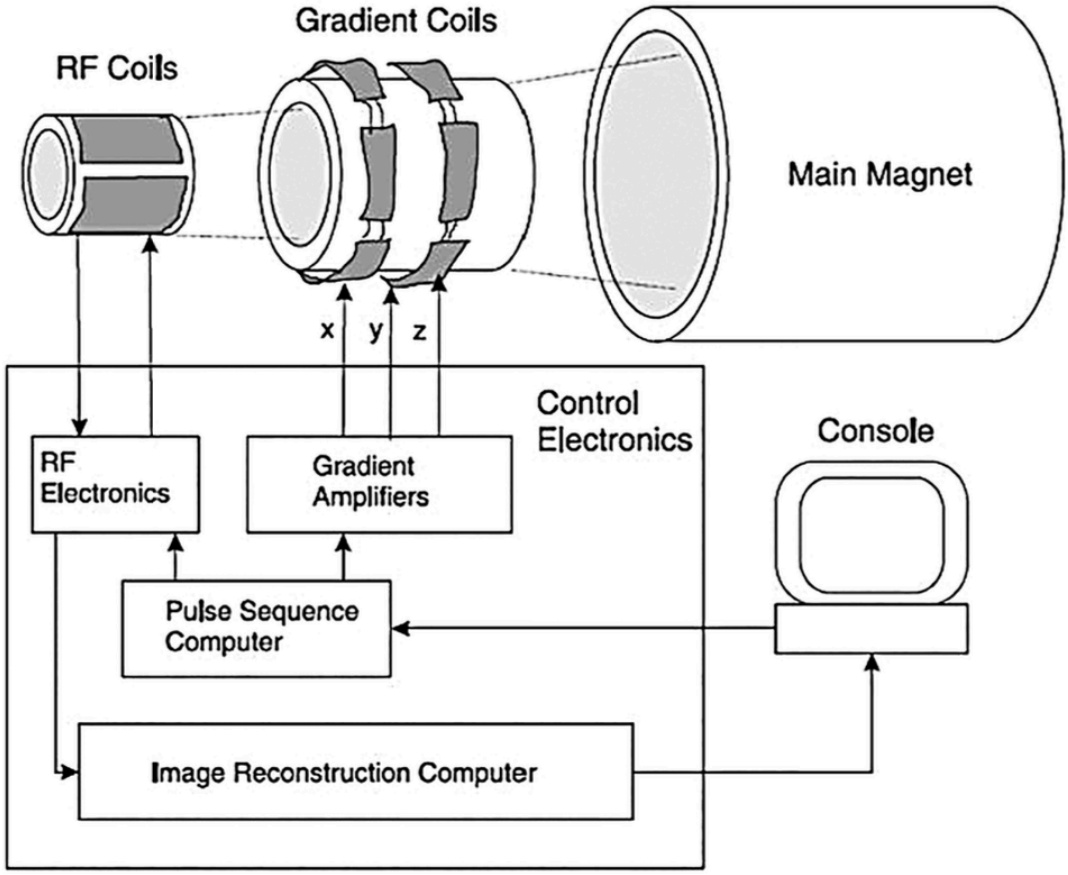


Figure 2.9. The MRI system and its basic components (reproduced from Gruber *et al* [141]); RF, radiofrequency.

The main magnet generates a powerful, static magnetic field B_0 which is applied to the patient's body to align the hydrogen protons (spins) in the body and achieve a state of equilibrium. Shim coils ensure good homogeneity within the magnetic field for better MR signal localisation [143]. Gradient coils allow encoding of the image in 3 orthogonal directions (x-frequency, y-phase, z-slice), placed concentrically within the magnet. Gradient coils then produce a magnetic field which is superimposed on top of B_0, making the strength of the main magnetic field change along the 3 directions depending on the orientation of the specific gradient field used. RF pulses generate an electromagnetic field (RF or B_1 field) which is emitted in a perpendicular plane to the main magnet. The aligned hydrogen protons are stimulated (excitation phase), spin out of equilibrium while absorbing the RF waves and transmit them as signals [143]. RF pulses are switched on and off and their frequency needs to coincide with the one of the protons, generally known as Larmor frequency. RF coils act as 'antennas' of the MR system and have 2 roles: 1) to transmit RF electromagnetic energy to the body part of interest; and 2) to receive output RF signal from the scanned body part. Some RF coils may achieve both or only one of these functions. The RF coil picks up the signal and sends it to a computer to

generate an MRI, as a reconstructed image of the specific body part of interest, following complex mathematical processing (see Figures 2.8 and 2.9) [143–146]. At this stage the hydrogen protons relax and return to their initial state of equilibrium, and the released energy is captured and converted into an image.

Moreover, multichannel coil systems are increasingly used. These systems contain multiple coil elements, individual electronic chains (amplifiers, filters, analog-to-digital conversion circuitry, demodulation/mixer devices) organised in specific geometric networks for homogenous imaging data acquisition. Independent information from each coil element is processed in receiver chains and each provides a partial view of the scanned object. The final MR image is a combination of the outputs from all channels. Multichannel coils provide improved spatial resolution, signal to noise ratio and efficiency of data transfer and handling [147–152].

2.5.4 Contrast detection and relaxation times

An MRI scan can show contrast between various soft tissues, with some of them appearing brighter or darker than other tissues or internal structures. A bright area will indicate a high level of hydrogen protons, while a dark area will indicate the opposite. Therefore, different substances in living tissues can be distinguished through MRI scanning according to their chemical and physical properties, including tissues containing water or fat. A high water content is often indicative of a pathology, so measuring this is essential in identifying specific tissues or diseases [139].

This differentiation between tissues is obtained by measuring the relaxation times of hydrogen protons i.e. time needed to completely relax. ‘Relaxation’ refers to a process whereby the hydrogen protons reverse to an equilibrium state once they absorb RF energy. The resulting energy is an estimation of the amount of hydrogen protons in a tissue and, broadly speaking, of the amount of water. Each substance has distinct relaxation times (relaxation occurs at specific rates when RF pulse is switched off) and can be detected individually and thus distinguished from each other [135,153,154].

Two relaxation times are generally measured: longitudinal relaxation time (T_1) and transverse relaxation time (T_2).

T_1 is also called ‘spin lattice relaxation’ and is characterised by the exchange of energy between hydrogen protons and the surrounding environment of the nucleus (lattice). It

indicates the time needed for the magnetic vector to reverse to its equilibrium/resting phase and distribute energy into the lattice, after a RF pulse is applied. Therefore, water may appear dark on T_1-weighted MR images because the water's T_1 values are long (3000–5000 ms). Conversely, fat may appear bright on MRI because its T_1 values are very short (260 ms) [135,139,153].

T_2 is referred to as 'spin-spin relaxation' and involves energy dissipation among the nuclei in a spin system, so not only to its lattice but also to other non-excited spins. During this relaxation, the nuclei return to a more randomly aligned organisation in space. T_2 indicates the time required for the axial spin to reverse to its equilibrium phase [135,139,153]. Water or other fluid-based tissues appear bright on T_2-weighted images, while fatty issues appear dark [154].

2.5.5 Pulse sequence parameters

The contrast of an image can be adjusted for specific purposes by using different pulse sequence parameters. Pulse sequences describe a series of RF pulses applied to a sample. Multiple pulse sequences, each with their specific parameters, are chosen and grouped together to form an MRI protocol by radiologists. They determine the timing, frequency and strength of RF pulses. There are two key parameters here: 1) the repetition time (TR), which is the length of time between two consecutive pulses; and 2) the echo time (TE), which is the length of time from the first RF pulse to the echo (received signal peak) [155–157]. They are measured in milliseconds (ms). An MRI scan is the result of repeating series of pulses and echoes, as it can be seen in Figure 2.10.

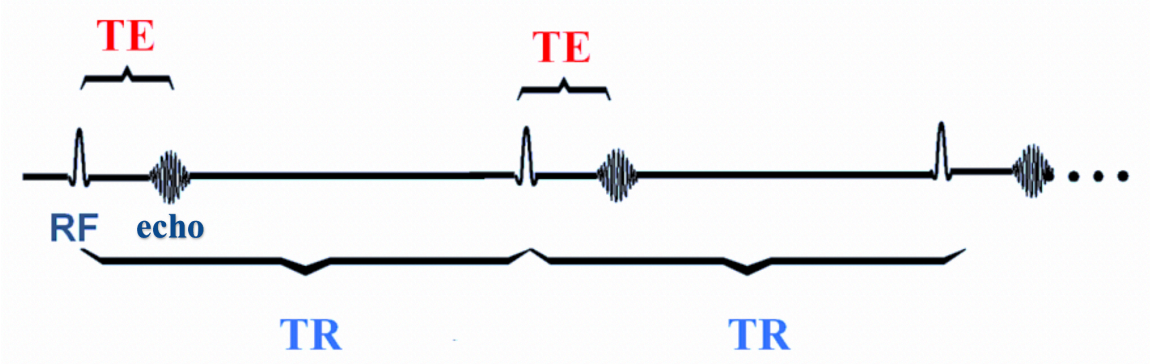


Figure 2.10. Repeating series of pulses and echoes during MR image formation (modified from mriquestions.com); RF, radiofrequency; TR, repetition time; TE, echo time.

Commonly used pulse sequences

The most commonly used pulse sequences are T_1-weighted and T_2-weighted sequences, followed by proton density (PD)-weighted sequences. T_1-weighted sequence include short TR (< 1000 ms) and TE (< 30 ms). T_2-weighted sequence include long TR (> 2000 ms) and TE (> 80 ms) [143,158]. PD-weighted sequences minimise the effect of T_1 and T_2 differences by having long TR and short TE. By combining features of both T_1 and T_2, PD-weighted sequences enable detection and differentiation of various fluids, cartilage and other internal substances in human body, therefore being commonly used in the evaluation of joints [159]. Moreover, the addition of fat-suppression (FS) sequences is preferred in many cases because the signal coming from fat is eliminated, the fluid-containing tissue is thus emphasised and it makes it easier to identify any surrounding pathologies [139].

Spin-echo (SE) pulse sequences are used for improved image quality and lower artefact sensitivity resulting from magnetic field distortions. They involve an excitation 90° pulse and then one or more 180° refocusing pulses with reversing effects on field inhomogeneities. SE sequences are commonly used in the form of fast or turbo spin-echo (FSE or TSE) with improved imaging speed, and can be designed to be T_1-, T_2- or PD-weighted [160,161].

Gradient echo (GRE) sequences have similar contrast benefits to SE, but they are based on gradient fields to produce transverse magnetisation and excitation pulses with flip angles of less than 90°. They have increased speed due to short TR and TE values allowing fast signal acquisition, however the absence of 180° refocusing pulses increases magnetic susceptibility and chemical artefacts, which are higher than in SE sequences. GRE sequences may not work well in scanners with magnetic fields lacking homogeneity [160–162].

Sometimes contrast agents are used in MRI, to enhance the visualisation of specific tissues of interest. Gadolinium-based contrast agents are often injected intravenously before MRI scanning takes place. This enhances the signal so that pathological tissues and areas of inflammation will appear brighter than other neighbouring tissues [163].

Different tissues may have similar T_1 value but very different T_2 values, therefore the image intensity and contrast will vary based on which specific pulse sequences and parameters are chosen [139].

While T_1-, T_2- and PD-weighted sequences are important in conducting morphological assessment of different joint structures, few other MRI sequences, or variations of the above mentioned ones, have been developed in order to undertake compositional analysis of certain tissues. It is known that morphological abnormalities of some tissues, as seen on MRI, may generally be the result of deterioration of their biological composition. For example, the alterations in the normal composition of the cartilage (changes in the collagen matrix, water and proteoglycan content) may indicate early cartilage disease progression, such as the development of OA [164–169]. Therefore, special sequences have been developed for the compositional analysis of cartilaginous tissues, particularly: T_{1rho} (deriving from T_1; T_1 relaxation time in a rotating frame) [170], T_{2*} [167,171] and dGEMRIC (delayed gadolinium-enhanced MR imaging of cartilage) [172]. Measurements of T_{1rho} indicate alterations in the extracellular matrix of the cartilage, including proteoglycan depletion, due to an increased movement of hydrogen protons, and thus elevated free motion of water molecules [165,173]. Also, T_2 relaxation time sequences help in monitoring the interactions between the extracellular water and collagen fibres in the tissue and depend on the concentration, orientation and other properties of the collagen. T_{2*} mapping technique is similar in that aspect with T_2 mapping and, additionally, is influenced by local susceptibility fields which may happen due to changes in the magnetic field strength or microscopic gradients; elevated T_{2*} values reveal an increased water content and better movement of water molecules, which are indicative of potential pathological findings [174–176]. Finally, the dGEMRIC technique can be used for quantifying the content of proteoglycan in the tissue by using the gadolinium contrast agent. The loss of proteoglycan in the tissue will be indicated by high concentration of contrast agent, thus suggesting abnormal matrix changes [164,169,177].

Other MRI scanning parameters include: matrix size, slice thickness, field of view (FOV), number of excitations (NEX). All parameters have an impact on the quality and level of resolution of the resulting image, particularly on the signal-to-noise ratio and spatial resolution. Spatial resolution is increased by increasing matrix size or reducing FOV and slice thickness, however this might reduce signal-to-noise or it may prolong the scan time [178,179].

Dixon sequences

Dixon pulse sequences provide a FS technique that relies on water and fat chemical changes, whereby the water/fat separation is done through postprocessing. These sequences are used especially in high-resolution MRI scanners and generate 4 types of images: in-phase, out-of-phase, water only, fat only. The fat-only images help in estimating the amount of fat in a tissue and is important in muscle analysis [180–184]. Initially, the Dixon technique generated two images only: water and fat signals in-phase, water and fat signals 180° out-of-phase. Summation and subtraction of these images resulted in two other images: water-only, fat-only. This concept can be used for various pulse sequences and multiple clinical purposes [184].

2.5.6 MRI data communication and archiving

Generally medical images are generated in a radiology department and then distributed across the hospital. The picture archiving and communication system (PACS) is commonly used to communicate, store and archive imaging data (images and processed data). PACS ensures the wide dissemination and transfer of medical data between computers, and can be used for both daily hospital evaluations and basic and clinical research. MR images are usually in the form of digital imaging and communications in medicine (DICOM) data. The raw data is usually discarded. Equipment having a DICOM interface will communicate efficiently with other DICOM equipment and medical imaging systems. The communication between these systems can be done on the premises of the same hospital where the MRI scanning took place, or remotely via Internet (see Figure 2.11).

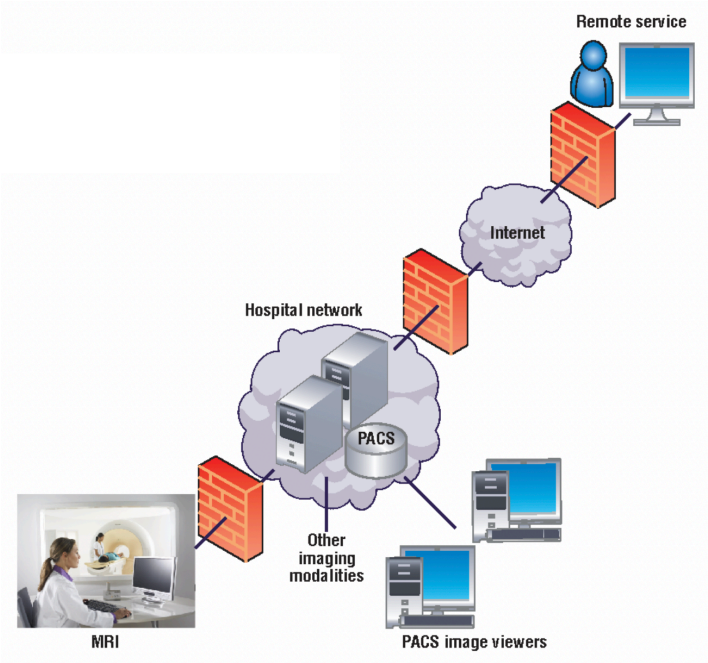


Figure 2.11. MRI data communication and network environment. The MRI system is linked with the hospital network which is connected to the Internet (reproduced from Hofland L & Linden JV [185]).

2.5.7 1.5 T versus 3.0 T MRI

MRI has been used in clinical settings for over two decades. Current MRI scanners are designed in different field strengths, with the commonly used clinical ones ranging from 0.5 T to 3.0 T (although in research settings scanners can reach 7.0 T and beyond for brain imaging [186]). The widely used field strength in clinical settings is 1.5 T, however the increasing availability of high-field 3.0 T MRI scanners in both research settings and clinics is becoming very promising in medical diagnosis including orthopaedics [135].

3.0 T MRI provides benefits of improved signal-to-noise ratio (SNR), spatial and temporal resolution and sensitivity – which are major determinants in obtaining high quality images, for better detection of anatomical structures and pathologies (see Figure 2.12). If this is compared with Earth's magnetic field, a 3.0 T MRI scanner would be around 50,000 times more powerful than the magnetic field of the planet. Some drawbacks of the technique may include: magnetic susceptibility, artefacts, high cost. However, they can be optimised for improved results [135,187,188]

According to several research studies, although 1.5 T is still the standard for musculoskeletal joints assessment in clinical practice, a number of limitations have been emphasised. The main disadvantage is the reported difficulty in identifying articular cartilage and meniscal lesions. In vitro studies showed a better detection of articular

cartilage and ligamentous abnormalities of the knee and ankle joints with 3.0 T MRI than with 1.5 T MRI [189–192]. This was also confirmed in comparative clinical studies [193,194]. Moreover, 3.0 T MRI scanners demonstrated better outcomes than arthroscopy in terms of improved sensitivity and specificity for the clinical diagnosis of meniscal tears, cartilage lesions and ligamentous abnormalities; however no direct comparisons of the same cohort with 1.5 T MRI were done here [194–197].

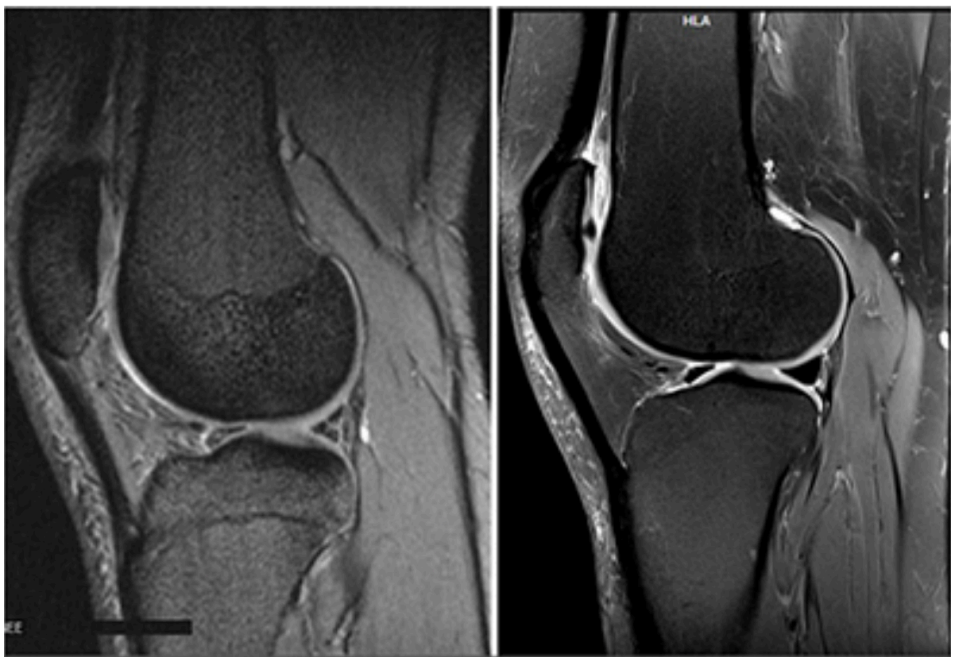


Figure 2.12. Comparison of image quality of two MRI scans in DICOM format: 1.5 T image (left) versus 3.0 T image right (modified from iseh.co.uk); DICOM, Digital Imaging and Communications in Medicine.

2.5.8 MRI use in orthopaedics and related pathologies

Since the development of imaging techniques for medical purposes, MRI has played a tremendous role in the assessment of musculoskeletal joint pathologies, especially for diagnosis and surgical procedures planning [198]. In addition to clinical examinations, orthopaedic surgeons and radiologists have increasingly and extensively relied on MRI readings for clinical decision-making, due to their perceived safety as a non-invasive procedure, as well as high contrast and resolution for detecting soft tissues and related pathologies. While radiography can assess bone structures with high contrast, other essential joint structures and surrounding tissues are very poorly visualised, plus the morphological distortion and geometric magnification associated with the use of radiography may complicate the interpretation and analysis of findings. By contrast, MRI has an unprecedented ability to differentiate between articular tissues, including menisci,

cartilage, bone marrow, tendons, ligaments, synovial fluid, muscles; this makes it an excellent tool for whole-organ imaging of the joints [199,200]. In particular, healthy cartilage (both articular cartilage and meniscal cartilage) and bone marrow are essential components for maintaining well-functioning joints and they can be effectively visualised using a variety of MRI techniques [201].

MRI is essential in understanding serious multifactorial and progressive musculoskeletal diseases such as OA of the knee and hip, which is a common disability among people all around the world. The underlying mechanisms behind OA, including structural and biochemical precursors of pain and mechanical failure, are yet unclear. Multiple factors and pathways interacting with each other have been proposed to be involved [202–205]. It is thought that once the articular cartilage starts to deteriorate, this results in increased friction between the ends of bones - which are covered in articular cartilage – and this may lead to OA or other conditions. OA is defined by the destruction of the micro and macro structure of the cartilage, which involves changes in the extracellular water content, disorganised collagen fibre networks, loss of proteoglycans [201,206]. While cartilage loss is primarily related to the pathophysiology of OA, it is yet not clearly understood whether these alterations precede, accompany, or are the consequence of changes occurring in other tissues, including the subchondral bone [207–216]. Therefore, MRI analysis of joints in research is essential to better understand the internal and external factors related to this condition, to identify early signs of lesion and propose strategies to prevent or delay the onset of OA.

2.5.9 Safety considerations

The use of MRI is generally not linked to adverse effects, pain, distress, intrusion or lifestyle changes. MRI is a non-invasive, non-intrusive procedure (non-ionising radiation) which provides a low-risk intervention for the assessment of internal structures and pathologies. In comparison to other imaging modalities, such as X-ray and computed tomography, MRI is the safest option in terms of radiation risks or other biological hazards. MRI is based on a radiation which is in the radiofrequency range which is found in our normal environment surrounding us from other sources and does not affect human tissues once applied. MRI does not change the shape, structure, characteristics and composition of atoms, as it happens in the case of ionising radiations. [217].

However, implanted devices in the body, such as pacemakers, metal clips, and metal valves can be potentially dangerous in an MRI examination since they can produce heat

from the contact with the RF field [218]. Also, the acoustic noise of an MRI scanner can be disturbing (loud tapping sounds), therefore protective earplugs/headphones are given to patients while they are inside the scanner. The long stay inside a confined space during MRI scanning can be potentially uncomfortable for patients with claustrophobia or anxiety, so this needs to be considered. Scanners come in different shapes and sizes, including wide-bore ones for increased comfort and with optimised protocols for shorter stay inside the scanner (e.g. from 40 to 20 minutes) [218–220]. The use of contrast agents for better image quality is generally well-tolerated, however they may have few side effects. The injection of 0.1 or 0.2 mmol/kg gadolinium-based agents has been linked to an incidence of adverse effects ranging from 0.07% to 2.4%, including complaints of headaches, nausea, itching [218]. Moreover, MRI scans are not generally recommended for pregnant or breastfeeding women. Although there is no evidence to suggest that there are harmful implications to the foetus from exposure to the magnetic field, the long-term effects on the developing child are currently unknown [218,221].

The radiographers or medical staff need to go through a thorough safety checklist with each patient before entering the scanner to test them for MRI compatibility.

2.6 THE USE OF MRI IN RUNNING STUDIES

2.6.1 The impact of marathon running on the knee joint

In sports orthopaedics, MRI is considered the most reliable tool in assessing internal joint structures and pathologies. When it comes to running, few studies used MRI to assess the joints of runners for research purposes in the past. Few early MRI studies analysed the effects of small to moderate doses of running (jogging up to half-marathon distances) on the knee joint. Only subtle, immediate and temporary changes were seen as a result, and no clinical significance of these findings could be concluded from these studies [222,223]. However, over the last decade, the growing popularity of marathon running, as well as the rise in related injuries, coupled with recent developments in imaging, have encouraged more research groups to investigate whether running a marathon alters the ‘normal structure of the knee’.

In particular, most study designs included cohorts of runners who underwent MRI scanning both before and after running a marathon race. Therefore comparative

assessments between MRI scans at different time points were conducted to better understand the impact of marathon running on human knee joints.

Based on the existing marathon running literature, three MRI scanning time points can be differentiated:

1) Time point 1 (pre-marathon MRI): hours to months before the marathon;

2) Time point 2 (post-marathon MRI, short-term): up to 3 days after the marathon;

3) Time point 3 (post-marathon MRI, medium-term and long-term): ≥1 month after the marathon:

- medium-term: <1 year after the marathon;
- long-term: ≥1 year after the marathon.

To date, a total of 9 research studies investigated the impact of marathon running on knee joints using MRI (see Table 2.3) [43,58,176,224–229]. More than half of these studies included 3 MRI scanning time points in their analysis (as detailed above), while the rest included 2 MRI scanning time points.

Firstly, in 2001 Krampla *et al* [58] used low-resolution 1.0 T MRI to assess the knees of 8 recreational marathon runners before and after running a marathon. Before the run, six knees had minor pre-existing abnormalities, and no negative alterations were reported within 1.5 months after the marathon. Only one knee of a runner with pre-existing high grade meniscal lesion progressed following the run. In the rest of the knees, only minor signal changes appeared in the meniscus and bone marrow shortly after the marathon and these were transitory and returned back to normal in less than 2 months later.

A further follow-up study of Krampla *et al* [224] used the same equipment to assess the knees of the same cohort of runners 10 years after the marathon. This is the only long-term marathon study to date – all other running studies conducted only short-term and/or medium-term follow-ups. The 10-year longitudinal study concluded that marathon running did not have any negative long-term repercussions in healthy knees, with no significant pre-existing damage. Also, it was suggested that long-distance running may have a protective value to the internal knee structures.

Hohmann *et al* (2004) found no BME, stress reactions or effusion on 1.5 T MRI scans neither before nor after running a marathon in 8 tested subjects, both recreational and semi-professional long-distance runners [43]. Only one runner who had a previous surgical reconstruction of an injured ACL showed small effusion before the run, which was sustained after the run. The authors concluded that the forces exerted during running are well tolerated since no post-marathon MRI changes were observed.

In Schueller-Weidekamm *et al*'s study (2006), the knees of 22 non-professional marathon runners were evaluated using 1.5 T MRI [225]. Before the marathon, 4 of these had some cartilage abnormality, 3 had BME, 2 presented with ACL abnormalities, 13 with meniscal abnormalities and 13 with knee joint effusion. After the marathon, only one meniscal signal in a knee progressed and 4 other cases of effusion increased in extent. All the other pre-marathon conditions remained unchanged following the run. This suggested that properly trained runners do not suffer from serious acute abnormalities of the articular cartilage, meniscus, ligaments, or bone marrow. Only minor signal alterations can occur in the meniscus and effusion levels after the run.

In 2008, Stahl *et al* [230] used 3.0 T MRI for the first time in a running study comparing between the knee outcomes of 10 asymptomatic recreational marathon runners and 12 active controls. On the initial MRI scans before the marathon, researchers reported a high number of cartilage abnormalities and/or BME in both groups: 8/10 knees of marathon runners and 7/12 knees of controls. The abnormalities were slightly increased in size and number in runners than controls, but not significantly. However the post-marathon scans did not show any significant changes in these features.

Two years later, Luke et al (2010) used 3.0 T MRI to assess not only morphological changes, but also biochemical changes (using T_{1rho} and T_2 sequences) in the knee structures of 10 asymptomatic marathon runners and 10 matched controls. Before running the marathon, morphological MRI assessment revealed cartilage abnormalities in 2/10 knees of runners (in the patella and medial femoral condyle) and 2/10 controls (patella and trochlea); another control had a meniscal tear. Also, BME was found in one runner and one control. No other abnormalities were identified on MRI, such meniscal lesions, osteophytes, subchondral cysts, ligament rupture, effusion or synovitis. After the marathon, no gross morphological MRI changes were detected.

The biochemical assessment however showed compositional changes occurring in the articular cartilage, with elevated levels of T_{1rho} and T_2 shortly after the marathon. The alterations were seen in the trochlea, patella, medial femoral condyle, and medial tibia. In a 3-month follow-up, T_2 values returned to baseline levels suggesting temporary running-related biochemical changes. However, the T_{1rho} values still remained high at this time point, therefore the implications of this are not clear and long-term studies are needed to understand whether reversibility occurs over a longer period of time or not. The biochemical analysis suggests that the cartilage of the patellofemoral joint and medial compartment may be more vulnerable to degeneration than other structures following a marathon run. This was a novel finding in marathon running research, considering that all previous studies focused on morphological analysis and showed no significant negative effects on knee joint structures. However the biochemical changes, particularly in the articular cartilage, may precede morphological changes and would require further investigation.

Stehling *et al* (2011) conducted a similar study, including both morphological and biochemical knee analyses using 3.0 T MRI, in a cohort of 13 recreational marathon runners and 10 controls. Morphologically, a number of abnormalities were detected on the MRI scans before the marathon race: meniscal abnormalities in 2/13 knees of marathon runners and 1/10 knees of controls; cartilage abnormalities in 6/13 knees of marathon runners and 4/10 (predominantly in the patella); BME in one marathon runner and one control; joint effusion in one knee of a marathon runner. There were no changes in these findings at the two post-marathon scans – 3 days shortly after the marathon and 3 months later. The biochemical analysis in this study only focused on the meniscal cartilage, and not on the articular cartilage as in Luke *et al* [227]. Immediately after the marathon, all runners reported a significant increase in T_{1rho} and T_2 values in all meniscal areas, suggesting changes in the composition of the meniscal tissue. At the 3-month follow-up, T_2 values decreased while T_{1rho} values still remained high, which might indicate persistent alterations in the meniscus after a marathon. However more investigations are needed to clarify this.

Hinterwimmer *et al* (2014) [229] used lower resolution 1.5 T MRI to measure the volume and thickness of the articular cartilage in a quantitative knee analysis of 10 asymptomatic marathon beginners. There were significant changes in the lateral femoral cartilage volume and thickness between the baseline and follow-up measurements which were done the day after the marathon. All the other articular cartilage areas showed no

significant differences between those time points. This is the only known study where the researchers conducted the first baseline MRI before the runners started their training for the marathon (6 months pre-marathon), and not just few days or weeks before the race, as it happened in previous studies. Also, it is the first study to analyse specifically novice marathoners who never ran a marathon before, although they had previous long-distance running experience of shorter distances. Therefore this study accounted for the impact of training, in addition to the race itself, on the cartilage characteristics of runners, which might have affected the findings. This is a very important consideration given that certain changes in the joint structures may develop over the course of training and not only during the race day, especially in novice marathon runners whose joints were exposed to their first intense training plan for a marathon. Nevertheless, the resulting values were similar to precision errors found in other quantitative measurements, therefore the authors disregarded the concern that they may be clinically relevant and concluded that the impact of long-distance running is well tolerated in healthy beginner marathon runners.

Hesper et al (2014) [176] conducted a quantitative T_{2*} assessment of the knee joint cartilage of 10 asymptomatic non-professional marathon runners using 3.0 T MRI. No runner had any apparent morphological cartilage deterioration neither before nor after marathon running. However, the comparison between the cartilage T_2^* values at different time points in relation to the marathon showed a slight increase in the T_2^* values within 2 days after the marathon, which then declined to similar levels to the pre-marathon ones one month later. Therefore, marathon running had a transient influence on T_{2*} values which is considered to be minor and not of clinical relevance. Lower T_{2*} values were found in the medial tibial plateau which may indicate early signs of deterioration of this region, however long-term follow-up studies are needed to better understand this.

Discussion and conclusions

Overall, the above mentioned studies demonstrated that marathon running does not result in significant acute lesions of the knee joints. Most of these studies showed minor to no apparent changes in the internal knee structures on MRI after a marathon run. However, few studies looked at the biochemical changes occurring after a marathon, apart from morphological changes, particularly in the different types of cartilage of the knee (meniscus and/or articular cartilage), and noticed potential compositional alterations in the matrix of the tissue, which may predict future morphological degradation.

Nevertheless, these latter findings are not properly understood and may require further investigation, and some current interpretations suggest that they may not be necessarily clinically relevant.

However, the existing evidence is still not sufficient and has a number of limitations. The main limitations derive from a number of variations in the study design, including differences in: sample size, types of runners, participant characteristics, MRI scanner field strength, knee structures being assessed, MRI scanning time points and follow-ups, unclear clinical significance.

Firstly, the *sample size* in these studies did not exceed 22 participants (range: 6-22). Larger cohorts of participants are needed to increase the statistical power and reliability of study findings. Moreover, only one of the knees of each runner was analysed (unilateral MRI scans) in all studies. The choice of knee side varied in the literature, ranging from the right knee, the dominant knee i.e. used for takeoff and landing[231]; and random knee, so there was some inconsistency in reporting the results from different knee sides.

Most of the *study participants* were experienced long-distance runners – either recreational (non-professional) or semi-professional marathon runners, and many of them ran marathons or longer distances in the past. Only one study included novice marathon runners who never ran a marathon before, however they still had some previous long-distance running experience. No study to date included completely beginner runners, with no long-distance running experience, who trained for their first marathon ever. This would have been a particularly interesting cohort to analyse considering that more and more of such inexperienced runners sign up for marathons nowadays, and this can imply a tremendous effort to the joints of untrained runners, thus raising concerns about running-related injuries. Also, most of these studies, except for Hinterwimmer *et al* [229], did not take into account the impact of marathon training, in addition to the race itself, on the knee joints of runners, so the first pre-marathon MRI scan was conducted shortly (hours to few weeks) before the marathon day, and not before the start of the training. This is probably because most of the selected participants in those studies were already well trained runners - from past marathons and other races - so their preparation for the marathon may potentially not have had a major impact on the study results. Moreover, no study had a standardised training programme for the marathon for all participants, so the

exact dose of exercise being undertaken and the effects on knees could not have been quantified.

Some studies were *gender-biased* since they did not include both males and females in their analysis (i.e. male runners included only), therefore the study findings could be applied to the specific gender group only.

Different *field strengths* varying from 1.0 to 3.0 T were used throughout these studies, resulting in low to high-resolution images. The majority of these studies used lower resolution MRI, while some of the existing high-resolution 3.0 T MRI studies detected a much higher prevalence of abnormalities, of different grades of severity, than in lower resolution studies, despite the absence of symptoms. This makes it hard to compare between individual study results to estimate the exact prevalence of MRI abnormalities in marathon runners.

Moreover, not all *knee joint structures* were analysed in these studies - some key structures were omitted such as tendon analysis. Also, some of the few existing 3.0 T MRI studies only assessed the cartilage (meniscus or articular cartilage) and did not evaluate other knee features. Therefore, previous studies may lack the appropriate level of robustness for a comprehensive analysis of all knee structures and processes.

In terms of *MRI scanning time points*, there was inconsistency in the choice of time lines and number of follow-ups among these studies. The majority of studies conducted MRI scans immediately before and after the marathon; however there were still variations, ranging from few hours to weeks for the pre-marathon scan (and in one study 6 months before the marathon, and thus before starting training); and ranging from few hours up to 3 days after the marathon for the post-marathon scan. Currently, there is no consensus on which period of time before and after the marathon is best for appropriate analysis of the impact of running on the joints. Also, a longer follow-up after the marathon (third time point) was not conducted in all studies and varied from one to 3 months. Only one study included a long-term follow-up of 10 years after the marathon. More medium-term and long-term follow-up studies are required to investigate any potential consequences of marathon running over time.

The controversial association between the increasing number of participants in marathon races and a spike in running-related injuries has not been clarified yet. The existing research data is not conclusive and have a number of limitations, however the key

message is that there is no evidence to suggest that marathon running damages the knee joints at the moment.

Table 2.3. MRI studies evaluating the impact of marathon running on the knee joint

Study authors (year)	MRI (T)	Knee	Pre-marathon (T1)	Post-marathon (T2, short-term)	Post-marathon (T3, medium-or long-term)	Participant characteristics
Krampla *et al* (2001) [58]	1.0	Random	24 hours	24 hours	1.5 months	• 8 recreational marathoners (male); 2/8 symptomatic; • 5-20 years of long-distance running experience; • Aged: 27-46 years; mean: 37 years.
Hohmann *et a*l (2004) [43]	1.5	Right	48 hours	24-48 hours	-	• 6 asymptomatic recreational and 2 semi-professional long-distance runners (male); • Aged: 23-58 years; mean: 38 years.
Schueller-Weidekamm *et al* (2006) [225]	1.5	Right	24 hours	1-4 hours	-	• 22 recreational marathoners (16 male, 6 female), 2/22 symptomatic; • Previously ran ≥1 marathon (range: 1-7); • Aged: 22-45 years; mean: 32.0 ± 5.3 years.
Stahl *et al* (2008) [230]	3.0	Non-dominant	48-72 hours	48-72 hours	-	• 10 asymptomatic, recreational marathoners (4 male, 6 female), 12 controls (8 male, 4 female); • Previously ran ≤3 marathons; no marathons in the past 4 months; • Aged: 31.1 ± 5.1 years (mean).

Krampla *et al* (2008) [224]	1.0	Random	24 hours	24 hours	1.5 months, 10 years	• 8 recreational marathoners (male) • 15-30 years of long-distance running experience; • Aged: 37-55 years; mean: 50 ± 7.1 years.
Luke *et al* (2010) [227]	3.0	Domi-nant	2 weeks	48 hours	2.5-3 months	• 10 asymptomatic recreational marathoners (4 male, 6 female); • Previously ran ≤3 marathons; no marathons in the past 4 months; • Aged: 18-40 years.
Stehling *et al* (2011) [228]	3.0	Right	3 weeks	48-72 hours	3 months	• 13 asymptomatic recreational marathoners (5 male, 8 female), 10 controls (4 male, 6 female); • Ran no marathon in the past 5 months; • Mean age: 32.3 ± 5.6 years (marathoners); 30.5 ± 5.3 years (controls).
Hinterw imm-er *et al* (2014) [229]	1.5	Unspeci -fied	6 months	24 hours	-	• 10 asymptomatic novice marathoners (5 male, 5 female), who did not participate in/trained for a marathon before; • Running experience of 34 months (range: 1–120); mean: 23.5 km/week (range 5–35); • Mean age: 39.9 ± 3.8 years.

Hesper *et al* (2014) [176]	3.0	Right	48 hours	48 hours	1 month	• 10 asymptomatic, recreational marathoners (3 male, 7 female); • Aged: 22-34 years; mean: 28.7 ± 3.97 years.

2.6.2 The impact of marathon running on the hip joint

Despite the increasing interest in using MRI in running studies, there is very little literature on the impact of marathon running on hip joints. Most marathon running studies focused on knee joint analysis which is considered to be a focus point when it comes to running and related injuries, however the evidence on the other lower limb joints is extremely scarce.

So far, only one study evaluated the effects of marathon running on the hips of runners using MRI. The study conducted by Hohmann *et al* in 2004 [43], and mentioned in the previous section, analysed the hip joints of 8 marathon runners (6 recreational and 2 semi-professional) using 1.5 T MRI, in addition to their knee joints. The hip joints of all runners had absolutely no lesion 48 hours before the marathon and no changes were found 48 hours after the marathon. This clearly indicated that marathon running does not have any negative effects on the hips and the forces acting during running on the joints are well tolerated.

However, few limitations of this study must be acknowledged: small sample size, cohort including only experienced long-distance runners, low-resolution MRI, no follow-ups over a longer period of time than 48 hours after the marathon (months to years). The latter would be needed to assess whether new lesions appear over time. Also, the use of high-resolution 3.0 T MRI equipment instead of 1.5 T MRI would have been beneficial in detecting early signs of lesions or pathologic conditions that 1.5 T MRI might have missed out.

Therefore, the key message from this study is that marathon running does not damage the hip joints of asymptomatic runners, but stronger evidence including improved study design is needed to clarify this.

2.6.3 MRI-based quantitative and semi-quantitative outcome measures

The above mentioned MRI studies used a variety of methods to grade the morphology and changes in MRI signal of different joint abnormalities on MRI according to their level of severity. These are important in detecting potential risk factors for the development of pathological conditions, such as OA and other diseases or lesions. The measuring techniques can be classified into two main categories: quantitative and semiquantitative [232,233].

Quantitative techniques fully make use of the three-dimensional nature of MRI scans and rely on digital image processing for the quantification of different joint structures' characteristics, such as analyses of the morphology (i.e. thickness, shape, size, surface areas, volume, position) of the cartilage, bone and other internal structures; as well as measurements of cartilage composition using techniques such as T_2, T_{1rho}, dGEMRIC and others [172,234].

By contrast, semi-quantitative measurements or scoring systems are generally based on observation of structural changes (analysis is done by one or more observers) and produce grades or scales instead of continuous outcomes [232]. There are a number of semi-quantitative scoring systems assessing multiple joint features using conventional MRI techniques [199,235–237]. Scoring systems were formed as a result of developing expertise from medical perceptions and guidance (including arthroscopic findings [238,239]) as to which features have important joint functions, what is considered morphologically normal and abnormal, what are the stages of progressing from one state to another, and how to differentiate between these stages through observation and simple measurements [232].

Both quantitative and semi-quantitative measures have advantages and disadvantages. Due to the reader dependence nature of semi-quantitative methodologies, a certain level of bias among readers (usually radiologists and/or physicians) and limited precision have been discussed. Also they can be time-consuming and require previous expertise and training to be able to perform a reliable grading of each internal structure with the naked eye, while quantitative measures are generally automatic, objective and may be much faster to perform. However, quantitative measures also have inherent limitations, including the requirement of specialised softwares and limited sensitivity to the appearance of small focal alterations within bigger joint structures on MRI, which may be observed immediately by the trained eye of an experienced reader (using semi-

quantitative measures), especially if the location of the focal change is different among various distinct joints. Also, semi-quantitative measures may be more time-intensive since the boundaries of each tissue require tracking for differentiation of various structures within the joint [232,234].

Studies comparing the clinical efficacy of quantitative and semi-quantitative measures showed conflicting results. Some research findings were supporting one type of quantification measurement over the other, while other studies showed the opposite, therefore currently there is no consensus on which type provides best outcomes [240,241]. One study reported that quantitative measures were more reliable in showing correlations between different risk factors (e.g. malalignment) and knee chondral pathologies than semi-quantitative measures [199,240], while another study proved that semi-quantitative scoring systems correctly identified knees with or without early OA, while quantitative measures failed to demonstrate much or any difference between the respective knees. [241].

The choice of the appropriate type of outcome measure for a study depends on the particular research question and context of the analysis, the research group's resources and expertise, and strategies for optimising the results from the assessment [234].

The majority of the running studies included semi-quantitative scoring systems (usually validated methods or in accordance with general radiological practice and the literature). The researchers chose different scoring systems for the assessment of joint structures of interest based on radiologists' preference, experience and standard practice in those specific clinics. In the following sections I will focus on MRI-based semi-quantitative scoring systems, particularly of the knee and hip joints, and will not cover more detail on quantitative scoring systems.

2.6.4 Knee joint semi-quantitative scoring systems

The most commonly known validated semi-quantitative scoring systems of the knee joint are: Whole-Organ Magnetic Resonance Imaging Score (WORMS) [199], Knee Osteoarthritis Scoring System (KOSS) [242], Boston Leeds Osteoarthritis Knee Score (BLOKS) [236], MRI Osteoarthritis Knee Score (MOAKS) [243], Anterior Cruciate Ligament OsteoArthritis Score (ACLOAS) [235].

WORMS was the first MRI-based semi-quantitative scoring system of knee lesions, primarily of knee OA, which was introduced by Peterfy and his research team in 2004 [199]. This validated method has been used a lot over the last decade in the assessment of the whole knee joint, in various observational cross-sectional and longitudinal studies all around the world. Conventional MRI techniques that are widely used in clinical settings were applied in these studies, then the radiological readings and subsequent scoring of the MRI scans was done by trained musculoskeletal radiologists. WORMS provides a reliable scoring instrument of multiple joint structures and features, as well as important features associated with knee OA. The following key independent articular features are described by WORMS: meniscus, articular cartilage, subarticular BME, subarticular cysts, ligamentous abnormalities, synovitis and effusion, periarticular cysts/bursae, osteophytes, loose bodies. For each feature, interclass correlation coefficients were calculated to assess interobserver agreement, and confirmed the validity and reliability of WORMS.

In 2005, a collaborative initiative formed between rheumatologists and radiologists, with vast experience in OA MRI research and outcome measures, resulted in the development of a new scoring system called KOSS [242]. KOSS entails similar MRI features as those described by WORMS, including meniscal lesions, cartilage abnormalities, subchondral BME and cysts. However, slightly different divisions of anatomical subregions are used by KOSS in comparison to WORMS. Each subregion is assigned a score by the selected observers (readers who receive training on using KOSS) during the assessment, based on the size and extent of the lesion. Moreover, meniscal subluxation is an additional feature which was assessed apart from meniscal morphology. Regarding the scoring of BME, a comparative analysis between WORMS and BLOKS showed slightly more accurate findings of the bone marrow condition by BLOKS than WORMS, however opinions may vary on this matter.

A modified version of KOSS, known as BLOKS [236], was then published later in 2008. BLOKS provides similar anatomical subdivisions of the articular surfaces as KOSS, with a greater emphasis on the weight-bearing compartments than the patellofemoral compartment.

MOAKS [243] is a combination of WORMS and BLOKS that became publicly available in 2011. MOAKS includes a refined version of scoring BME, adds more detailed subregional evaluation, excludes some apparently redundant information in assessing the

cartilage and BME-like lesions, and provides a more complete analysis of meniscal characteristics in terms of appearance and abnormal conditions.

ACLOAS [235] was published in 2014 and known primarily as a reliable scoring of ACL injuries and other ligament abnormalities. Also, ACLOAS included revised versions of previously published scoring systems for other knee features, such as the meniscus, providing a more detailed analysis of these, including morphology and extrusion.

Also, few other scoring systems were developed for specific joint structures. A review of the most commonly used validated scoring systems is available in Table 2.4. In particular, for the articular cartilage, a number of specific classifications and scoring systems have been proposed since 1961. The first one was the Outerbridge system which was primarily a descriptive scoring system of the stages of chondromalacia of the patella. Outerbridge was designed on a 0-4 scale, as a simple to use and easily reproducible grading system. It was based on surgical/arthroscopic findings (from direct visualisation of the joint) and was used among surgeons to define the severity of cartilage lesions, as well as for diagnosis and clinical purposes. This system went through a number of modifications over time for improved outcomes. More notably, in 1989 Noyes and Stabler [239] introduced an altered version of the original scoring system in an attempt to overcome previous limitations and provide a more detailed analysis of cartilage lesions. This included information such as description of the articular surface, depth of lesioned area, diameter and specific location within the joint. A modified version of Noyes was then developed to refine details of the classification as seen on MRI [244,245]. Then new modified versions of this latter one were proposed and they are commonly used nowadays [231,246–248], although there is no specific widely accepted grading system for cartilage defects in the literature.

Specifically regarding OA, few studies [11,249] assessed the roles of different knee features described in these scoring systems in the development of arthritic conditions, focusing on the meniscus, articular cartilage and BME-like lesions, and revealed both strengths and limitations of each individual scoring system. However, all available scoring systems are validated, with good general reliability, therefore can be used in research studies and improved/modified scoring versions of certain features for specific research questions can be considered.

All of the above mentioned MRI-based scoring systems exclude the use of intravenous or intraarticular contrast agents, while other systems have been created to include such agents especially for the evaluation of OA-related synovitis [250].

Table 2.4. MRI-based semi-quantitative scoring systems for knee joint abnormalities

Knee feature	Scoring system	Pros and Cons

Meniscus	**Lotysch *et al*** [251]
	• 1=a small focal area of increased signal intensity on T_2-weighted images, which does not extend to the articular surface
	• 2=linear areas of increased signal intensity, with no extension to the articular surface
	• 3=abnormal high signal intensity of the central portion of the meniscus, extending to at least one articular surface, usually indicating a definite meniscal tear.
	
	WORMS [199]
	• 0=intact;
	• 1=minor radial tear or parrot-beak tear/intrasubstance abnormalities;
	• 2=non-displaced tear;
	• 3=displaced or complex tear;
	• 4=complete maceration/destruction
	
	BLOKS [236]**, MOAKS** [252]
	• Meniscal signal (not a tear)
	  • Absent: N
	  • Present: Y
	• Type of tear:
	  • Vertical tear: Y/N
	  • Horizontal & radial tear: Y/N
	  • Complex tear: Y/N
	  • Root tear: Y/N
	  • Partial maceration: Y/N
	  • Complete maceration: Y/N
	
	ACLOAS [235]
	• 0=normal meniscus with absence of tear, maceration and hypointense signal
	• 1=intrameniscal hyperintensity not extending to meniscal surface
		Lotysch *et al* [251]
		(+) General analysis of meniscal signal changes on MRI
		
		(-) No description of the types of meniscal tears and specific patterns, or other characteristics of the meniscus such as maceration
		
		WORMS [199]
		(+) More detail was included in the description of this scoring system than in Lotysch et al
		
		(-) Not all types and features of the meniscus were specified
		
		BLOKS [236]**, MOAKS** [252]
		(+) More detailed scoring system than the previous ones, including different types of tears: vertical, horizontal, radial, root; also partial maceration. These help in better differentiation and diagnosis of various types of tears
		
		(-) Few missing features or conditions: bucket-handle tear, meniscal repair
		
		ACLOAS [235]
		(+) More inclusive analysis of all types of meniscal abnormalities and patterns of meniscal tears

	• 2=horizontal tear • 3=radial and vertical tear • 4=bucket-handle tear, displaced tear (including root tears) and complex tears • 5=meniscal repair • 6=partial meniscectomy and partial maceration • 7=progressive partial maceration or re-partial meniscectomy (i.e., loss of morphological substance of the meniscus) as compared to the previous visit • 8=complete maceration or resection.	(-) Scores 3 and 4, respectively, include more than one type of tear, therefore each type of tear is nor properly differentiated

Articular cartilage	**Outerbridge** [253]
	
	• 0=normal
	• 1=cartilage with softening and swelling
	• 2=a partial-thickness defect with fissures on the surface that do not reach subchondral bone or exceed 1.5 cm in diameter
	• 3=fissuring to the level of subchondral bone in an area with a diameter more than 1.5 cm
	• 4=exposed subchondral bone
	
	Noyes & Stabler [239]
	
	• 1=intact cartilage surface
	  o A=definite softening with some resilience remaining
	  o B=extensive softening with loss of resilience (deformation)
	• 2=damaged cartilage surface (blisters, cracks, fissures, fibrillations, fragmentations)
	  o A=<1/2 thickness
	  o B=≥ 1/2 thickness
	• 3=exposed bone
	  o A=intact bone surface
	  o B=cavitation bone surface
	
	Modified Noyes [244]
	
	• **0=**normal cartilage
	• 1=increased T_2 signal intensity of morphologically-normal cartilage not orientated at 55° to the external magnetic field
		Outerbridge [253]
		
		(+) First grading system developed by physicians. Good description of different grades of cartilage abnormalities based on arthroscopic findings
		
		(-) Not specifically designed for MRI findings; Outerbridge is based on arthroscopic findings with its inherent limitations and risk of bias i.e. the terms used do not enable a full characterisation of the cartilage abnormality as they have different connotations to distinct observers
		
		(-) The extent of involvement from surface to bone in any stage is not considered in this system. The grades are differentiated solely based on diameter of involvement
		
		Noyes & Stabler [239]
		
		(+) Derived from Outerbridge but improved to allow descriptive analysis of the cartilage and to overcome limitations of the previous system i.e. add missing details and prevent potential misinterpretations among observers
		
		(+) Includes separate and distinct variables: the description of the articular surface, the extent (depth) of

	• **2a=**superficial partial-thickness cartilage defect <50% of total articular surface thickness • **2b=**deep partial-thickness cartilage defect >50% of total articular surface thickness • 3=full-thickness cartilage defect **New Modified Noyes** [231,246] • 1=have areas of heterogenous signal intensity on fat-saturated intermediate-weighted fast spin-echo sequences • 2=cartilage defects that involve <1/2 of cartilage thickness • 3=cartilage defects that involve >1/2 of cartilage thickness but < full thickness • 4=full thickness cartilage defects exposing the bone **WORMS** [199] • 0=normal thickness and signal • 1=normal thickness but increased signal on T_2-weighted images • 2.0=partial- thickness focal defect <1 cm in greatest width; • 2.5=full- thickness focal defect <1 cm in greatest width • 3=multiple areas of partial-thickness (Grade 2.0) defects intermixed with areas of normal thickness, or a Grade 2.0 defect wider than 1 cm but <75% of the region • 4=diffuse (≥75% of the region) partial-thickness loss • 5=multiple areas of full- thickness loss (grade 2.5) or a grade 2.5 lesion wider than 1 cm but <75% of the region • 6=diffuse (≥75% of the region) full-thickness loss	involvement, the diameter of the lesion (size), and the location of the lesion (-) Not specifically designed for MRI findings; this is based on arthroscopic findings **Modified Noyes** [244] (+) Derived from Noyes & Stabler system, but divided into 4 grades by MRI, using fat saturated proton density sequences (not arthroscopic findings) (+) Simplified version of Noyes and Stabler **New Modified Noyes** [231,246] (+) Simplified version of Modified Noyes (+) Subgrades 2a and 2b of Modified Noyes turned into separate grades in this New Modified Noyes system **WORMS** [199] (+) More detailed scoring system (on a 0-6 grading scale) than the previous ones; includes assessment of focal defects <1 cm in width, as well as defects >1 cm and multiple areas of thickness defects (-) Not commonly used in radiological practice - not all radiologists agree with this as it is not easy to use and prefer previous simplified versions

Bone marrow	**Subchondral BME** **WORMS** [199] • 0=none • 1=<25% of the region • 2=25% to 50% of the region • 3=>50% of the region **KOSS** [242] • 0=absent • 1=minimal (d <5 mm) • 2=moderate (d=5-20 mm) • 3=severe (d >20 mm) **BLOKS** [236] • 1=<10% of subregional volume • 2=10-85% of subregional volume • 3=>85% of subregional volume	**Subchondral cyst** **WORMS** [199] • 0=none • 1=<25% of the region • 2=25% to 50% of the region • 3=>50% of the region **KOSS** [242] • 0=absent • 1=minimal (<3 mm greatest dimension measures) • 2=moderate (3-5 mm) • 3=severe (>5 mm) **BLOKS** [236] • 1=<10% of subregional volume • 2=10-85% of subregional volume • 3=>85% of subregional volume	**WORMS** [199] (+) Detailed scoring system of the volume of bone marrow lesions. Scoring system is applied in several different articular subregions. Individual size scores are given to each lesion within a subregion (+) Comparable to BLOKS, but includes simpler counting and equivalent data to the number of bone marrow lesions (-) Percentage area may not be accurately measured. Some radiologists prefer looking at the diameter as in KOSS **KOSS** [242] (+) Detailed scoring system. Bone marrow lesions are graded individually for each subregion. Scores are differentiated according to the size of the lesion (+) Scoring is easier and less time-consuming than WORMS, BLOKS or MOAKS (-) Some risk of bias **BLOKS** [236] (+) Detailed scoring system applied in several different articular subregions. Percentage of any subregion occupied by a single bone marrow lesion is measured (-) Application of the scoring system was considered to be time-consuming and complex and not adding much extra information than other previously used scoring systems

	MOAKS [243] • 0=none; • 1=<33% of subregional volume • 2=33-66% of subregional volume • 3=>66% of subregional volume	**MOAKS** [243] • 0=none; • 1=<33% of subregional volume • 2=33-66% of subregional volume • 3=>66% of subregional volume	**MOAKS** [243] (+) Modified threshold from BLOKS 10-85% to 33-66%. The whole subregion gets one size score instead of scoring each lesion separately i.e. multiple bone marrow lesions in one subregion are accounted into one percentage (-) Percentages may not be accurately measured. Some radiologists prefer looking at the diameter as in KOSS
Tendons	**Johnson *et al*** [254–256] • 0=normal tendon appearances • 1=increased signal intensity in less than 25% of the axial cross-sectional tendon width • 2=increased high-signal intensity in 25% to 50% of the axial cross-sectional tendon width • 3=increased high-signal intensity occupying more than 50% of the axial cross-sectional tendon width **WORMS** [199] • 0=normal • 1=low • 2=moderate • 3=large		**Johnson *et al*** [254–256] (+) Detailed description of various tendon appearances, based on % of axial cross-sectional tendon width (-) Additional measurements are needed; may be time-consuming for radiologists **WORMS** [199] (+) Simple description of grades, easy to use (-) No detailed description of what is referred by each grade or any specific parameters to define them (-) Higher risk of bias and misinterpretation
Iliotibial band	**Mansour *et al*** [257] • 0=normal iliotibial band • 1=minor sprain/peritendinous edema with normal iliotibial band girth/sprain • 2=severe sprain/focal or diffuse band thickening/partial thickness tear • 3=torn/interrupted or avulsed band/full-thickness tear **MOAKS** [243] • absent		**Mansour *et al*** [257] (+) Detailed description of the grades of severity of iliotibial band lesion **MOAKS** [243]

	• present	(+) Simple scoring system, easy to use; particularly useful for minor iliotibial band signal changes (-) Not enough detail if severe cases are considered and patients complaining of pain or other symptoms are involved
Ligaments	**WORMS** [199] • 0=no lesion (normal) • 1=Grade1 sprain (<33% of maximum potential distention) • 2=Grade 2 sprain (33–66% of maximum potential distention) • 3=Grade 3 sprain for ligaments (>66% of maximum potential distention for joint effusion) **BLOKS** [236]**, MOAKS** [243] • 0=intact • 1=torn **ACLOAS for ACL and PCL** [235] • 0=normal ligament with hypointense signal and regular thickness and continuity • 1=thickened ligament and/or high intraligamentous signal with normal course and continuity • 2=thinned or elongated but continuous ligament • 3=absent ligament or complete discontinuity **ACLOAS for MCL and LCL** [235] • 0=continuous ligament with normal signal, no surrounding hyperintensity/edema • 1=continuous ligament with normal signal, surrounding hyperintensity reflecting edema and/or hematoma • 2=partial rupture/discontinuity with some preserved fibres • 3=complete disruption	**WORMS** [199] (+) General description of ligament appearance, focusing on % of maximum potential distention (-) May be challenging to measure the precise % of maximum potential distention i.e. 33%, 66% **BLOKS** [236]**, MOAKS** [243] (+) Simple, easy to use (-) More scores are needed to define the intermediate conditions in between 'intact' and 'torn' **ACLOAS** [235] (+) Specifically designed scoring system for ligaments, which includes acute traumatic and degenerative changes i.e. especially for ACL (+) Detailed analysis of individual ligaments
Joint effusion	**WORMS** [199]	**WORMS** [199]

	• 0=normal; • 1=<33% of maximum potential distention; • 2=33%–66% of maximum potential distention; • 3=>66% of maximum potential distention. **BLOKS** [236] • 0=normal • 1=small • 2=medium • 3=large **KOSS** [242] • 0=physiological shiver of synovial fluid • 1=small amount of fluid distended one or two joint recesses • 2=>two joint recesses partially distended • 3=full distension of all joint recesses **MOAKS** [243] • 0=physiological amount/normal • 1=small • 2=medium • 3=large	(+) Good description of joint effusion grades, focusing on % of maximum potential distention (-) May be challenging to measure the precise % of maximum potential distention i.e. 33%, 66% **BLOKS** [236] (+) Simple description of grades, easy to use (-) No detailed description of what is referred by each grade or any specific parameters to define them (-) Risk of bias and misinterpretation **KOSS** [242] (+) Good description of joint effusion grades (-) Not clearly described what 'partial distention' means and how can be measured appropriately **MOAKS** [243] Same as BLOKS
Hoffa's synovitis	**MOAKS** [243] • 0=normal • 1=mild • 2=moderate • 3=severe	**MOAKS** [243] (+) Simple description of grades of different levels of severity, easy to use (-) No detailed description of what is referred by each grade or any specific parameters to define them (-) Risk of bias
Synovial cysts and bursal collections:	**WORMS** [199] • 1=low	**WORMS** [199]

Baker's/popliteal cyst, other ganglion cysts, prepatellar bursitis, pes anserine bursitis	• 2=moderate • 3=large **MOAKS** [243] • 0=absent • 1=present	(+) Simple description of different severity grades of lesions, easy to use (-) No detailed description of what is referred by each grade or any specific parameters to define them **MOAKS** [243] (+) Simple, easy to use; Particularly useful for minor signal changes (-) Not enough detail if severe cases are considered and patients complaining of pain or other symptoms are involved
Other findings	• 0=absent • 1=present	Non-specific grading system accounting for the presence of any other pathologic findings by radiologists.

BLOKS, Boston Leeds Osteoarthritis Score; ACLOAS, Anterior Cruciate Ligament OsteoArthritis Score; KOSS, Knee Osteoarthritis Scoring System; MOAKS, MRI Osteoarthritis Knee Score; WORMS, Whole-Organ Magnetic Resonance Imaging score; BME, bone marrow edema; ACL, anterior cruciate ligament; PCL, posterior cruciate ligament; MCL, medial collateral ligament; LCL, lateral collateral ligament; N, no; Y, yes; d, diameter; (+), Pros; (-), Cons.

2.6.5 Hip joint semi-quantitative scoring systems

The very first hip joint semi-quantitative scoring system was proposed by Neumann *et al* [258] and was based on direct MR arthrography. During this technique a contrast agent is injected into the joint and X-rays of the joint are conducted. The scoring system evaluated only few hip joint features in patients with mechanical hip symptoms: labrum, cartilage, subchondral BME and cysts.

Hip Osteoarthritis MRI Scoring System (HOAMS) is the first MRI-based scoring system and was published in 2011 [259]. This scoring system describes a detailed classification of the cartilage and a number of other hip joint features for 'whole-organ' assessment (Table 2.5), including the labrum, articular cartilage, subchondral bone marrow (BME and cysts). HOAMS proved to be an excellent tool for quantifying the level of damage and progression of intraarticular alterations related to hip OA. It is a well-recognised

validated scoring system with great reproducibility, and the scores are well correlated with radiographic findings and patient reported outcomes.

Another effective multi-feature MRI-based scoring system is Scoring Hip Osteoarthritis with MRI (SHOMRI) [260]. This method evaluated abnormalities of the cartilage, BME, subchondral cysts (divided in 10 subregions; each subregion was assigned a score) and labral lesions (4 subregions). Also, the presence of paralabral cysts, ligamentum teres, effusion and other findings was specified (Table 2.5). SHOMRI showed moderate to excellent reproducibility and strong correlations with radiographic and clinical findings. Additionally, SHOMRI is a convenient tool for use in imaging research centres and clinical settings anywhere around the world.

HOAMS and SHOMRI are the two most reliable and validated tools for assessing most hip joint feature in a non-invasive way, especially the ones related to arthritis, and can effectively be used in observational research studies and clinical trials.

Table 2.5. MRI-based semi-quantitative scoring systems for hip joint abnormalities.

Hip feature	Scoring system	Pros and Cons
Labrum	**HOAMS** [259] • 0=no signal changes or alterations in morphology • 1=intralabral signal alteration • 2=definite labral tear • 3=partial or complete labral maceration **Paralabral cysts** • 0=absent • 1=present **SHOMRI** [260] • 0=normal variant such as aplasia or hypoplasia • 1=abnormal signal and/or fraying • 2=simple tear • 3=labrocartilage separation • 4=complex tear • 5=maceration **Paralabral cysts**	**HOAMS** [259] (+) Standard scoring system with description of the main labrum abnormalities (-) Missing some labral features **SHOMRI** [260] (+) More detailed scoring system which includes additional features to those described in HOAMS

	• 0=absent • 1=present		
Articular cartilage	**HOAMS** [259] • 0=normal cartilage • 1=focal partial thickness defect (≤25% of subregional area affected) • 2=focal full thickness defect (≤25% of subregional area affected) • 3=several partial thickness defects or single but larger superficial defect (>25% of subregional area affected) • 4=several large full thickness defects or single full thickness defect (>25% of subregional area affected). **SHOMRI** [260] • 0=no loss • 1=partial thickness • 2=full thickness loss For large lesions that spanned more than one region, if it was greater than 1 cm in maximal diameter, it was scored in both subregions, and if it was less than 1 cm it was scored in the subregion where more than 50% of the lesion was located.		**HOAMS** [259] (+) Detailed scoring system of cartilage grades of severity (-) Not very practical – increases misclassification issues when cut-off point is subjective and may be time-consuming (-) Some features did not correlate with radiographic osteoarthritis severity or clinical symptoms **SHOMRI** [260] (+) Simple, practical scoring system, easy to use, aligned with what radiologists use in clinical practice (+) Significant correlation with radiographic osteoarthritis and clinical manifestations (-) Not same level of detail as HOAMS, but considered to be accurate
Bone marrow	**Subchondral BME** **HOAMS** [259] • 0=absent • 1=mild: <33% of subregional volume involved • 2=moderate: 33–66% of subregional volume involved • 3=severe: >66% of subregional volume involved.	**Subchondral cyst** **HOAMS** [259] • 0=absent • 1=mild: <33% of subregional volume involved • 2=moderate: 33–66% of subregional volume involved • 3=severe: >66% of subregional	**HOAMS** [259] (+) Joint is subdivided into several subregions and marrow changes are graded based on percent involvement of each subregion. This enables analysis of the structures next to it (-) Percent involvement of each subregion may be cumbersome and time-consuming to measure and the risk of bias can be increased

	SHOMRI [260] • 0=no lesion is present • 1=≤0.5 cm in size • 2=>0.5 cm but ≤1.5 cm • 3=>1.5 cm in size	volume involved. **SHOMRI** [260] • 0=absent lesion • 1=≤0.5 cm in size • 2=>0.5 cm in size	**SHOMRI** [260] (+) Lesions were scored in subregions. Measurements were taken perpendicular to the articular surface of the longest dimension. Each subregion was assessed individually and then a total lesion score was calculated. (+) More practical than HOAMS and less time-consuming to measure parameters without using percentages (-) Risk of bias
Tendons	**Chi *et al*** [261] • 0=normal • 1=tendinosis (intermediate signal, not fluid) • 2=low-grade partial thickness tear (<50% tendon fluid signal) • 3=high grade partial thickness tear (≥50% tendon fluid signal) • 4=full thickness tear (complete fluid signal)		**Chi *et al*** [261] (+) Reliable and easy to use scoring system; aligned with clinical practice scoring by radiologists
Ligamentum teres	**SHOMRI** [260] • 0=normal • 1=signal abnormalities or fraying • 2=partial tear • 3=complete tear.		**SHOMRI** [260] (+) Reliable and easy to use scoring system; aligned with clinical practice scoring by radiologists (-) Exact parameters not specified so a risk of bias might need to be considered, but the classification is commonly used by radiologists
Joint effusion	**SHOMRI** [260] • 0=absent • 1=present Fluid signal at the femoral neck region >0.7 cm in thickness.		**SHOMRI** [260] (+) Simple and effective scoring system accounting for the presence of effusion, based on fluid thickness measurements

Trochanteric bursitis	**HOAMS** [259] • 0=absent • 1=present **Chi *et al*** [261] • 0=none • 1=mild (slip of fluid) • 2=moderate (distended bursa with round margins) • 3=severe (displacement of adjacent structures)	**HOAMS** [259] (+) Simple and effective scoring system accounting for the presence of trochanteric bursitis based on its specific appearance on MRI (-) Does not take into account the different levels of severity; however in case the detected fluid is small in all study samples, then using a more detailed complex grading scale may be redundant **Chi *et al*** [261] (+) More detailed scoring system than HOAMS, describing different grades of severity based on the size of bursitis (-) May be time-consuming when all study samples present only with small minor bursitis. In that case HOAMS can be more convenient to use
Muscles	**Goutallier *et al*** [262] • 0=normal muscle (no fat) • 1=some fatty streaks (for minimal atrophy) • 2=less than 50% fatty muscle atrophy (for mild atrophy - fat infiltration less than muscle) • 3=50% fatty muscle atrophy (for moderate atrophy - fat infiltration equal to muscle) • 4=greater than 50% fatty muscle atrophy (for marked atrophy - fat infiltration greater than muscle)	(+) Standard grading system used by radiologists to quantify muscle atrophy. High grades correlate with poor function outcomes (-) Small risk of bias
Other findings	• 0=absent • 1=present	Non-specific grading system accounting for the presence of any other pathologic findings by radiologists.

HOAMS, Hip Osteoarthritis MRI Scoring System; SHOMRI, Scoring Hip Osteoarthritis with MRI; BME, bone marrow edema; (+), Pros; (-), Cons.

2.6.6 Selection of semi-quantitative scoring systems for research projects

Regarding the research projects presented in this thesis, first of all, I did a thorough review of the scoring systems in the literature, then our whole research team, including radiologists, discussed together and decided on the most appropriate scoring systems to

be used in the planned research studies. The research team carefully evaluated and discussed both the advantages and disadvantages of using each specific scoring system for the joint structures of interest. The radiologists' opinions and experience were also considered in the decision-making process, as aligned with our research purposes.

For the knee joint project, BLOKS and ACLOAS were both found to be the most detailed and reliable scoring systems in meniscus analysis when compared to previous ones. However each of them is missing some meniscal features that the other has therefore they were selected to be used together in the study since they complement each other well. The articular cartilage was assessed using New Modified Noyes system – which is the newest version of the original Outerbridge system and a detailed yet simplified and easy to use version of previous systems. Also, radiologists consider this to be a more practical system in comparison to other proposed systems such as WORMS. Bone marrow grading was done following KOSS scoring system because this was considered to be the most practical and least time-consuming yet reliable tool out of all the other existing scoring systems for our research purposes. Tendons were evaluated following Johnson *et al* scoring system which is more detailed than WORMS classification for tendon lesions and in line with what radiologists use in clinical practice. Iliotibial band signal was specified based on MOAKS – other more detailed scoring systems assessing levels of severity of iliotibial band lesions were not considered for the purposes of this study (i.e. no patients are included in the study, but only asymptomatic healthy volunteers), however in case any non-minor lesion would be detected, the radiologists would make a note of the finding as well as the size of it. Ligaments were assessed using ACLOAS system which was specifically designed for a comprehensive and individualised analysis of each of the ligament types, and thus provides the most reliable and complete assessment of ligaments. WORMS was selected for joint effusion grading out of a number of similar scoring systems (all with both pros and cons) because it is a detailed validated scoring system and was preferred by the radiologists involved in the study. Hoffa's synovitis was graded based on MOAKS scoring systems which is the only validated scoring system that was identified in the literature and considered to be reliable and easy to use. The presence of any synovial cysts or bursal collections was recorded using a binary system as mentioned by MOAKS. The specific sizes were not taken into account unless non-minor lesions were detected; in that case the radiologists would make a separate note of the finding including its size.

The presence of any other findings was specified.

For the hip joint project, we selected SHOMRI scoring system to conduct a complete analysis of all labral features instead of the alternative one which is missing some important labral features. SHOMRI was also selected for both cartilage and bone marrow evaluation for its practical reasons, ease of use and significant correlation with radiographic osteoarthritis and clinical symptoms in comparison to other scoring systems. Tendons were assessed based on Chi *et al* system, while ligamentum teres and joint effusion were assessed with SHOMRI since these are reliable and easy to use scoring systems, and no other scoring options were identified for the respective internal joint features. Trochanteric bursitis was scored based on a binary HOAMS scoring system – the use of more complex detailed scoring systems was considered redundant given that the study participants are not patients and only little to no bursitis is expected to be found. However the radiologists will reconsider the use of an alternative Chi *et al* system in case moderately-sized or large bursitis is detected. Muscle atrophy was graded following Goutallier *et al* scoring system as this is the main reliable system available and commonly used by radiologists.

2.6.7 Knee and hip joint self-assessment questionnaires

Questionnaires assessing the opinions of patients regarding their joint condition are important tools in understanding the symptomatic manifestation of different joint pathologies or early signs of lesions. In addition to the MRI analysis, the data captured in these questionnaires help put the MRI results into a clinical perspective and make correlations between specific symptoms and functional limitations of patients with their corresponding MRI results. This is useful in establishing the clinical significance of findings. However, previous running studies did not use self-reported questionnaires in their analysis which limited the interpretation of their findings.

The Western Ontario and McMaster Universities Arthritis Index (WOMAC) is a well-known validated questionnaire-based outcome measure for knee and hip OA and related conditions [263]. This questionnaire was first introduced in 1982, then tested and validated in 1988. Since then it has been used by healthcare professionals to understand the lower limb condition of their patients after answering the questions from the questionnaire. It includes 24 questions covering 3 main joint-related items: pain (5 questions: score range 0-20), stiffness (2 questions: score range 0-8) and functional limitation (17 questions: score range 0-68). The sum of all scores from these items give a WOMAC score. Higher WOMAC scores are indicative of joint problems, however

various methods can be used to combine the scores for specific outcomes. WOMAC can be particularly useful for assessing patient-reported outcomes after total hip replacement, in response to OA treatment.

The Knee injury and Osteoarthritis Outcome Score (KOOS) [264,265] was published in 1998 as an extension of WOMAC, a more detailed questionnaire focusing specifically on the knee joint. KOOS is now recognised as a validated and reliable self-administered questionnaire for evaluating both short-term and long-term outcomes of knee injury and OA. This questionnaire consists of 5 subscales, with a total of 42 questions: pain (9 questions), other symptoms (7 questions), function in daily living (17 questions), function in sports and recreational activities (5 questions), and knee-related quality of life (4 questions). Each question has a score range 0-4. The sum of the scores for each item is then transformed into a 0–100 scale: 0 is indicative of extreme knee disability; 100 is indicative of no knee issues, as defined in orthopaedic scales ad generic measurements. KOOS shares similarities with WOMAC, given that KOOS's function and daily living item is the same as the WOMAC's function item. However, the questions related to sport and recreational activities and quality of life in KOOS were taken (either reproduced or modified) from other outcome measurements evaluating ACL injuries [266,267].

The Hip disability and Osteoarthritis Outcome Score (HOOS) [268] was developed in 2003 and was specifically designed to evaluate hip injury and OA, including symptoms and functional limitations of the hip. HOOS contains the WOMAC questions in an unchanged form, but is an extended version of it, consisting of 40 questions in total. Therefore, WOMAC scores can be estimated based on a HOOS questionnaire directly. The structure of the questionnaire is similar to the KOOS questionnaire', and includes 5 distinct items: pain (10 questions), other symptoms (5 questions), activity of daily living (17 questions), sport and recreation function (4 questions) and hip-related quality of life (4 questions). Each question answer is assigned a score ranging 0-4. The HOOS scores are calculated on a 0–100 scale, worst to best.

These questionnaires are validated and reliable methods of assessing patients' opinion about their knee and hip related health condition and are very useful in research and clinical trials.

2.6 SUMMARY

In this literature review, a number of aspects related to the topic of interest have been discussed: an overview of running in general, running injuries - particularly those affecting lower limb joints, MRI characteristics and various techniques used in orthopaedics research, MRI-based outcome measures for lower limb joint analysis, and previous MRI research on marathon running. Based on this review, several gaps in knowledge have been identified:

- Despite the increasing popularity of marathon running, the exact prevalence and potential risks of getting lower limb injuries are still not well understood. There is ongoing controversy regarding the impact of marathon running on knees and hips, which are commonly reported to be two of the most injury-prone joints although current scientific evidence fails to demonstrate any significant running-related lesions.
- The significant increase in the participation of beginner runners in marathon races has given rise to concerns about their safety and joint health. Nevertheless, no study to date specifically assessed the joints of first-time marathoners lacking extensive previous long-distance running experience using MRI technology.
- The existing literature on running is not sufficient and includes a number of study design limitations. Few MRI studies analysed the knee joints of marathon runners and only one assessed their hip joints. Moreover, those studies had limited reliability due to one or more of the following factors: small sample size, types of runners being included, low MRI scanner field strength, limited internal joint features being evaluated, questionable reliability of MRI-based scoring systems used, no short-term or medium-term follow-ups, questionable clinical relevance.
- No self-assessment questionnaires were given to participants in previous running studies to reliably correlate the MRI findings with their specific symptomatic manifestations.

Chapter 3 – Knee study

Assessing the prevalence of MRI abnormalities in asymptomatic knee joints of novice marathon runners before marathon running

(pre-marathon data)

Work presented in this chapter has been published[1]

[1]Horga LM, Hirschmann AC, Henckel J, Fotiadou A, Di Laura A, Torlasco C, D'Silva A, Sharma S, Moon JC, Hart AJ. Prevalence of abnormal findings in 230 knees of asymptomatic adults using 3.0 T MRI. *Skeletal Radiol* 2020;49(7):1099-1107. doi:10.1007/s00256-020-03394-z

3.1 INTRODUCTION

Knee-related pathologies are thought to increase with age, and may be detected on MRI even before middle age; some may show no signs of pain, discomfort or physical limitations i.e. asymptomatic knees [269].

Both asymptomatic and symptomatic patients, with good and poor physical knee functioning, respectively, may have similar damage of the internal joint structures. This means that the damage seen on MRI may not correlate with the patient's symptoms and perceived knee condition [231,270,271]. Therefore, a number of questions arise about the clinical significance of MRI findings in asymptomatic knees: how severe those lesions are, whether different types of concomitant lesions increase the risk of disease progression, whether immediate action or closer monitoring should be taken, whether they progress into serious conditions or remain unchanged over time, and if so, when would this occur and what would be the most appropriate prevention strategies that should be employed. Also, in general, it is very challenging to identify and clinically diagnose individuals who present with MRI lesions despite having no symptoms, unless they conduct a routine MRI scan and discover by chance. Currently, there is no widely-approved evidence-based guidance or medical advice on establishing the optimal load and stress limits for maintaining healthy knees, particularly in asymptomatic knees [269]. This would be needed to prevent or delay the progression of OA and other knee conditions. More research involving specialised imaging techniques with great visualisation capabilities are required for a good visualisation of MRI lesions in asymptomatic individuals, to learn about their prevalence rates, types and grade of severity, and monitor them carefully over time, with or without the added impact of specific doses of exercise.

MRI is an excellent tool for identifying all signal changes in internal joint structures, including subtle ones and early signs of lesions [191,193]. There is a big discrepancy among studies regarding the overall estimated prevalence of MRI abnormalities, varying from 0 to 75% [231,270]. This can be explained by the use of different study designs and methodologies, such as: MRI scanners of various field strengths from low to high-resolution, the choice of MRI sequences which may result in wide ranges of diagnostic sensitivity, varying sample sizes and fitness levels [269]. High-resolution 3.0 T MRI has double the strength of the widely clinically used 1.5 T MRI, and offers multiple clinical benefits for the accurate detection of various tissues and joint pathologies [193,272]. 1.5 T MRI has limited efficiency in identifying and properly visualising cartilage lesions,

which are important features in the onset of OA, chondral pathologies and other joint diseases [273–275]. Also multichannel coils can be used for better diagnostic outcomes in terms of sensitivity and specificity [276,277].

3.1.1 Motivation

It is important to understand the prevalence, types, severity and locations of pre-existing abnormalities in the asymptomatic knees of physically inactive individuals, before starting any running activity. This assessment will reveal their knee condition before marathon training - 6 months prior to the marathon race, and also serves as a general evaluation of the knee health status of the general asymptomatic population of non-runners.

3.1.2 Aim

To assess the knee health status of asymptomatic physically inactive individuals before the exposure to their first marathon training programme.

3.1.3 Objectives

To evaluate the prevalence and type of knee joint abnormalities in a cohort of asymptomatic novice marathon runners before their marathon run, using morphological high-resolution 3.0 T MRI, validated MRI-based knee scoring systems and self-reported questionnaires.

3.2 MATERIALS AND METHODS

As a PhD student, I was involved in reviewing the relevant literature and collecting the data. The senior musculoskeletal radiologists were responsible for designing the most optimal MRI protocol in accordance with the study objectives and for reporting and quantifying the MRI results. The scoring systems were selected based on a literature review (provided by me) and the informed opinion and experience of the radiologists. The Chief investigator and the other PhD supervisors who are part of the research team were involved in organising the first part of the knee study while providing me with relevant training in imaging and research study organisation.

3.2.1 Study design and participants

The study was based in London and the participants were recruited from the UK. The research team prospectively identified volunteers who were successful in securing a spot for the 2017 Virgin Money London Marathon through the ballot system. We collaborated with Virgin Money which invited all marathon entrants to participate in our study via email. A call centre was organised whereby the volunteers contacted our research team to express their interest in participating in the study, then they were screened against our specific inclusion and exclusion criteria. As a result, 115 eligible volunteers were recruited following this process. All volunteers read the study information sheet and gave written consent form before being recruited to the study.

The main eligibility/inclusion criteria were the following: 1) physically inactive adults i.e. sedentary individuals doing low to no physical activity/week, not meeting the physical activity requirements recommended in public health guidelines: 30 minutes of moderate-intensity exercise (5 times/week), or 20 minutes of vigorous (>moderate dose) physical activity (3 times/week) [52,278,279]; 2) amateur runners, who never ran a marathon before; 3) asymptomatic knee joints, with no present or past known knee injuries or pathologies; 4) no past knee surgical procedure; 5) no cardiovascular health problems.

Exclusion criteria included: 1) pregnant or breastfeeding women; 2) individuals with contraindications to MRI scanning (including those with a history of claustrophobia, anxiety or panic attacks); 3) marathon runners or other experienced long-distance runners; 4) aged < 18 years old; 5) current knee complaints or a history of knee injuries or pathologies; 6) cardiovascular disorders or other cardiac abnormalities.

All participants were tested for good heart condition by a specialised cardiac team who collaborated with us and organised a separate study on their hearts. They used electrocardiogram, exercise stress testing and cardiac MRI, and confirmed good cardiovascular health of the volunteers. However the full cardiac results were not made available to our research team.

3.2.2 MRI protocol

The equipment used is a Prisma Siemens Healthcare 3.0 T MRI scanner (manufactured in Erlangen, Germany) and a 15-channel knee coil. The MRI protocol was designed by a senior musculoskeletal radiologist for a morphological evaluation of the joints and included optimised sequences in 3 planes: axial, sagittal and coronal. The protocol

involved proton density–weighted fat-suppressed turbo spin-echo (PD FS TSE) sequences in the 3 planes mentioned before, with specifically selected parameters (TR/TE; measured in ms) for appropriate high contrast and image resolution: axial (4630/37), sagittal (4200/41) and coronal planes (5240/41). The slice thickness was 3 mm. The size of the MR image was 320 × 320 pixels. Both knees of each volunteer were scanned at a time and the estimated scanning duration per volunteer was 25 minutes.

3.2.3 Image analysis

PACS was used to review the MRI scans. Also, an image processing software called OsiriX (OsiriX MD v.9.0, Pixmeo Sarl 2016) helped in the analysis of images which were displayed in DICOM form. All images were analysed and reported by a senior musculoskeletal radiologist with 10 years of experience in musculoskeletal imaging. A subset of all study participants' scans was double-reported in an independent assessment by a second musculoskeletal radiologist who had 9 years of experience. We decided internally for the subset to comprise of 20% randomly-selected participants of the total cohort (n=23). The radiologists were blinded to participants' demographics and clinical information.

In case of divergent results regarding the two radiologists' findings, a consensus reading was organised in a second MRI reporting session to achieve score agreement for those specific cases (consensus scores).

3.2.4 Quantification of MRI findings

The findings from all MRI scans were evaluated using semi-quantitative validated scoring/grading systems, selected by the research team in agreement with the radiologists based on common practice and literature search. A comprehensive analysis of all knee joint structures and their related pathologies was performed, including: menisci, articular cartilage, bone marrow, tendons, iliotibial band, ligaments, joint effusion, Hoffa's synovitis, synovial cysts and bursal collections (Baker's cyst, other ganglion cysts, prepatellar bursitis, pes anserine bursitis). A complete list of all scoring systems used and grading details for each knee joint feature is available in Table 3.1.

For the assessment of the meniscus, both ACLOAS [235] and BLOKS [236] scoring systems were used. Each scoring system provides important meniscus features, some which are missing from the other, therefore they complement each other well. ACLOAS

covers some aspects about the stages/status of maceration i.e. partial maceration and progressive maceration, which are not mentioned in BLOKS. BLOKS only includes complete maceration. The meniscus was divided into medial and lateral sides, and each side was subdivided into further subregions: anterior horn and posterior horn. Each subregion of each meniscus was given a score.

The articular cartilage was evaluated based on a New Modified Noyes grading scale [231,244,246], which was derived from arthroscopic findings and modified over time into this revised version. The articular areas covered by cartilage were each evaluated independently: femur, tibia, trochlea, patella. The femur and the tibia were each divided into medial and lateral regions. The trochlea was treated separately, with the following subdivisions: medial, central and lateral. The patella was divided into two regions: medial and lateral; the patellar ridge was scored as being part of the medial region.
The bone marrow was assessed based on the KOSS system [242]. The size of the edema-like lesion and/or subchondral cysts was measured on the scale described by KOSS. The key bones that were assessed are the ones mentioned above: femur, tibia, trochlea, patella; the same anatomical divisions were considered and each subregion was assigned a score.

Regarding tendon analysis, we used a validated scoring system to assess the severity of lesions for the following tendons: patellar, quadriceps, sartorius, gracilis. Johnson *et al* [254]grading system was primarily designed for the patellar tendon and then was adjusted to include all the other tendons. Other previous studies also used variations of this scale as described above [255,256]. The presence of iliotibial band signal indicating irritation of the band was specified, as in MOAKS system [243].

The ligaments were evaluated with the ACLOAS [235] system which is a refined scoring system for ligament analysis.

Joint effusion and Hoffa's synovitis were graded based on their severity levels as described by WORMS [199] and MOAKS [243], respectively. The presence of other findings, including cysts and bursal collections, was specified [243].

All knee joint abnormalities with a score > 0 were counted. The analysis was done at individual knee level.

Table 3.1. Knee joint scoring systems

Scoring system per knee feature	Scores	
BLOKS 0-7 [236] **& ACLOAS 0-8** [235]**: Meniscus (medial, lateral)** 2 areas: AH, PH.*	**BLOKS** • **Meniscal signal (not a tear)** o 0=absent o 1=present • **Type of tear:** o 2=vertical tear o 3=horizontal & radial tear o 4=complex tear o 5=root tear o 6=complete maceration o 7=meniscal cyst	**ACLOAS** • 0=normal meniscus with absence of tear, maceration and hypointense signal • 1=intrameniscal hyperintensity not extending to meniscal surface • 2=horizontal tear • 3=radial and vertical tear • 4=bucket-handle tear, displaced tear (including root tears) and complex tears • 5=meniscal repair • 6=partial meniscectomy and partial maceration • 7=progressive partial maceration or re-partial meniscectomy (i.e., loss of morphological substance of the meniscus) as compared to the previous visit • 8=complete maceration or resection
New Modified Noyes 0-4 [231,244,246]: **Cartilage** MFC, LFC, MTC, LTC, trochlea (medial, lateral, central), patella (medial, lateral)	**Cartilage abnormalities** • 0=normal • 1=have areas of heterogenous signal intensity on fat saturated IW FSE sequences • 2=cartilage defects that involve <1/2 of cartilage thickness • 3=cartilage defects that involve >1/2 of cartilage thickness but < full thickness • 4=full thickness cartilage defects exposing the bone	
KOSS 0-3 [242]**: Bone marrow** MFC, LFC, MTC, LTC, trochlea (medial, lateral, central), patella (medial, lateral)	**Subchondral BME** • 0=absent • 1=minimal (d <5 mm) • 2=moderate (d=5-20 mm) • 3=severe (d >20mm)	**Subchondral cyst** • 0=absent • 1=minimal (<3 mm) • 2=moderate (3–5 mm) • 3=severe (>5 mm).
Johnson *et al* 0-3 [254–256]:	**Tendinopathy** • 0=normal tendon appearances	

Tendons (patellar, quadriceps, sartorius, gracilis)	• 1=increased signal intensity in less than 25% of the axial cross-sectional tendon width • 2=increased high-signal intensity in 25% to 50% of the axial cross-sectional tendon width • 3=increased high-signal intensity occupying more than 50% of the axial cross-sectional tendon width	
MOAKS 0-1 [243]: **Iliotibial band**	**Iliotibial band signal** • 0=absent • 1=present	
ACLOAS 0-3 [235]: **Ligaments** ACL, PCL, MCL, LCL	**Ligamentous abnormalities** **ACL & PCL** • 0=normal ligament with hypointense signal and regular thickness and continuity • 1=thickened ligament and/or high intraligamentous signal with normal course and continuity • 2=thinned or elongated but continuous ligament • 3=absent ligament or complete discontinuity	**MCL & LCL** • 0=continuous ligament with normal signal, no surrounding hyperintensity/oedema • 1=continuous ligament with normal signal, surrounding hyperintensity reflecting edema and/or hematoma • 2=partial rupture/discontinuity with some preserved fibres • 3=complete disruption
WORMS 0-3 [199]**: Joint effusion**	• 0=absent • 1=<33% of maximum potential distention • 2=33%–66% of maximum potential distention • 3=>66% of maximum potential distention	
MOAKS 0-3 [243]**: Hoffa's synovitis**	• 0=absent • 1=mild • 2=moderate • 3=severe	
MOAKS 0-1 [243]: **Baker's/popliteal cyst Other ganglion cysts Prepatellar bursitis Pes anserine bursitis Other findings**	• 0=absent • 1=present	

*Both horns of the meniscus were assessed, apart from the body; BLOKS, Boston Leeds Osteoarthritis Score; BME, bone marrow edema; ACLOAS, Anterior Cruciate Ligament OsteoArthritis Score; AH, anterior horn of the meniscus; PH, posterior horn of the meniscus; MFC, medial femoral condyle; LFC, lateral femoral condyle; MTC, medial tibial condyle; LTC, lateral tibial condyle; KOSS, Knee Osteoarthritis Scoring System; ACL, anterior cruciate ligament; PCL, posterior cruciate ligament; MCL, medial collateral ligament; LCL, lateral collateral ligament; IW FSE, intermediate-weighted fast spin-echo; MOAKS, MRI Osteoarthritis Knee Score; WORMS, Whole-Organ Magnetic Resonance Imaging score; BME, bone marrow edema, d, diameter.

3.2.5 Knee Osteoarthritis Outcome Score (KOOS) questionnaire

We used KOOS questionnaires to test the perceived self-reported knee health condition of our participants, in terms of pain (questions P1-P9), other symptoms (questions Sy1-Sy7), function in daily living (questions A1-A17), function in sports and recreational activities (questions Sp1-Sp5) and knee-related quality of life (questions Q1-Q4). All participants completed KOOS questionnaires on the MRI scanning day. This questionnaire takes around 10 minutes to complete and served as a confirmation that participants had asymptomatic knee joints, as they mentioned at recruitment. Also, we aimed to compare the knee MRI results from the scores assigned by radiologists (based on the semi-quantitative scoring systems used) with the KOOS questionnaire results. The questions from the KOOS questionnaire are displayed below (Figure 3.1).

Knee Injury and Osteoarthritis Outcome Score (KOOS)

Pain

P1 How often is your knee painful?	☐ Never	☐ Monthly	☐ Weekly	☐ Daily	☐ Always

What degree of pain have you experienced the last week when…?

P2 Twisting/pivoting on your knee	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P3 Straightening knee fully	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P4 Bending knee fully	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P5 Walking on flat surface	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P6 Going up or down stairs	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P7 At night while in bed	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P8 Sitting or lying	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P9 Standing upright	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme

Symptoms

Sy1 How severe is your knee stiffness after first wakening in the morning?	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
Sy2 How severe is your knee stiffness after sitting, lying, or resting later in the day?	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
Sy3 Do you have swelling in your knee?	☐ Never	☐ Rarely	☐ Sometimes	☐ Often	☐ Always
Sy4 Do you feel grinding, hear clicking or any other type of noise when your knee moves?	☐ Never	☐ Rarely	☐ Sometimes	☐ Often	☐ Always
Sy5 Does your knee catch or hang up when moving?	☐ Never	☐ Rarely	☐ Sometimes	☐ Often	☐ Always
Sy6 Can you straighten your knee fully?	☐ Always	☐ Often	☐ Sometimes	☐ Rarely	☐ Never
Sy7 Can you bend your knee fully?	☐ Always	☐ Often	☐ Sometimes	☐ Rarely	☐ Never

Activities of daily living

What difficulty have you experienced the last week…?

A1 Descending	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A2 Ascending stairs	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A3 Rising from sitting	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A4 Standing	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A5 Bending to floor/picking up an object	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A6 Walking on flat surface	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A7 Getting in/out of car	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A8 Going shopping	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A9 Putting on socks/stockings	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A10 Rising from bed	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A11 Taking off socks/stockings	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A12 Lying in bed (turning over, maintaining knee position)	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A13 Getting in/out of bath	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A14 Sitting	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A15 Getting on/off toilet	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A16 Heavy domestic duties (shovelling, scrubbing floors, etc)	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A17 Light domestic duties (cooking, dusting, etc)	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme

Sport and recreation function

What difficulty have you experienced the last week…?

Sp1 Squatting	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
Sp2 Running	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
Sp3 Jumping	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
Sp4 Turning/twisting on your injured knee	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
Sp5 Kneeling	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme

Knee-related quality of life

Q1 How often are you aware of your knee problems?	☐ Never	☐ Monthly	☐ Weekly	☐ Daily	☐ Always
Q2 Have you modified your lifestyle to avoid potentially damaging activities to your knee?	☐ Not at all	☐ Mildly	☐ Moderately	☐ Severely	☐ Totally
Q3 How troubled are you with lack of confidence in your knee?	☐ Not at all	☐ Mildly	☐ Moderately	☐ Severely	☐ Totally
Q4 In general, how much difficulty do you have with your knee?	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme

Figure 3.1. KOOS questionnaire (reproduced from worksafe.qld.gov.au).

KOOS score calculation

Each item score is calculated separately. Firstly, scores 0-4 are assigned in each box, with scores corresponding to the listed answers in ascending order i.e. score 0 corresponds to the answer in the first box and score 4 to the answer in the last box for each question. The score for each of the 5 items for each individual participant is estimated by calculating the mean score for each item, divided by 4 (the greatest possible score for an answer) and multiplied by 100. The resulting number is then subtracted from 100. Scores range from 0 to 100: 0=worst possible knee outcomes; 100=no knee symptoms or functional problems. The calculation is summarised in the formulae below:

1. PAIN: $$100 - \frac{Mean\ score\ (P1-P9)x100}{4} = KOOS\ Pain$$

2. SYMPTOMS: $$100 - \frac{Mean\ score\ (Sy1-Sy7)\ x\ 100}{4} = KOOS\ Symptoms$$

3. ADL: $$100 - \frac{Mean\ score\ (A1-A17)\ x\ 100}{4} = KOOS\ ADL$$

4. SPORT/REC: $$100 - \frac{Mean\ score\ (Sp1-Sp5)\ x\ 100}{4} = KOOS\ Sport/Rec$$

5. QOL: $$100 - \frac{Mean\ score\ (Q1-Q4)\ x\ 100}{4} = KOOS\ QOL$$

3.2.6 Statistical analysis

Statistical analysis was performed on GraphPad Prism (version 6.0c). The statistical tests that I used are the following: unpaired *t* test, Mann–Whitney *U* test or Chi-squared. These were performed to compare between different subgroups of participants with MRI lesions and without MRI lesions, between different participants' demographics and MRI results, between the frequency of MRI lesions in distinct knee structures. Associations between different outcomes were calculated using odds ratios (OR), with 95% confidence intervals

(CI). The results were considered statistically significant when the p-value was below 0.05 ($p < 0.05$). Interreader agreement (between the scores reported by radiologists) was calculated using kappa statistics, whereby kappa values between 0.610 and 0.800 indicate substantial agreement and 0.810 and 1.000 indicate almost perfect agreement [280]. All graphs, charts and analyses were produced in GraphPad Prism.

3.3 RESULTS

I was involved in synthesising and analysing all the data including the scores reported by radiologists and the self-reported questionnaires, performing statistical tests, writing the manuscript and disseminating the research. MRI interpretation was discussed with the radiologists. The supervisors evaluated the analysis of the study data and write-up.

3.3.1 Participant characteristics

Out of the 115 participants who met the eligibility criteria and were recruited to our study, the vast majority (78%; n=90) of participants were aged ≥ 40 years old, and the remaining participants (22%; n=25) were aged <40 years old; 95% of them had white ethnicity: Welsh/English/Scottish/Northern Irish/British; and 44% were males, 56% females. All participants were right-handed and their dominant leg was the right one. Also, 52% participants (n=60) had a body mass index (BMI) ≥ 25 kg/m^2 (overweight), while 33% participants (n=55) with BMI < 25 kg/m^2 (normal range). The BMI ranged from 19.6 to 38.1 kg/m^2 and physical activity of low intensity ranged from 0 to 4 hours/week (mean: 2 hours/week). The baseline characteristics details are included in Table 3.2.

Table 3.2. Baseline characteristics of study participants

Characteristics	Study participants	
	Mean ± SD/Ratio	Range
Age (years)	44.7 ± 8.7	25–73
Male : female (ratio)	51 : 64	-
BMI (kg/m^2)	25.8 ± 3.9	19.6–38.1

BMI, body mass index; SD, standard deviation.

3.3.2 MRI findings

I evaluated the MRI results from all 230 knees (bilateral scans of 115 participants). The majority of knees (97%; 227/230) had MRI abnormalities affecting at least one joint

feature, of varying level of severity. The findings that were revealed on MRI included meniscal tears, cartilage abnormalities, bone marrow lesions, tendon abnormalities, ligament abnormalities and other joint processes (effusion, synovitis, bursitis).

Meniscal tears: prevalence, location, type

The MRI scans showed that meniscal signal (not a tear) was prevalent in 18% knees, while meniscal tears were identified in 30% knees (Table 3.3). The same knees could present more than one type of meniscal abnormality in more than one region and/or subregion of the knee.

Table 3.3. Prevalence of meniscal tears and degeneration in 230 asymptomatic knees

Meniscal anatomy		Number (%) of knees with meniscal abnormalities*								
		Meniscal signal	Meniscal extrusion	Meniscal tears						
				Horizontal	Vertical	Radial	Root	Bucket-handle	Complex	Any type of tear (at least 1)
Medial	AH	2 (1%)	0 (0%)	6 (3%)	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	7 (3%)
	PH	37 (16%)	5(2%)	53 (23%)	5 (2%)	5 (2%)	0 (0%)	2 (1%)	5 (2%)	70 (30%)
Lateral	AH	3 (1%)	0 (0%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	3 (1%)
	PH	5 (2%)	1 (0.4%)	2 (1%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (1%)
Any location		41 (18%)	6 (3%)	53 (23%)	5 (2%)	5 (2%)	0 (0%)	2 (1%)	6 (3%)	70 (30%)

*Grades were defined according to modified BLOKS [236] and ACLOAS [235] systems; BLOKS, Boston Leeds Osteoarthritis Knee Score; ACLOAS, Anterior Cruciate Ligament OsteoArthritis; AH, anterior horn; PH, posterior meniscal horn. The percentages do not all add up to 100% because each knee could have more than one type of meniscal abnormality and in more than one segment of the meniscus.

Most of the meniscal abnormalities were detected in the medial region, in the posterior horn subregion. Specifically, medial meniscal signal (non-tears) in the posterior horn was found in 16% knees (this is 90% of the total knees with meniscal signal), while medial meniscal tears located in the posterior horn were found in 30% knees (this is all knees out of all those presenting with meniscal tears). Meniscal tears of the lateral anterior horn and lateral posterior horn were present concomitantly in the same knees as the ones showing medial posterior horn tears, but in much smaller amounts. I found very few lateral meniscal abnormalities, and those were located almost equally in the anterior and posterior horns: 1% and 2% knees, respectively, in the case of meniscal degeneration; and 1% and 1% knees, respectively, in the case of meniscal tears.

Medial meniscal abnormalities were significantly more frequent in knees than lateral meniscal abnormalities ($p<0.0001$; Chi-squared test).

The meniscal tears had the following patterns: horizontal (23% knees), complex (3%), vertical (2%), radial (2%) and bucket handle tears (1%). Meniscal extrusion was found in 3% knees (Table 3.3, Figure 3.2).

Regarding the number of abnormalities in knees, there were 93 cases of meniscal signal in total (77 medial and 16 lateral) and 120 meniscal tears (107 medial and 13 lateral).

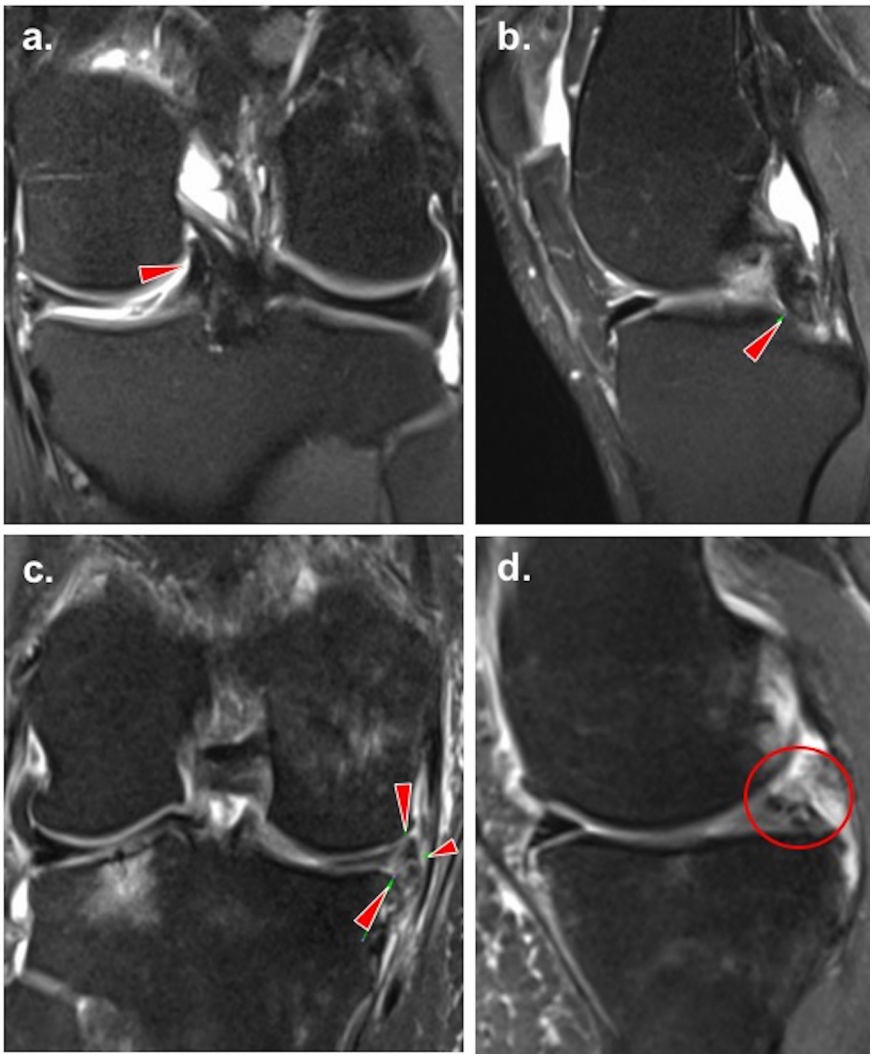


Figure 3.2. Coronal proton-density fat-saturated MR images (a, c) and sagittal images (b, d) demonstrate bucket-handle tear (a, b; arrowheads) in the left knee of a 54-year-old man, and complex macerated (c, arrowheads; d, circle) meniscal tear in the right knee of a 57-year-old woman.

Articular cartilage abnormalities: prevalence, severity, location

There were 62% knees presenting with cartilage abnormalities on the MRI scans.

I found a number of knees with various types of cartilage defects, of different severity levels: grade 1 minor cartilage lesions (20% knees), grade 2 cartilage lesions (19%), grade 3 moderate cartilage lesions (19% knees), grade 4 severe cartilage lesions (31% knees). High-grade lesions (grade 3 and/or 4) were found in 41% knees (Table 3.4-3.5, Figure 3.3). Each knee could have multiple types of cartilage lesions of varying grades of severity in more than one location.

The most affected knee compartment was the patellofemoral joint (57% knees), with the prevalence of lesions being significantly higher than in the medial or lateral tibiofemoral compartments ($p<0.0001$, respectively; Chi-squared test).

In terms of the number of lesions in knees, there were 253 cartilage lesions in total: 180 patellofemoral and 73 tibiofemoral ones; 56 grade 1, 45 grade 2, 45 grade 3, 107 grade 4.

Table 3.4. Prevalence of MRI abnormalities of the articular cartilage and bone marrow in 230 asymptomatic knees (per knee compartments)

Anatomical structure	Number (%) of knees graded per structure*					
	0	**1**	**2**	**3**	**4**	**Any grade≥1**
Cartilage	Cartilage abnormalities					
Patellofemoral	100 (43%)	37 (16%)	32 (14%)	28 (12%)	57 (25%)	130 (57%)
Medial tibiofemoral	190 (83%)	11 (5%)	9 (4%)	6 (3%)	14 (6%)	40 (17%)
Lateral tibiofemoral	207 (90%)	9 (4%)	2 (1%)	4 (2%)	10 (4%)	23 (10%)
Any knee compartment**	87 (38%)	46 (20%)	43 (19%)	43 (19%)	71 (31%)	143 (62%)
Bone marrow	BME					
Patellofemoral	132 (57%)	24 (10%)	39 (17%)	11 (5%)	-	98 (43%)
Medial tibiofemoral	200 (87%)	13 (6%)	14 (6%)	5 (2%)	-	30 (13%)
Lateral tibiofemoral	215 (93%)	5 (2%)	9 (4%)	2 (1%)	-	15 (7%)
Any knee compartment**	111 (48%)	42 (18%)	57 (25%)	16 (7%)	-	119 (52%)

*Grades were defined according to a modified Noyes system [231,244,246] for cartilage lesions and KOSS, Knee Osteoarthritis Scoring System [242], for BME, bone marrow edema. **Any abnormalities in any of the knee joints. The percentages do not add up to 100% because each knee could have more than one type/grade of lesion, in more than one location or subregion. All knees with any type of lesion 1-4 were counted separately to avoid counting the same knees more than once.

Table 3.5. Prevalence of MRI abnormalities of the cartilage and bone marrow in 230 asymptomatic knees (per knee compartment subregions)

Anatomical structure		Number (%) of knees graded per structure*					
		0	**1**	**2**	**3**	**4**	**Any grade≥1**
Cartilage		Cartilage abnormalities					
Patella	Medial	144 (63%)	19 (8%)	16 (7%)	17 (7%)	34 (15%)	86 (37%)
	Lateral	159 (69%)	15 (7%)	15 (7%)	11 (5%)	30 (12%)	71 (31%)
Trochlea	Medial	225 (98%)	0 (0%)	0 (0%)	3 (1%)	2 (1%)	5 (2%)
	Central	218 (95%)	0 (0%)	2 (1%)	3 (1%)	7 (3%)	12 (5%)
	Lateral	224 (97%)	0 (0%)	1 (0.4%)	0 (0%)	5 (2%)	6 (3%)
Femur	Medial	193 (84%)	11 (5%)	8 (3%)	6 (3%)	12 (5%)	37 (16%)
	Lateral	211 (92%)	6 (2%)	1 (0.4%)	4 (2%)	8 (3%)	19 (8%)
Tibia	Medial	222 (97%)	1 (0.4%)	1 (0.4%)	0 (0%)	6 (3%)	8 (3%)
	Lateral	221 (96%)	4 (2%)	1 (0.4%)	1 (0.4%)	3 (1%)	9 (4%)
Bone marrow		BME					
Patella	Medial	192 (83%)	13 (6%)	19 (8%)	6 (3%)	-	38 (17%)
	Lateral	190 (83%)	12 (5%)	20 (9%)	8 (3%)	-	40 (17%)
Trochlea	Medial	226 (98%)	0 (0%)	4 (2%)	0 (0%)	-	4 (2%)
	Central	225 (98%)	0 (0%)	4 (2%)	1 (0.4%)	-	5 (2%)
	Lateral	222 (97%)	3 (1%)	4 (2%)	1 (0.4%)	-	8 (3%)
Femur	Medial	207 (90%)	10 (4%)	11 (5%)	2 (1%)	-	23 (10%)
	Lateral	222 (97%)	2 (1%)	6 (3%)	0 (0%)	-	8 (3%)
Tibia	Medial	213 (93%)	5 (2%)	8 (3%)	4 (2%)	-	17 (7%)
	Lateral	219 (95%)	4 (2%)	5 (2%)	2 (1%)	-	11 (5%)

*Grades were defined according to a modified Noyes system [231,244,246] for cartilage lesions and KOSS, Knee Osteoarthritis Scoring System [242], for BME, bone marrow edema. The percentages do not add up to 100% because each knee could have more than one type/grade of lesion, in more than one location.

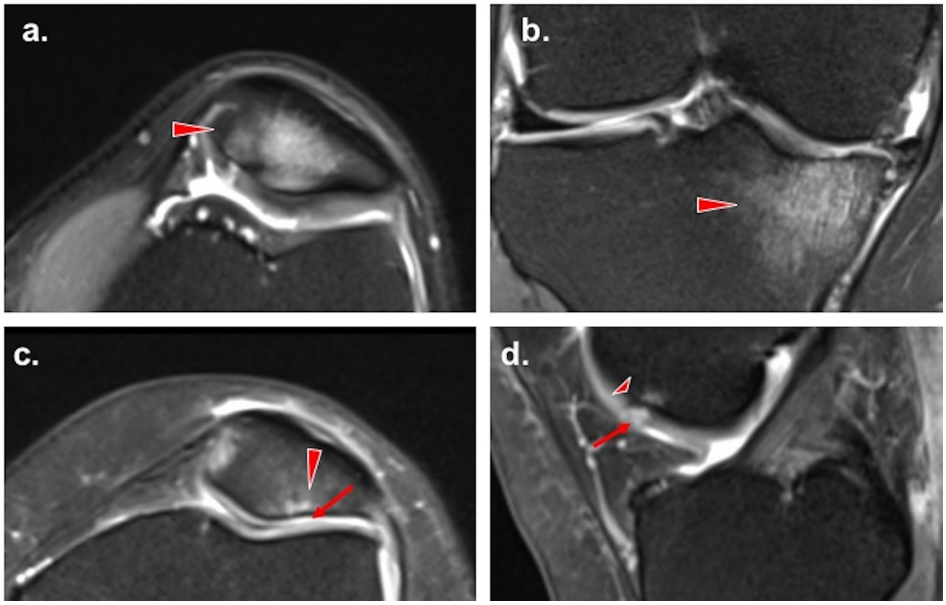


Figure 3.3. Axial proton-density fat-saturated MR images (a, c), coronal (b) and sagittal images (d) of high grade BME-like lesion (grade 3: diameter ≥20mm; in the a-patella of the left knee of a 40-year-old man, b-tibia of the right knee of a 59-year-old man; arrowheads) **and high grade cartilage defect** (grade 4: full thickness defect exposing the bone; in the c–patella of the left knee of a 44-year-old woman; arrow; with subchondral BME, arrowhead; d–femur of the right knee of a 31-year-old woman; arrow; with subchondral ganglion cyst; small arrowhead). Grading is based on KOSS, Knee Osteoarhritis scoring system [242]; BME, bone marrow edema.

Bone marrow abnormalities: prevalence, severity, location

I identified 52% knees with BME on the MRI scans (see Tables 3.4-3.5). In terms of grades of severity based on the size of edema-like lesions, there were grade 1 minor lesions (18% knees), grade 2 moderate lesions (25% knees), grade 3 severe lesions (7% knees). High-grade lesions (grade 2 and/or 3) were found in 27% knees (Figure 3.3). Each knee could have a number of BME-like lesions of different grades of severity in more than one location.

Similarly to the cartilage, the region of the knee with the highest prevalence of BME was the patellofemoral compartment (43% knees); the difference between the different compartments was statistically significant ($p < 0.0001$, respectively; Chi-squared test).

Regarding the total number of lesions in these knees, there were 154 BME cases in total: 95 patellofemoral and 59 tibiofemoral ones; 49 grade 1, 81 grade 2, 24 grade 3.

Additionally, there were 16% knees with subchondral cysts. Specifically, 5% hips had grade 1 minor lesions, 9% had grade 2 moderate lesions and 3% grade 3 severe lesions. The patellofemoral compartment was most affected, in 13% knees, while the medial and lateral tibiofemoral compartments presented with cysts in 3% knees each, respectively.

Lesions of different grades of severity could have been present in more than one subregion of the same knee. In total, there were 50 subchondral cysts in knees, out of which 33 were in the patellofemoral compartment; 25 grade 1, 24 grade 2, 11 grade 3.

Tendon abnormalities: prevalence, severity, location

Tendon abnormalities were present in 46% knees (Figure 3.4, Table 3.6). The degree of severity varied from: grade 1 minor increased signal intensity (22% knees), grade 2 moderate signal intensity (21% knees) and grade 3 lesions/high-grade tendonitis (6% knees; Figure 3.4).

The patellar tendon was the most affected tendon in terms of abnormal MRI appearances (27% knees), followed by the quadriceps tendon (13% knees), semimembranosus (10% knees), gracilis (3% knees) and sartorius (1% knees). Each knee could have multiple tendon abnormalities of varying grades of severity in more than one location. There were 123 abnormalities in total: 61 patellar, 29 quadriceps, 23 semimembranosus, 8 gracilis, 2 sartorius; 55 grade 1, 51 grade 2, 17 grade 3.

Iliotibial band signal was found in 1% knees (3 abnormalities).

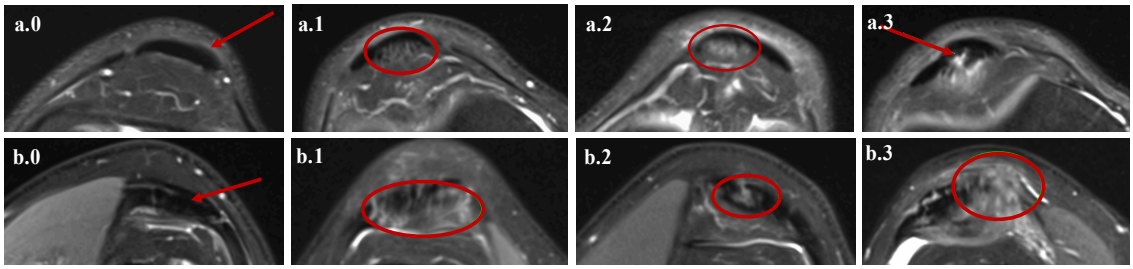


Figure 3.4. Axial proton-density fat-saturated MR images of (a) patellar tendons (a.0, grade 0; in the left knee of a 40-year-old man; a.1, grade 1; in the right knee of a 62-year-old man; a.2, grade 2; in the left knee of a 56-year-old man; a.3, grade 3; in the right knee of a 44-year-old man) **and (b) quadriceps tendons** (b.0, grade 0; left knee of a 40-year-old man; b.1, grade 1; in the right knee of a 40-year-old woman; b.2, grade 2; in the left knee of a 44-year-old man; b.3, grade 3; in the right knee of a 48-year-old man). The tendons and their related abnormalities are indicated by red arrows or circles, and grading is based on Johnson *et al* [254].

Table 3.6. Prevalence of MRI abnormalities of the knee tendons and ligaments of 230 asymptomatic knees

Anatomical structure	Number (%) of knees graded per structure*				
	0	**1**	**2**	**3**	**Any grade≥1**
Tendons	Tendon abnormalities				
Patellar	169 (73%)	30 (13%)	26 (11%)	5 (2%)	61 (27%)
Quadriceps	201 (87%)	9 (4%)	16 (7%)	4 (2%)	29 (13%)
Semimembranosus	207 (90%)	11 (5%)	9 (4%)	3 (1%)	23 (10%)
Sartorius	228 (99%)	1 (0.4%)	0 (0%)	1 (0.4%)	2 (1%)
Gracilis	222 (97%)	4 (2%)	0 (0%)	4 (2%)	8 (3%)
Any tendon	124 (54%)	51 (22%)	48 (21%)	14 (6%)	106 (46%)
Iliotibial band	227 (99%)	3 (1%)	0 (0%)	9 (0%)	3 (1%)
Ligaments	Ligament abnormalities				
ACL	151 (66%)	75 (33%)	4 (2%)	0 (0%)	79 (34%)
PCL	228 (99%)	1 (0.4%)	1 (0.4%)	0 (0%)	2 (1%)
MCL	224 (97%)	4 (2%)	2 (1%)	0 (0%)	6 (3%)
LCL	227 (99%)	3 (1%)	0 (0%)	0 (0%)	3 (1%)
Any ligament	143 (62%)	81 (35%)	7 (3%)	0 (0%)	87 (38%)

*Grades were defined according to Johnson *et al* [254] for tendon abnormalities and ACLOAS, Anterior Cruciate Ligament Osteoarthritis Score [235] for ligamentous abnormalities. The presence of iliotibial band signal was specified [243]. The percentages do not add up to 100% because each knee could have more than one type/grade of lesion, in more than one location. All knees with any type of lesion 1-3 were counted separately to avoid counting the same knees more than once; ACL, anterior cruciate ligament; PCL, posterior cruciate ligament; MCL, medial collateral ligament; LCL, lateral collateral ligament.

Ligamentous abnormalities: prevalence, severity, location

Ligamentous abnormalities were showed on 38% MRI knee scans (Table 3.6). Varying grades of severity were identified: grade 1 thickened ligament (35% knees), grade 2 partial ligament rupture (3% knees). No grade 3 lesions were found. Each knee could have multiple types of ligament abnormalities on MRI of varying levels of severity in more than one location.

Out of all the ligaments around the knee joint, the ACL had the highest prevalence of abnormalities (34% knees). Other types of ligaments presented only with few abnormalities, ranging from 1%-3% knees (Table 3.5).

In total, there were 90 abnormalities: 79 ACL, 6 MCL, 3 LCL, 2 PCL; 83 grade 1, 7 grade 2.

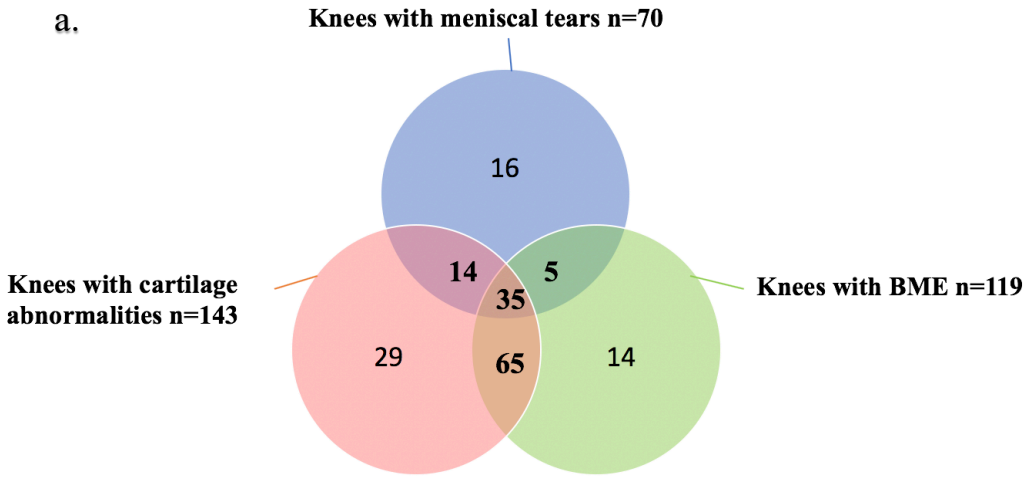
Other findings

There were 49% knees with joint effusion (n=113), with most of these knees having grade 1 small effusion (n=105) and few presenting with grade 2 moderate (n=7) and grade 3 severe effusion (n=1). Hoffa's synovitis was present in 23% knees - all grade 1 mild synovitis.

A number of other findings were detected, including cysts and bursal collections: Baker's cyst (33% knees), other ganglion cysts (20% knees), prepatellar bursitis (26% knees), pes anserine bursitis (6% knees).

3.3.3 Associations between different MRI findings

I analysed all the knees presenting with different types of joint structure abnormalities to identify any associations between the presence of certain types of abnormalities and the presence of other type of abnormalities in the same knees (Figure 3.5, Table 3.7). I found that the presence of abnormal cartilage signal (score >0) was associated with an increased prevalence of BME-like lesions in knees ($p<0.0001$). Specifically, the odds of the participants' knees presenting with cartilage abnormalities to be accompanied by BME were 8.0 (95% CI, 1.6–10.3; $p=0.002$), especially within the same corresponding knee compartment. There were no other associations between other types of lesions on the knee MRIs.



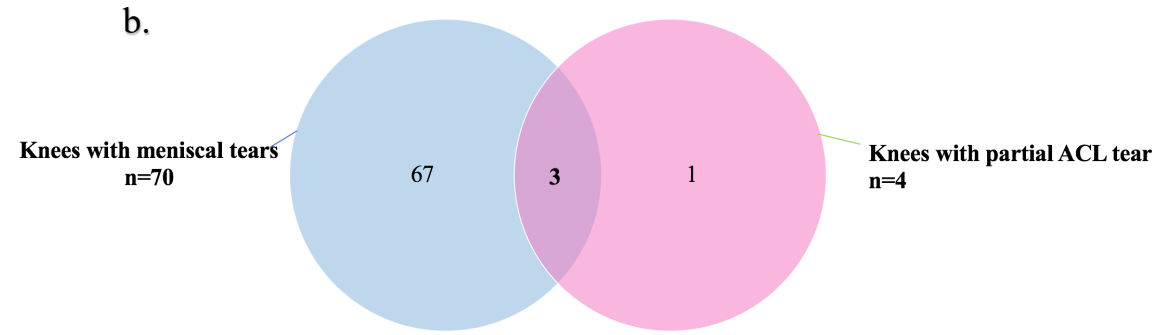


Figure 3.5. Associations between key outcomes: Number of knees with concomitant different types of abnormalities (Venn diagrams a, b).

Table 3.7. Concomitant abnormalities in 230 knees

Types of concomitant abnormalities	Number of knees with concomitant abnormalities
Knees with meniscal tears and cartilage abnormalities (no BME)	14
Knees with meniscal tears and BME (no cartilage abnormalities)	5
Knees with cartilage abnormalities and BME (no meniscal tears)	65
Knees with meniscal tears, cartilage abnormalities and BME	35
Knees with meniscal tears and ACL rupture	3

ACL, anterior cruciate ligament; BME, bone marrow edema.

3.3.4 Distribution of MRI findings in participants and per knee side

The majority of cartilage abnormalities and BME-like lesions were found in both knees of participants (74% and 65%, respectively; see Table 3.8). Regarding the menisci, tendons and ligaments, just under half of each type of lesion, in each case, were found in both knees of participants presenting with abnormalities, with the rest being located in either the left or right side.

Table 3.8. **Number of participants with both knees or single knees showing abnormalities on MRI, respectively, and total number of affected knees, in the meniscus, articular cartilage, bone marrow, tendons and ligaments.**

Key knee abnormalities	No. of participants (%) with changes in both knees	No. of participants (%) with changes in single knee sides		Total no. of participants (%) with changes in knees	Total no. of knees (%) with changes		
		Right knee	Left knee		Right knee	Left knee	All knees
Meniscal tears	23 (49%)	8 (17%)	16 (34%)	47 (100%)	31 (44%)	39 (56%)	70 (100%)
Cartilage abnormalities	61 (74%)	13 (16%)	8 (10%)	82 (100%)	74 (52%)	69 (49%)	143 (100%)
BME	47 (65%)	15 (21%)	10 (14%)	72 (100%)	62 (52%)	57 (48%)	119 (100%)
Tendon abnormalities	31 (41%)	26 (35%)	18 (24%)	75 (100%)	57 (54%)	49 (46%)	106 (100%)
Ligament abnormalities	28 (47%)	16 (27%)	15 (25%)	59 (100%)	44 (51%)	43 (49%)	87 (100%)

BME, bone marrow edema.

Other findings which were not included in the table included those with **1) increased prevalences in both knees**: effusion [in 76 participants – 17 right (22%), 22 left (29%), 37 both (49%)], Hoffa's synovitis [33 participants – 6 right (18%), 7 left (21%), 20 both (61%)], or **2) slightly more in the right knee than the left knee or both knees**: subchondral cysts [27 participants – 13 right (48%), 5 left (19%), 9 both (33%)], iliotibial band signal [3 participants – 2 right (67%), 1 left (33%)], ganglion cysts [38 participants – 19 right (50%), 11 left (29%), 8 both (21%)], prepatellar bursitis [44 participants – 18 right (41%), 11 left (25%), 15 both (34%)], or **3) slightly more in the left knee**: Baker's cyst [56 participants – 11 right (20%), 25 left (45%), 20 both (35%)], or **4) similar prevalences in either the left or right knee**: meniscal signal [in 37 participants – 16 right (43%), 17 left (46%), 4 both (11%], pes anserine bursitis [11 participants – 4 right (36%), 5 left (45%), 2 both (18%)].

3.3.5 Associations between MRI findings and participant characteristics

The prevalence of MRI abnormalities was found to be higher with increasing age. The mean age for participants presenting with meniscal tears (47.5 ± 9.9 years; n=50) tended to be greater than that of tear-free individuals (42.6 ± 7.0; n=65); p=0.0027, unpaired *t* test. The mean age for participants showing edema on MRI was 46.4 ± 8.9 years (*n*=72), which was slightly greater than the mean age for participants with no edema: 42.0 ± 7.8 (*n* = 43); p=0.0071, unpaired *t* test. Regarding cartilage lesions,

I found that participants who were aged 40 years old or over (n=90) were 4.0 times more likely to encounter such abnormalities on MRI (95% CI, 1.6–10.3; p=0.0023). High grade abnormalities (score 3 or 4) were present in 57% of the participants aged ≥40 years old (51/90) and in 40% of those aged <40 years old (10/25). The differences were not found to be statistically significant for these associations; p=0.140, Chi-squared test.

There were no associations between the presence of specific MRI abnormalities and gender.

In terms of BMI, there were no significant differences between the BMIs of the participants with most types of MRI abnormalities and those without abnormalities. Only for tendon abnormalities significant differences were found (p=0.0002). The participants with BMI ≥ 25 kg/m^2 were 3.3 times more likely to have tendon abnormalities on MRI (95% CI, 1.5–7.6). High grade tendonitis (score 2 or 3) were identified in 47% participants with BMI ≥ 25 kg/m^2 (28/60), and in 33% participants with BMI < 25 kg/m^2 (18/55). However, the differences did not appear to be statistically significant; p=0.128, Chi-squared test.

3.3.6 Double-reporting consensus

There was substantial interobserver agreement between the scores assigned by the 2 radiologists for the double-reported subset of MRI scans (kappa 0.790). Any discrepancy between the scores was discussed in a meeting between the radiologists and consensus scores were decided on.

3.3.7 KOOS results

The KOOS scores for each individual questionnaire item were on average $\geq 90/100$, specifically: symptoms (90.0 ± 14.0); pain (94.9 ± 8.8); function in daily living (97.1 ± 6.5); function in sport and recreation (92.3 ± 11.6); knee-related quality of life (90.4 ± 13.8).

3.4 DISCUSSION AND CONCLUSIONS

Overall, a high prevalence of knee joint abnormalities were reported on the 3.0 T MRI scans of asymptomatic physically inactive adults, before engaging into the marathon training programme. A number of pathologies were identified: meniscal tears (including bucket-handle and complex tears for the first time in asymptomatic knees), cartilage lesions and BME (including moderate to severe grade lesions), tendon and ligament abnormalities, joint effusion, cysts and bursal collections. The meniscal tears were commonly reported in the medial region, while cartilage lesions and BME-like lesions were most frequently found in the patellofemoral compartment. Also, the patellar tendon and ACL were the most affected tendons and ligaments, respectively. This suggests that the patellofemoral compartment was the area of the knee presenting with the highest incidence of asymptomatic abnormalities among the assessed structures. Moreover, our data showed that the prevalence of MRI findings increased with age, and also with weight, in certain cases i.e. tendon abnormalities.

The types of MRI pathologies of uninjured adults that were identified in our study were consistently found in the literature. However, the prevalence of these pathologies adults exceeded the estimated prevalences in the literature. This is perhaps because we used high-resolution 3.0 T MRI to detect even subtle lesions, in comparison to most other studies which included lower resolution MRI techniques (80% studies), plus our analysis included a thorough assessment of all knee regions and subregions.

The KOSS questionnaire scores ($\geq 90/100$) indicated that our study participants did not self-report any pain, symptoms or other complaints of functional limitations. Therefore this confirmed that they had no perceived knee problems, despite the observed abnormalities that the radiologists reported on MRI.

3.4.1 Study strengths

The key strengths of our study are the following: big sample size, reliable MRI technology and equipment (high-resolution 3.0 T MRI and multichannel coil), comprehensive analysis of all knee joint features based on validated scoring systems.

Firstly, this study included the largest number of knees ever scanned with high-resolution 3.0 T MRI in a study of asymptomatic physically inactive adults (230 knee MRI scans). Eleven studies to date used 3.0 T MRI to evaluate the health status of asymptomatic knees of adults (non-runners). The number of assessed knees in these MRI studies was not

higher than 95 [209,226,237,252,281–287], and our study included more than twice this number for increased reliability of the findings.

In comparison with the commonly used 1.5 T MRI scanner, the improved diagnostic reliability of the 3.0 T MRI scanner was demonstrated by higher sensitivity for detecting the morphological characteristics of a number of joint structures and related pathologies [191,193,288]. Additionally, the use of multichannel coil equipment provides further advantages of increased spatial resolution and excellent accuracy in identifying and differentiating between different tissues surrounding the joint [276,277].

Furthermore, our study provided a detailed evaluation of all knee joint features, including an in-depth assessment of all regions, subregions, knee compartments. Also, each type of lesion was classified based on its specific grade of severity according to validated scoring systems. These helped us understand not only the presence of a lesion in a specific location, but also the extent of injury. In comparison to previous studies which only focused on assessing certain knee structures or did not report full details on the specific location of lesions, as well as affected subregions, here we conducted a very comprehensive analysis of all asymptomatic knees, revealing which knee areas are most susceptible to lesions and signal changes and how severe those abnormalities are on MRI.

3.4.2 Study limitations

Firstly, double-reporting was not performed for all the knee MRI scans of our participants, but only for a subset of scans. We agreed internally to have one experienced senior musculoskeletal radiologist at consultant level to report all MRI scans, while a second radiologist, with similar level of experience, to co-report 20% of the cohort's MRI scans in our study. I did not find any major discrepancies between the reports of the two radiologists, so we decided, as a research team, to stick to 20% instead of co-reporting all the scans for the whole cohort. We considered that the single-reporting of the remaining scans (80%) was reliable. A number of studies only included one radiologist for MRI reporting, therefore we consider it as an additional advantage to the study to include a second radiologist and thus confirm the findings from a subset of the sample. In previous imaging studies, double-reporting was done for a 10% subset of the total number of study participants [289]. Therefore, to increase reliability of our study findings our research group decided to double this to a 20% subset. I randomly selected those 20% of the cohort to avoid bias.

Moreover, a recent systematic review identified only low discrepancy rates following double-reporting of all scans in studies. There are conflicting opinions on the value of double reading and the benefits need to be balanced for each research group considering that the process is resource and time consuming and errors may be negligible [290].

Another limitation of our study may be the use of self-reported KOOS questionnaires and self-reported personal data collection at recruitment, which may involve a certain degree of bias. However, in general, self-reported data collection may have some disadvantages due to the intrinsically biased nature of questionnaires, which cannot be avoided. This will depend on the feelings and behaviour of respondents at the time of completing the questionnaires. The answers to the KOOS questions may sometimes be exaggerated, or, on the contrary, minimised, or influenced by a variety of subjective reasons [291–293]. When it comes to questions regarding their history of past injuries and previous physical activity levels, there is a risk that participants might have omitted or forgotten certain details, or some participants may not keep track of minor injuries suffered in the past which could potentially be related to specific asymptomatic abnormalities discovered on the MRI scans in our study. Also, we did not organise an orthopaedic exam of each knee to test their clinical symptoms, however we used the validated KOOS questionnaire to confirm the participants' perceived knee condition which is considered to have great reliability.

Another potential limitation is that our study evaluated participants from one ethnic group only, therefore the study results may not be generalised and applied directly to other ethnicities. Further multicentre studies including various population groups of different ethnic background and nationalities, are needed to clarify this aspect.

Moreover, our evaluation of the meniscus included the medial and lateral menisci, as well as the main two subregions – anterior horn and posterior horn, however the meniscal body was not assessed separately. Therefore, there is a possibility that few meniscal abnormalities might have been missed out in this way or counted as part of the two horns depending on the extent of the abnormality.

Finally, the clinical significance of our MRI findings in asymptomatic knees is currently not very clear. Long-term follow-up studies are required to better understand the clinical importance of our MRI results, to clarify whether symptoms develop over time or whether progression of knee joint pathologies such as OA may occur later on. Specifically,

changes in the key knee joint structures will need to be monitored over time: meniscus, articular cartilage, bone marrow, tendons and ligaments.

3.4.3 Comparison with previous studies

So far, a number of research groups investigated the internal knee joint structures of uninjured individuals using MRI. Recently, Culvenor *et al* [269] summarised the existing evidence on the prevalence of knee abnormalities on MRI in asymptomatic adults. The pooled results from 63 studies (5397 knees of 4751 adults) were presented in this systematic review.

One of the most interesting findings is the prevalence of meniscal tears in symptom-free knees. There were 44 studies (3761 knees from 2817 adults) that analysed the participants' knees for changes in meniscal morphology on MRI and the pooled prevalence of the meniscal tears that they found was 10% (95% CI, 7 to 13%; $I^2 = 87.2\%$, whereby I^2 is a measure of quantifying the degree of heterogeneity among studies) [269]. In our study, I identified a much higher prevalence of meniscal tears in 30% knees – three times higher than in the literature. Also, meniscal tears were significantly more prevalent in the medial region than the lateral region, in studies including participants aged ≥40 years old (p=0.009). This is in agreement with our study whereby medial meniscal tears were most common on the MRI scans. Furthermore, I found a wide range of meniscal tears patterns which are not all commonly identified in asymptomatic adults. Specifically, the radiologists reported the presence of horizontal, vertical, radial, bucket-handle and complex tears. While horizontal meniscal tears may be encountered more often in both symptomatic and asymptomatic populations and may not be related to symptoms, other types of tears such as bucket-handle and complex tears are usually exclusively found in symptomatic populations. Consequently, this might suggest that they could have a particular clinical relevance which needs to be investigated further. Degraded or torn meniscus may result in increased cartilage contact stress leading to cartilage loss which can be linked to a possible OA disease process [294,295].

Regarding high-grade cartilage lesions, Culvenor *et al* identified 42 studies (4322 knees from 3446 adults) and, overall, estimated a pooled prevalence of 24% knees with partial and/or full thickness cartilage loss (95% CI, 15 to 34%; $I^2 = 97.8\%$) [269]. In our study, a greater prevalence of 41% cartilage lesions of moderate to severe grading was reported. Moreover, grade 4 lesions were the most frequently encountered type of cartilage lesions

on the MRI scans (31% knees). Therefore, it is essential to better understand the clinical significance of these findings, including the multitude of factors that may increase the risk of getting cartilage injuries and also the mechanisms of pathology that may involve to then develop strategies to prevent cartilage deterioration. Also, another interesting finding was that the patellofemoral compartment was the most affected region in our study, while the results from the systematic review showed no significant difference between the patellofemoral and tibiofemoral compartments.

BME-like lesions were specified in 34 studies (4089 knees from 3255 adults). The overall pooled prevalence from these studies was calculated to be 18% (95% CI, 12 to 24%). Our study demonstrated a higher prevalence than in the literature, particularly of 27% knees presenting with BME of moderate to severe grade. This is again important to investigate further given the fact that BME, along with cartilage lesions, are thought to be associated with the early stages and progression of OA [296–298]. Also, regarding the location of abnormalities, the patellofemoral compartment was significantly more lesioned than the other knee regions, while in previous studies there were no significant differences in the number of lesions between the different knee compartments.

The prevalence of ligament tears was reported in 20 studies. In 16 of these studies, there were no ligament tears while in the remaining 4 studies the authors mentioned the presence of partial tears of the ACL or collateral ligaments, with prevalence rates ranging from 1-30% [269]. No full tears in asymptomatic knees were reported in any of these studies. In accordance with these findings, our study did not find any complete ligament tears and only few partial tears of the ACL and LCL were detected on MRI. Specifically, the prevalence reported in our study was 3%.

There is very limited evidence about the prevalence of tendon abnormalities in asymptomatic knees. Culvenor *et al* [269] did not report information about tendons in the literature review since the reviewed studies on asymptomatic adults did not collect MRI data on tendons. However, another study conducted by Matiotti *et al* [299] estimated a prevalence of 10.9% of tendon abnormality cases in adolescent soccer players with no knee symptoms. The cohort included young and physically active participants, differing significantly from our study participants who were physically inactive adults. Matiotti *et al* also included a group of controls who were young physically inactive volunteers and the prevalence was 4.9% in their case. Our study identified a higher prevalence of 26% knees with tendon abnormalities. The patellar tendon was most commonly affected both

in our study and in Matiotti *et al'*s study, which may indicate that this type of injury may lead to symptoms, pain or functional limitations in the future, and supports the need for closer surveillance of those cases. Early diagnosis can potentially inform preventive strategies against the progression of those injuries to serious symptomatic conditions [300–302].

In terms of participants' demographics, Culvenor *et al* [269] showed that the increased age is a risk factor for different types of MRI lesions. Similarly, our study also showed that the prevalence of MRI abnormalities is higher with age. Moreover, we demonstrated that overweight adults are more likely to develop load-bearing tendon thickening than adults with healthy weight (BMI values in normal range), and this has been confirmed by other studies [303–307].

3.4.3 Clinical significance and future work

The results of our study question the process of clinical decision making when it comes to arthroscopy and its use in treating injuries and alleviating symptoms. The large prevalence of knee abnormalities on the MRI scans of asymptomatic uninjured adults, as demonstrated in our study and other previous studies, provides evidence as to why surgical procedures based on MRI data may not necessarily be required unless certain circumstances are met. This is supported by several studies showing that the clinical efficacy of arthroscopy and other surgical procedures may not be significantly better than that of sham (placebo) surgery [269,308]. Sham surgery is a faked surgery that omits the presumably therapeutically-required intervention, and thus neutralises biases. For instance, the surgical removal of all or part of a torn meniscus (meniscectomy) does not seem to provide additional improved outcomes, such as reduced symptoms or functional limitations, than sham surgery [309]. Moreover, any surgical intervention has inherent risks which may develop into further complications after the surgery. The articular cartilage may be sensitised following a surgical procedure such as meniscectomy and potentially increase the risk of developing OA [138,310,311]. The loss of the load-protective function of the menisci after meniscectomy is speculated to lead to joint remodelling, with radiographic changes being frequently reported afterwards [295].

Although the use of high-resolution MRI has been on rise in the last years in both research and clinical settings, diagnosis and treatment-related decisions should not be made solely on the basis of MRI findings. Appropriate diagnosis should primarily involve a complete assessment of the patient's health history (including past injuries and other medical

conditions), a physical examination by a physician or experienced clinician (including an evaluation of the patient's symptoms and other clinical manifestations), and then imaging findings. The scans resulting from imaging modalities may help in supporting the conclusions from clinical assessments, however they should never substitute the clinical assessment or rely entirely on imaging results [312,313].

The MRI abnormalities that were found in our study, including meniscal tears, cartilage lesions, BME, tendon and ligament abnormalities, may be indicative of early signs of serious pathologies such as OA. Although no symptoms have been reported by the participants, there was a high prevalence of high grade lesions of increased severity level on the MRI scans, which cannot be neglected. The clinical implications of these findings need to be analysed in further studies with long-term follow-ups, to understand whether any changes in the MRI signal or in the self-reported knee symptoms occur over time and how these findings can be correlated better between each other. Future studies could assess whether the knee condition of those participants with MRI abnormalities will worsen over time in comparison to the knee condition of those participants with no apparent abnormalities on MRI. This will help in guiding the evaluation of those lesions to support diagnosis, treatment and prevention of injuries across the lifespan.

I planned to analyse the fate of these abnormalities with the impact of training for the marathon and the race itself in the next thesis chapters. Therefore I will discuss this in more detail in the following sections.

Chapter 4 – Knee study

Analysing the impact of marathon running on the knee joints of novice marathon runners

(short-term post-marathon data)

Work presented in this chapter has been published[1]

[1]Horga LM, Henckel J, Fotiadou A, Hirschmann AC, Di Laura A, Torlasco C, D'Silva A, Sharma S, Moon JC, Hart AJ. Can marathon running improve knee damage of middle-aged adults? A prospective cohort study. *BMJ Open Sport & Exercise Medicine* 2019;5:e000586. doi: 10.1136/bmjsem-2019-000586

4.1 INTRODUCTION

Long-distance running has gained significant popularity all around the world over the last decade [57]. Marathon running in particular has been anecdotally associated with musculoskeletal injuries, especially in relation to the knee joints. Given the increasing number of inexperienced runners as marathon entrants, of all ages and physical ability levels, this has resulted in increasing concerns regarding the effects of running on their health [314,315]. Furthermore, there has been a rise in the participation of older first-time marathon runners, which may, questionably, pose greater OA-related risks [314–317]. Currently, there is a lack of scientific and clinical data to support that a marathon may have detrimental effects on lower limb joints. Therefore, the effects of marathon running on the knee joint remain unclear.

Few studies have investigated the effects of marathon running on the internal knee structures by means of MRI and even fewer using high-resolution 3.0 T MRI, with inconclusive evidence as to whether this long-distance run is bad for the knees. The comparison between short-term post-marathon and pre-marathon results is very important to understand the spontaneous changes induced by marathon running. So far, short-term post-marathon intervals in studies varied from few minutes up to 3 days after the run. The main limitations of previous studies were the small sample size (<22 participants) and the varying study designs e.g. different MR field strength scanners (especially low-resolution MRIs), types of runners (only experienced long-distance runners), different pre-marathon and post-marathon follow-up intervals, varying choice of knee structures being evaluated, limited or no use of reliable validated scoring systems to assess all knee features, undetermined clinical relevance [43,176,225–229,318]. Having said that, there is no data to suggest that taking part in a marathon run may result in significant morphologic changes in the knee MRI scans of runners shortly after the run. Moreover, no study to date evaluated the impact of a marathon running and training on the knees of inexperienced long-distance runners, participating in their first marathon ever.

4.1.1 Motivation

It is essential to better understand how the knee condition of totally inexperienced novice marathon runners changes after the impact of both a 4-month beginner training plan with gradual increase in mileage and the marathon run itself. The motivation was to understand how marathon running impacts the knee joint shortly after the run – specifically 2 weeks

later - which regions and structures of the knee are most affected and how to best minimise or prevent the risk of injury.

4.1.2 Aim

To compare between the knee outcomes of novice marathon runners before starting the training for the marathon run and then shortly after completing the marathon run.

4.1.3 Objectives

To assess the short-term effects of marathon running and preceding training plan on the knee joints of novice marathon runners using morphological high-resolution 3.0 T MRI, MRI-based knee scoring systems and self-reported questionnaires.

4.2 MATERIALS AND METHODS

I was responsible for reviewing the relevant literature and collecting the data. The experienced radiologists used the same MRI sequences and methodology as the ones in Chapter 3 and reported the MRI results based on the same scoring systems. The Chief investigator and the other PhD supervisors from the research team were involved in organising the post-marathon scans while providing the appropriate training to me while I was assisting the process.

4.2.1 Study design and participants

This is a prospective, longitudinal cohort study. All participants provided written informed consent before joining the study.

As discussed in Chapter 3, 115 asymptomatic volunteers were initially recruited who signed up for their first marathon ever, the 2017 Virgin Money London Marathon. The inclusion criteria were described in Chapter 3, and included: physically inactive adult volunteers, with no long-distance running experience, no present knee injuries, no history of knee injuries, no history of cardiac health issues. Volunteers aged under 18 years old, pregnant or breastfeeding women, experienced marathon runners or long-distance runners, individuals with contraindications to MRI scanning, or presenting with symptomatic knee injuries (present or past lesions) or poor cardiac outcomes were not included in our study.

All 115 participants had MRI scans of both knees 2 months before starting a 4-month beginner training plan for the marathon, so 6 months before the actual race day (pre-marathon/trainings scans). The training programme for all participants was a 4-month standardised running schedule in preparation for the marathon run, which was provided by the organisers of the Virgin London Marathon and was available for free on their website. The beginner training plan was based on a gradual increase in the number of miles run throughout the 4-month period of time (www.virginmoneylondonmarathon.com/trainingplans; Appendix A.1.2).

Shortly after the race, all marathon participants were invited to come to a second MRI scanning session to assess any changes occurring in their knees following the training for the marathon and the marathon run itself (post-marathon/training scans). The short-term post-marathon scanning sessions were organised 2 weeks after the race day, according to participants' availability and our research groups' resources for facilitating the scanning sessions.

In this study the knee MRI scans of novice marathoners were compared at two different time points: time point 1 (6 months pre-marathon), time point 2 (2 weeks post-marathon).

4.2.2 MRI protocol

The same equipment was used to perform morphological MRI assessment of both knees of participants 6 months before and 2 weeks after the marathon: a 3.0 T MRI scanner (Prisma, Siemens Healthcare, Germany) and dedicated multichannel knee coil. Each bilateral MRI scan per participant took 25 minutes to complete. We used PD FS TSE sequences for the acquisition of images, in the appropriate contrast, for the visualisation of knee joints and surrounding soft tissues. The full protocol is described in Chapter 3.

4.2.3 Image analysis

Both the pre-marathon and post-marathon MRI scans were analysed and compared on a PACS workstation by an experienced musculoskeletal radiologist. Additionally, the scans from 20% of the initial cohort were reviewed separately by a second experienced radiologist, at both time points. The same two radiologists described in Chapter 3 were included here.

Any differences in the scores assigned by the two radiologists in the process of co-reporting the MRI scans were reviewed and discussed. Consensus scores were agreed on during a second MRI scanning session.

4.2.4 Quantification of MRI findings

All knee joint features were assessed at both time points using validated scoring systems. The main internal knee structures that were evaluated are: meniscus, articular cartilage, bone marrow, tendons, ligaments. A summary of the scoring systems used in this study is provided in Table 4.1. The full description of anatomical divisions and scoring systems for each knee feature is described in Chapter 3. The radiologists assigned scores for each individual region and subregion for each structure.

Table 4.1. MRI-based scoring systems for knee joint features

Knee feature	Scoring system name (scale)
Meniscus	BLOKS (0-7) [236] and ACLOAS (0-8) [235]
Articular cartilage	New Modified Noyes (0-4) [231,244,246]
Bone marrow	KOSS (0-3) [242]
Tendons	Johnson et al (0-3)
Iliotibial band	MOAKS (0-1) [243]
Ligaments	ACLOAS (0-3) [235]
Joint effusion	WORMS (0-3) [199]
Hoffa's synovitis	MOAKS (0-3) [243]
Bursal collections*	MOAKS (0-1) [243]
Cysts**	MOAKS (0-1) [243]
Other findings	MOAKS (0-1) [243]

BLOKS, Boston Leeds Osteoarthritis Knee Score; ACLOAS, Anterior Cruciate Ligament OsteoArthritis; KOSS, Knee Osteoarthritis Scoring System; WORMS, Whole-Organ Magnetic Resonance Imaging Score; MOAKS, MRI Osteoarthritis Knee Score. *Bursal collections: prepatellar bursitis, pes anserine bursitis; **Cysts: Baker's cyst, other ganglion cysts.

4.2.5 KOOS questionnaire

KOOS questionnaires were given to all participants at the two time points in relation to the marathon, on the specific day of each MRI scanning session. The same unmodified copy of the KOOS questionnaire was provided at each time point. Firstly, the pre-marathon KOOS questionnaire aimed to confirm the symptom-free status and good functioning of all the participants' knees at the beginning of the study, before starting the marathon training plan. Then, the post-marathon KOOS questionnaire aimed to provide information about any changes in their perceived knee symptoms, function and impact on their activities, after the training for/and the marathon run. KOOS score calculations were made based on the explanation provided in Chapter 3.

4.2.6 Statistical analysis

Both knees of our study participants were assessed independently in our analysis. Unpaired t-test was performed to evaluate differences in age between the two groups of participants (those who finished the training for/and the marathon, and those who stopped during training). Two sample t-test compared and evaluated if there were any significant differences in BMI between the groups of participants. Gender differences were assessed using Chi-squared test. Paired t-test was used to assess significant differences between the BMI values before and after the marathon. The pre-marathon and post-marathon datasets of assigned scores per each region of each knee were compared with Wilcoxon test. The KOOS scores of study participants before and after the marathon were compared for each questionnaire item. Interreader agreement was estimated based on kappa analyses. Statistically significant results were indicated by p-values<0.05 (GraphPad Prism, V.6.0 c).

4.3 RESULTS

I was responsible for all the data collation, synthesis and analysis including the MRI-based scores reported by radiologists and the data from the self-reported questionnaires completed by the study participants. Also I conducted statistical tests, wrote the manuscript and worked on disseminating the research findings. I received some radiology training on MRI interpretation, however the MRI data and clinical implications were

discussed with the radiologists and medical research team. The supervisors evaluated the analysis and write-up.

4.3.1 Participant characteristics

Out of the 115 participants who were initially recruited to our study and started the training for the marathon, 31 were not able to complete the 4-month training programme and stopped due to various reasons. None of those 31 training non-finishers attempted to run on the marathon day. The reasons for training discontinuation were not related to their pre-training health status: 1 bronchitis, 1 bradycardia, 2 knee injury during training, 2 calf issues, 1 plantar fasciitis, 1 Achilles tendonitis, 2 metatarsal stress fracture, 2 personal reasons, 19 undisclosed reasons.

The remaining 84 participants completed the 4-month training and started the race on the London Marathon day. Out of the 84 marathon starters, only one did not finish the race while all the others completed the marathon run.

All study participants - both marathon finishers and training non-finishers – were invited to attend the post-marathon MRI scanning session held 2 weeks after the race day. There were 82 participants who agreed to attend the scans: 71/83 marathon finishers and 11/31 training non-finishers; the rest who did not attend were study dropouts. Thus, these 82 participants underwent MRI scans at two time points, both pre-marathon/pre-training and post-marathon/post-training. Training non-finishers were included and scanned again at the 2nd time point in order to compare their knee outcomes to those of marathon runners' (see Figure 4.1 for a summary of the study design).

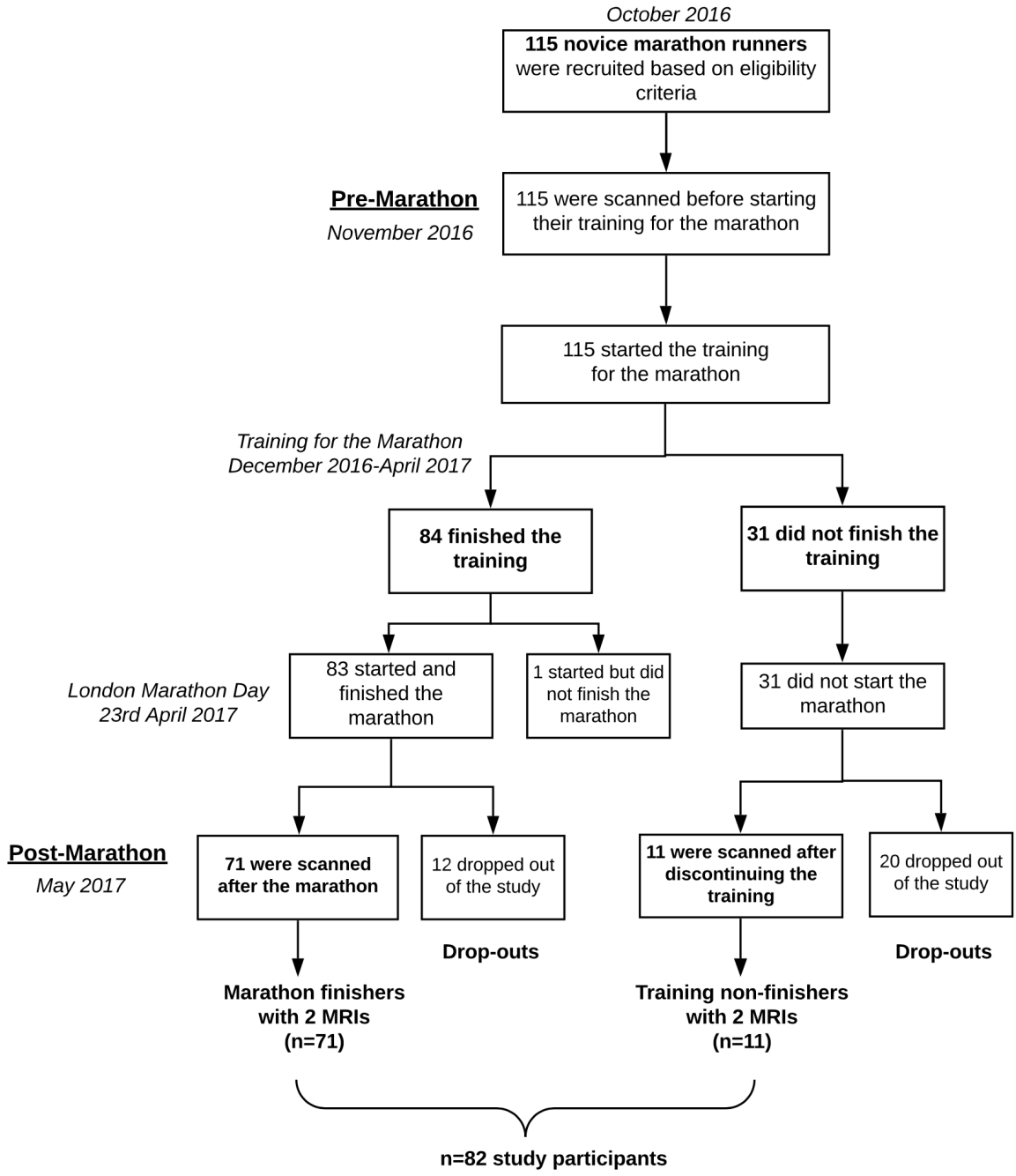


Figure 4.1. Study design

No significant differences were reported between marathon finishers and training non-finishers in terms of baseline demographics: age (p=0.795), BMI (p=0.375), gender (0.981).

Out of 71 marathon finishers, the majority were aged ≥ 40 years old (77%; n=55), while the remaining ones (23%; n=16) were aged <40 years old (range: 26-69 years old). Similarly, 10 out of 11 training non-finishers were aged ≥ 40 years old (91%) and only

one was younger than 40 years old (range: 31-57 years old). In terms of BMI, there were almost even numbers of participants in the normal range and overweight ones. Specifically, 37/71 (52%) marathon finishers and 6/11 (55%) training non-finishers had a BMI ≥ 25 kg/m^2, while the rest had a BMI <25 kg/m^2. The BMI of marathon finishers was in the range of 19.6-35.2 kg/m^2, whereas the BMI of training non-finishers was in the range of 21.3-38.1kg/m^2 (see Table 4.2 for participant characteristics).

Table 4.2. Baseline characteristics of study participants

Characteristics	Marathon finishers (n=71)	Training non-finishers (n=11)
Age (years)	44 ± 8.5	44 ± 7.0
Male : Female ratio	32 : 39	5 : 6
BMI (kg/m^2)*	25.2 ± 3.6	24.2 ± 2.2

*There were 2 outliers for BMI (≥30kg/m^2) so we excluded those participants from the BMI analysis. Mean ± standard deviation were calculated for age and BMI. BMI, body mass index.

However, after the marathon, the BMI values of marathon finishers changed significantly from the pre-marathon BMI values (p=0.009). There has been a reduction in the BMI values of most marathon finishers (67%) over the course of the training for the marathon based on the post-marathon BMI values. The median BMI values decreased from 25.2±3.6 to 24.9±3.5. No significant differences were reported between the BMI values of training non-finishers measured on the two MRI scanning sessions (p=0.800)

4.3.2 MRI findings

Here I provide the reported knee outcomes of the 82 study participants who underwent both MRI scans at the two different time points in relation to the marathon run (164 knee MRI scans). Also, I compared between the MRI results of the 71 marathon finishers (142 knees) and the 11 training non-finishers (22 knees), respectively. I counted all lesions for each compartment and each knee subregion (in both knees).

Meniscus

Prior to the marathon, 51/142 (36%) knees of marathon finishers presented with asymptomatic meniscal tears, while 23/142 (16%) showed signal hyperintensity (non-tears) on the MRI scans. No significant differences in the prevalence of meniscal abnormalities were found between the MRI scans conducted before and after the marathon. Only one knee of a runner developed a tear in a normal meniscus following

the marathon run. Specifically, a meniscal tear of horizontal pattern was identified in the left knee of a 40-year-old woman, who completed the marathon in 6 hours 20 minutes. All the other knees showed no change in the MRI scans after the marathon run (Figure 4.2, Table 4.3).

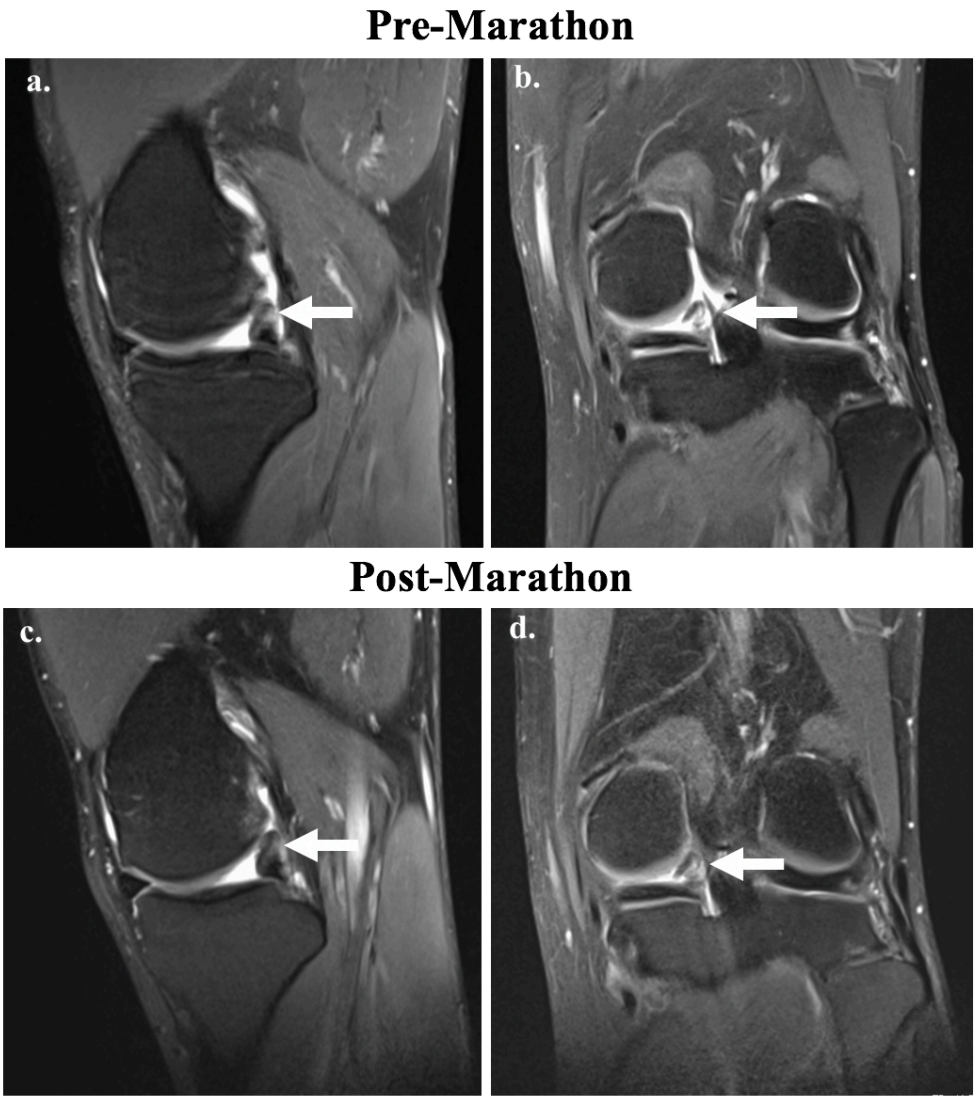


Figure 4.2. MRI scans of a 45 year old marathon runner with finishing time 3 hours and 51 min who was diagnosed during the pre-training period with bucket-handle tear of the posterior horn of the medial meniscus as it is indicated by (a) the sagittal proton-density fat-saturated image (white arrow) and the (b) coronal image where the meniscal flap within the intercondylar notch (arrow) is shown. The status of the meniscal tear did not change in 2 weeks after the marathon (see c, d).

Table 4.3: Number and types of post-marathon/training lesions in different structures, in 142 knees of 71 marathon finishers and 22 knees of 11 training non-finishers

Knee abnormalities per structure	Marathon finishers (n=142 knees)			Training non-finishers (n=22 knees)		
	Number of Post-M lesions		Significant change from Pre-M	Number of Post-M lesions		Significant change from Pre-M
	New/ Worsened*	Improved**		New/ Worsened	Improved	
Meniscal lesions	1	0	ns	0	0	.
Cartilage lesions	25	2	**Lateral patella p=0.0005***	4	0	ns
Patellofemoral	21	1		3	0	
Medial tibiofemoral	1	1		1	0	
Lateral tibiofemoral	3	0		0	0	
BME lesions	26	23	**Medial tibia p=0.011****	3	3	ns
Patellofemoral	19	2		3	1	
Medial tibiofemoral	3	19		0	1	
Lateral tibiofemoral	4	2		0	1	
Tendon lesions	13	2	**Semimembranosus p=0.016***	2	0	ns
Iliotibial band signal	12	0	**Iliotibial band p=0.004****	1	0	ns
Ligament lesions	2	2	ns	0	0	ns

All abnormalities were recorded including Grade 1 abnormalities (all grades different from 0 were defined as 'lesions'). BME, bone marrow edema; Post-M, post-marathon; p-values<0.05 indicate significant changes in the knees between the pre- and post-marathon/training time points; p values marked with '*' indicate significant worsening and those marked with '**' indicate significant improvement in the extent of lesion, respectively; ns, not significant.

In the training non-finishers' group, there were 6/22 (27%) knees with meniscal tears and 5/22 (23%) knees with meniscal degeneration at the first MRI scanning session. No apparent alteration were found at the second MRI scanning session, after training discontinuation (Table 4.3).

Articular cartilage

Pre-marathon, over half of all knees of marathon finishers (92/142, 65%) showed pre-existing asymptomatic cartilage abnormalities on the MRI scans (Table 4.3, Figures 4.3-4.4). Post-marathon, 17/92 (18%) of those knees with pre-marathon abnormalities had

new ones, in any of their other regions of the knee, or worsened in the extent of their pre-existing abnormalities. And 3/50 (6%) of the remaining lesion-free knees developed new ones after the marathon (Figure 4.3). The knees with pre-existing abnormalities were more likely to develop new/extended abnormalities than the lesion-free knees to develop new ones (p=0.041).

Regarding the specific number of abnormalities in these knees, the total number of pre-marathon cartilage abnormalities in all knee compartments and subregions was 168: 118 in the patellofemoral compartment and 50 in the tibiofemoral compartment. Post-marathon, this increased by 15%, with 25 abnormalities either newly appearing or progressing from pre-existing ones: 17 were new and 8 worsened in extent from pre-marathon ones. Location-wise, the number of lesions increased by 18% in the patellofemoral compartment (21 lesions) and by 8% in the tibiofemoral one (4 lesions). Out of all knee compartments, the patellofemoral one showed a significantly higher number of lesions than the tibiofemoral compartments (Table 4.3, Figure 4.4). Significant differences in the extent of lesions was only seen in the patellofemoral compartment, specifically in the lateral patellar facet, which had more than half of all patellofemoral lesions (12 lesions; p=0.0005). Further details on grading changes are in Appendix A.1.2. Also, 2 pre-marathon abnormalities improved/reduced their extent after the run (in 2 separate knees), one in the patellofemoral compartment and one in the tibiofemoral one.

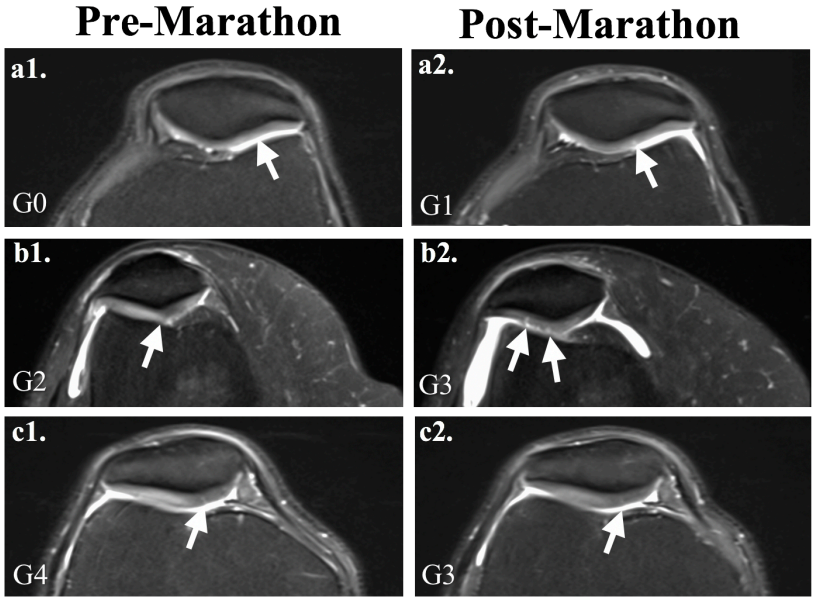


Figure 4.3. Axial proton-density fat-saturated MR images of 3 individual knees of 3 marathon finishers showing different patellar cartilage changes after the marathon: a1-2) appearance of small new cartilage abnormality in a previously normal knee; b1-2) progression of a pre-marathon abnormality to a higher extent after the run; c1-2) improvement in the extent of a high-grade pre-marathon abnormality after the run. The specific location of cartilage changes is indicated by arrows and the lesion grade (G) is included in the left bottom corner. The new modified Noyes scoring system was used.

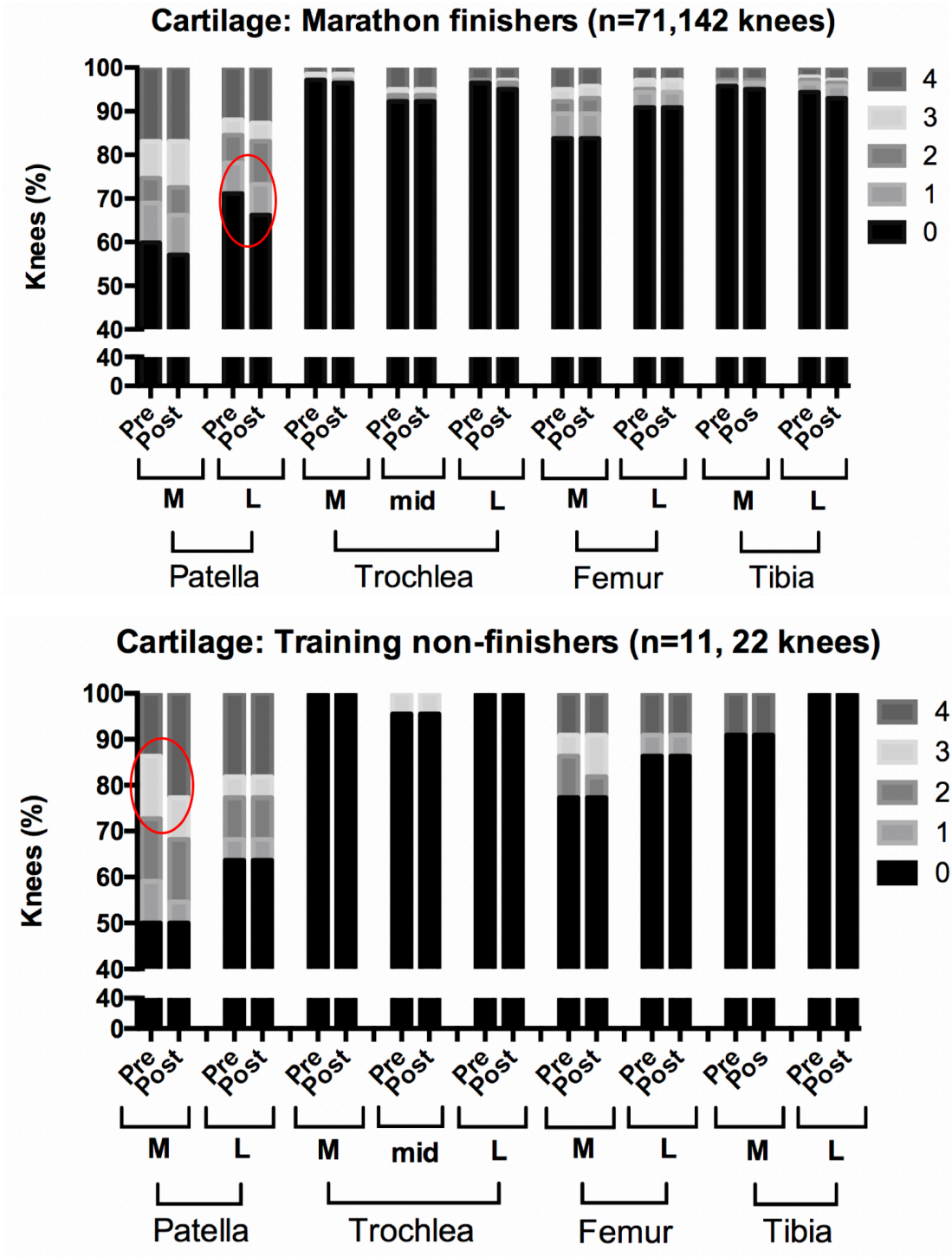


Figure 4.4. The prevalence of knees with pre-marathon/training and post-marathon/training cartilage lesions, in marathon finishers and training non-finishers. The lesions were graded using the modified Noyes scoring system and scores 0–4 were assigned; C, central; L, lateral; M, medial.

Likewise, over half of all knees of training non-finishers (15/22, 68%) had cartilage abnormalities before starting their marathon training on the MRI scans. After the training discontinuation, 3 of these 15 knees (20%) showed worsening in the extent of their pre-

existing lesions. None of the lesion-free knees developed new abnormalities after the training.

Pre-training, there were 30 abnormalities in total, most of them in the patellofemoral compartment (20/30; 67%). Four abnormalities progressed in extent at the 2nd MRI scanning time point, showing a 13% increase in the number of lesions. Three of these abnormalities (75%) were found in the patellofemoral compartment (Table 4.3, Figure 4.4) which reported a 15% compartment-specific increase in the number of lesions. The tibiofemoral compartment showed a 10% increase.

Bone marrow

Pre-marathon, I identified 58/142 (41%) knees with subchondral BME on the MRI scans of those runners who completed the training for and the marathon run (Table 4.3, Figure 4.6). Post-marathon, 17/58 (29%) knees with pre-existing edema showed new lesions in other areas of the knee or worsening of the same pre-existing ones, while 16/58 (28%) showed improvement in the extent of pre-existing edema. Only 7/84 (8%) remaining edema-free knees showed new edema-like signal appearance after the marathon. The knees with pre-marathon edema were more likely to show progression in extent or develop new ones in other regions of the knee than the lesion-free knees to develop new ones (p=0.001).

The total sum of pre-marathon BME in all knee compartments was 105: 58 in the patellofemoral compartment and 47 in the tibiofemoral compartment. After the marathon, the number went up in the patellofemoral compartment by 33% (although not statistically significant), specifically 19 abnormalities were observed: 16 were new and 3 progressed in extent from pre-existing ones; while 2 other pre-marathon lesions improved in extent after the run (4% decrease). The tibiofemoral compartment had a 15% increase in the number of abnormalities (7 in total): 6 new and 1 progressed from pre-marathon. Also, in this compartment there was post-marathon reduction in the extent of 21 lesions: 19 reversed completely to a normal status, while 2 reduced in extent to a lower grade. The reported decrease was of 45% of the total pre-marathon tibiofemoral lesions. The majority of improved cases were seen in the medial tibiofemoral compartment [19/33 (58%) lesions decreased in extent: 10 in the tibia, 9 in the femur; Table 4.3; Figure 4.5]. The improvement in the medial compartment was statistically significant, particularly in the medial tibia (p=0.082; Figure 4.5). Further details can be found in Appendix A.1.2.

Also, BME was reported in 9/22 (41%) knees of training non-finishers before the training for the marathon on the MRI scans. Following their training discontinuation, none of these progressed in extent, but in 2/13 (15%) remaining knees with no pre-existing edema showed new edema appearances; 3/9 (33%) knees showed reduction in the severity of edema.

There were 16 pre-marathon BME lesions in total, with half of them being located in the patellofemoral compartment; 3 new BME lesions appeared after training discontinuation, particularly in the patella, while 3 other BME lesions improved in extent in the same knee region (Figure 4.6). In the tibiofemoral compartment there were no new lesions, but an improvement in the extent of 2 pre-existing ones was reported (25% decrease in the number of cases).

Additionally, marathon finishers had pre-existing subchondral cysts in 29/142 (20%) knees before the marathon. Post-marathon, 3/29 (10%) knees with pre-marathon cysts developed new ones in other regions of those knees, while 2 other knees (7%) showed reversibility in the extent of their pre-existing ones. Also, 1/113 (1%) cyst-free knees developed one after the run.

In total, there were 39 cysts before the marathon (25 patellofemoral and 14 tibiofemoral). Post-marathon, 1 new cyst developed (4% increase in number of cysts) and 2 pre-existing cysts improved in extent (8% decrease) in the patellofemoral compartment, while 3 new ones appeared in the tibiofemoral region (21% increase). Meanwhile, 3/22 (14%) knees of training non-finishers had 6 pre-existing cysts before the start of their training – 4 patellofemoral and 2 tibiofemoral - and 2 new ones developed in the patellofemoral compartment of 2 knees with no pre-existing lesions, one in each knee respectively (2/19; 11%).

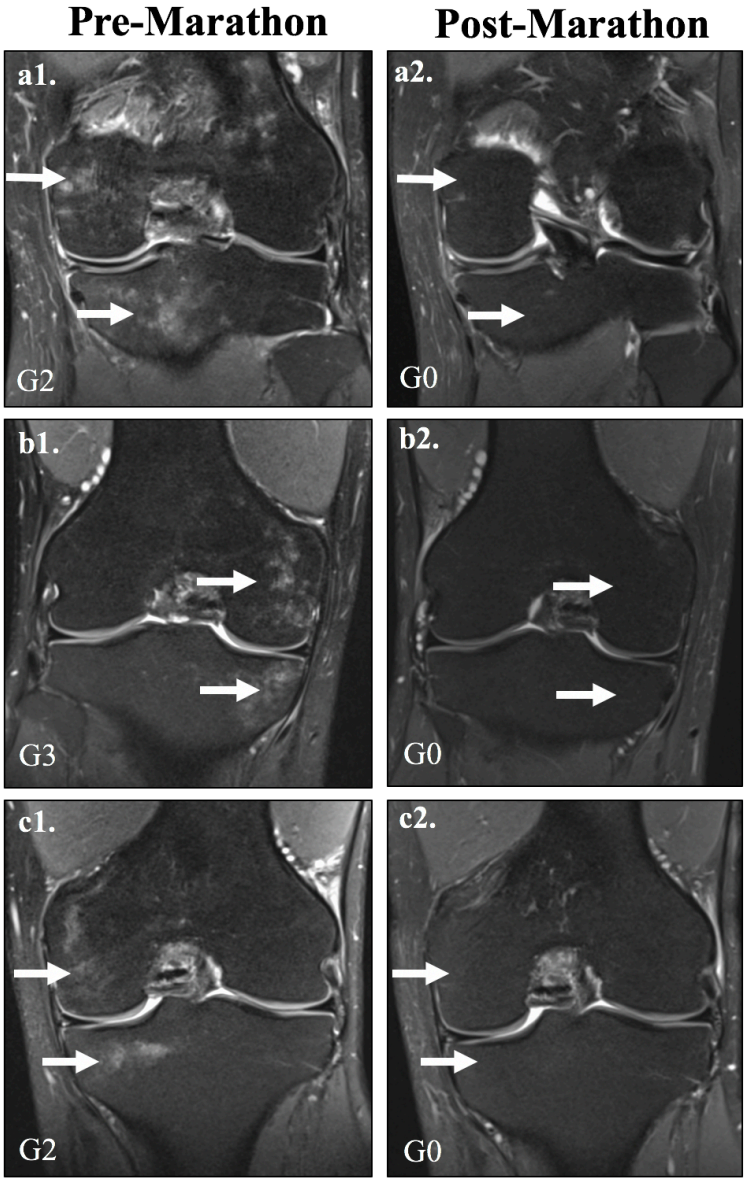


Figure 4.5. Coronal proton-density fat-saturated MR images of 3 individual knees of 3 marathon finishers (a1-2, b1-2, c1-2) presenting with complete resolution of pre-marathon BME after the marathon in the tibiofemoral compartment. The specific location of bone marrow changes is indicated by arrows (the upper arrow indicates the femoral condyle, while the lower down arrow indicates the tibial condyle). The lesion grade (G) is included in the left bottom corner, and grading was based on the KOSS, Knee Osteoarthritis Scoring System; BME, bone marrow edema.

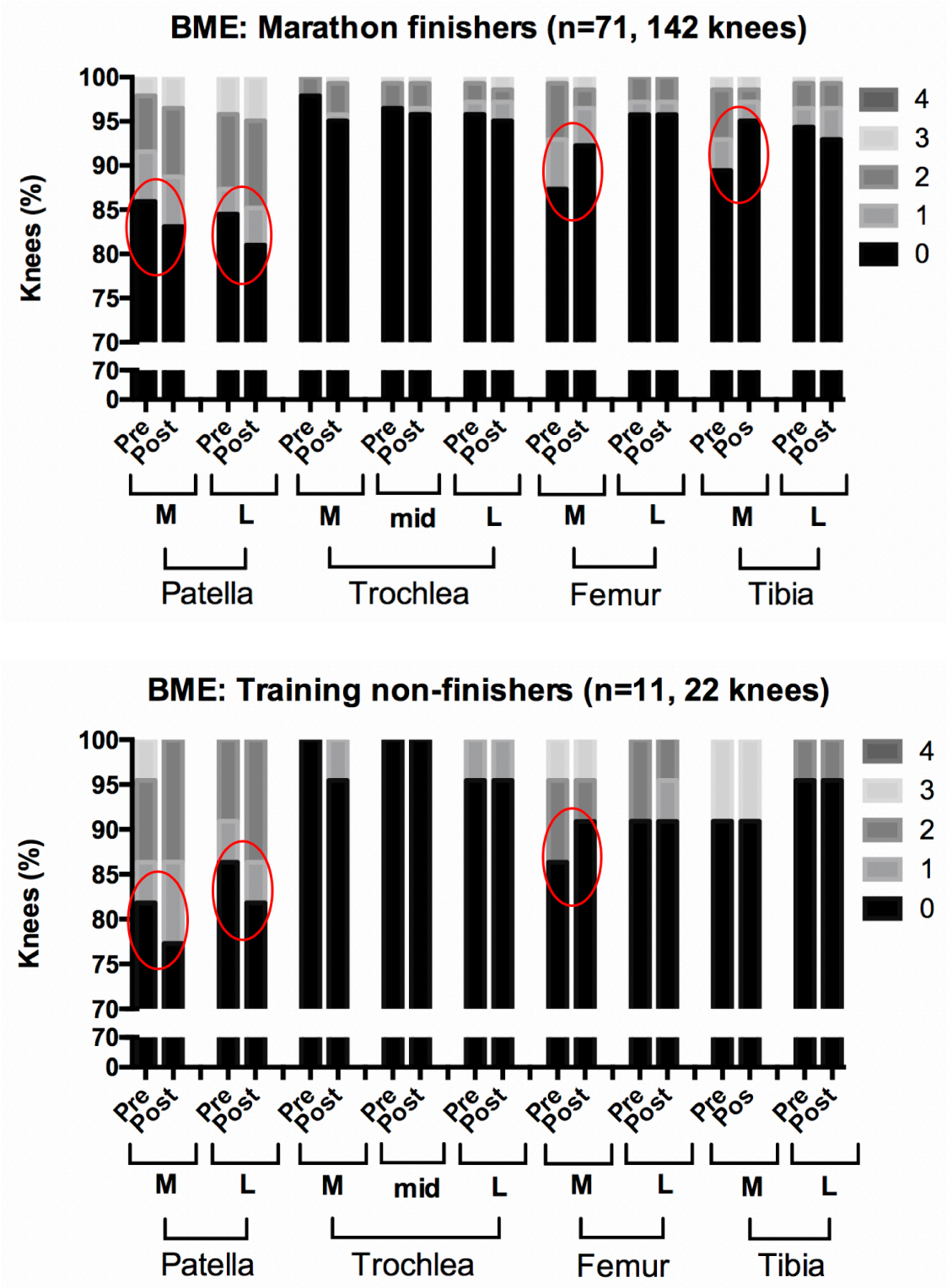


Figure 4.6. The prevalence of knees with pre-marathon/training and post-marathon/training subchondral BME, in marathon finishers and training non-finishers. The lesions were graded using the KOSS scoring system and scores 0–3 were assigned. Red circles indicate changes in the grading of lesions in the knees of participants between the pre-marathon/training and post-marathon/training scans. BME, bone marrow oedema; C, central; d, diameter; KOSS, Knee Osteoarthritis Scoring System; L, lateral; M, medial.

Tendons

Pre-marathon, tendon abnormalities were detected in 60/142 (42%) knees of those runners who became marathon finishers later on. Post-marathon, 3 of the knees with pre-

existing tendon abnormalities (3/60; 5%) showed new minimal signal appearance, in other tendons in the same knees, or increased grade of pre-existing lesions. Also, there were 8/82 (10%) knees with no pre-marathon tendon abnormalities which had new signal appearances on MRI.

The total number of tendon abnormalities was 72. The highest number was found in the patellar tendon (n=21), followed by the quadriceps (n=21) and semimembranosus tendons (n=14), then gracilis (n=5) and sartorius (n=1). After the marathon, 13 abnormalities appeared (12 new, 1 worsened) and 2 pre-existing ones improved in extent (Table 4.3). More than half of the post-marathon abnormalities were of the semimembranosus tendon. There were 6 additional semimembranosus tendon abnormalities and 1 that progressed on the MRI scans (43% increase of abnormalities from the pre-marathon number), which developed over the course of the marathon training and/or after the race. This was statistically significant (p=0.016). Also, there were additional abnormalities in the patellar (3 lesions), gracilis (2 lesions) and sartorius (1 lesion). The post-marathon improvement was detected in the patellar and gracilis tendons. Moreover, iliotibial band signal was present in 3/142 (2%) knees before the marathon run (3 lesions in total). Post-marathon, 12 new lesions developed so the total number of lesions was 5 times higher than the one before the marathon; this was statistically significant (p=0.004).

Training non-finishers had 5/22 (23%) knees with pre-existing tendon abnormalities before starting their training for the marathon. None worsened after the training, but 2/17 (12%) of the knees with no pre-existing abnormalities showed the appearance of new signal after the training. I counted 14 pre-marathon abnormalities in the following tendons: patellar (n=5), gracilis (n=4), semimembranosus (n=3), quadriceps (n=2), sartorius (n=1). Following their training cessation, patellar tendon abnormalities appeared in 2 previously normal knees (40% increase; Table 4.3, Appendix A.1.2). Also, iliotibial band signal was not present in knees before training, and only one appeared in one knee of a training non-finisher after training cessation.

Ligaments

The prevalence of knees of marathon finishers with ligamentous abnormalities was 42% (59/142) before the marathon training and race. Two knees developed abnormalities: one had previous abnormality and developed another one in a different ligament, while another one with no pre-existing lesions spontaneously developed signal ligament appearances.

Overall, there were 69 pre-marathon abnormalities, with the majority being ACL ones (ACL; n=61), followed by medial collateral ligament (MCL; n=2), and lateral collateral ligament (LCL; n=2) abnormalities. After the marathon run, the collateral ligaments were slightly altered on the MRI scans, specifically 2 abnormalities of the MCL disappeared, while 2 other abnormalities developed in the LCL (Table 4.3, Appendix A.1.2). Also, 2 pre-existing MCL abnormalities disappeared after the run.

Also, the prevalence of knees of training non-finishers with ligamentous abnormalities was 32% (7/22) before starting their training plan. No changes were seen on MRI after training discontinuation (Table 4.3).

Other findings

Prior to the marathon, I found a number of other pre-existing conditions on the knee MRI reports of marathon finishers: effusion (74/142; 52% knees), prepatellar bursitis (35/142; 25%), pes anserine bursitis (11/142; 8%) Baker's cyst (48/142; 34%). Following the race, there were not many differences in the number of knees showing new abnormalities: 7 additional prepatellar bursitis cases, 4 pes anserine, 5 Baker cysts.

Regarding training non-finishers, I found similar prevalences in their knees before the start of training: effusion (11/22; 50%), prepatellar bursitis (6/22; 27%), Baker's cysts (9/22; 41%). These were unchanged on the 2nd MRI scan after training cessation.

4.3.3 Marathon finishing times

The mean finishing time of the marathon run was estimated to be 5 hours 20 minutes ± 58 minutes.

There were 84 participants who finished the training for the marathon and started the race. Out of these, 37 had meniscal tears and 47 did not have meniscal tears on the pre-marathon MRI scan. Only one of these participants did not complete the race and was part of the group of runners with meniscal tears. However, no statistically significant differences in the marathon finishing times were found between the runners with meniscal tears and the ones who were tear-free (p=0.135; Figure 4.7). The runner who dropped out during the race was not involved in the statistical analysis (i.e. no finishing time). No other MRI abnormalities were found in this runner and no associations could be made between the presence of asymptomatic meniscal tears and running cessation from this isolated case only.

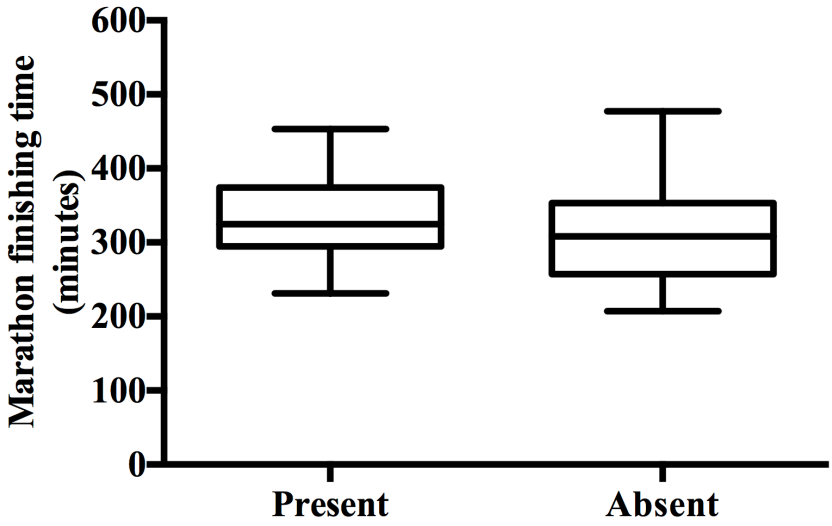


Figure 4.7. **Marathon finishing times divided into two groups: presence or absence of pre-marathon meniscal tears**; 83 participants finished the race, either presenting with meniscal tears (n=36) or without meniscal tears (n=47).

Also, the presence of any other knee abnormality did not affect marathon finishing times: articular cartilage (p=0.348), BME (p=0.575), abnormal ligament signal (p=0.632), tendinosis (p=0.712), effusion/bursitis (p=0.378).

4.3.4. Associations between different MRI findings

I found associations between the post-marathon development of articular cartilage lesions and the development of BME-like lesions in marathon finishers' knees. A knee was 4.4 times more likely to simultaneously develop post-marathon cartilage abnormalities and BME (95% CI, 1.6–12.5; p=0.003), in the same knee compartment. Also, the knees with pre-existing cartilage abnormalities were more likely to experience new or increased post-marathon BME within the same knee compartment (95% CI, OR=4.9; 1.4–17.4; p=0.007) The single meniscal tear which developed after the marathon run was not associated with the appearance of any other type of lesion. No other associations were identified in either marathon finishers or training non-finishers.

4.3.5 Distribution of MRI findings in participants and per knee side

The main analysis in this study was done per total number of knees and counted lesions at compartment-level. Table 4.4 describes which knees (single right/left or both) were affected in participants and a summary of the main post-marathon changes (new/worse lesions or improved ones) in participants. Post-marathon lesions (new/worsened) developed more frequently in the contralateral side of those knees which already had pre-

existing sustained lesions. Specifically, the right knee was more affected by post-marathon cartilage and/or BME lesions (70% cases), where the corresponding left knee already had pre-marathon lesions. Simultaneous improvement in both knees of participants was most prevalent i.e. 60% of all marathon finishers had bilateral post-marathon improvement in the extent of BME. No other associations could be made.

Other few post-marathon findings not listed in the table include: subchondral cysts (in 4 right knees of 4 different participants; and 2 improvements in the pre-existing cysts of two separate knees, right and left, respectively, of 2 participants); prepatellar bursitis (in 8 participants - 4 individual right knees and 4 left ones), pes anserine bursitis (in 3 participants – 3 right knees), Baker's cyst (in 4 participants - 2 right, 1 left, 1 both knees).

Table 4.4. Number of participants with both knees or single knees showing post-marathon MRI changes, either development of lesions (new/worse) or improvement in the extent of pre-existing lesion, and total number of affected knees, in the meniscus, articular cartilage, bone marrow, tendons, iliotibial band and ligaments

Key knee abnormalities	Type of Post-M change	No. of participants with changes in both knees	No. of participants with changes in single knee sides		Total no. of participants with changes in either knee	Total no. of knees with changes		
			Right knee	Left knee		Right knee	Left knee	All knees
Marathon finishers (N=71 participants, 142 knees)								
Meniscal tears	New/worse	0	0	1	1	0	1	1
	Improved	0	0	0	0	0	0	0
Cartilage lesions	New/worse	3	9	5	17	12	8	20
	Improved	0	1	1	2	1	1	2
BME lesions	New/worse	6	8	4	18	14	10	24
	Improved	6	1	3	10	7	9	16
Tendon lesions	New/worse	2	4	3	9	6	5	11
	Improved	0	2	0	2	2	0	2
Iliotibial band signal	New/worse	2	3	5	10	5	7	12
	Improved	0	0	0	0	0	0	0
Ligament lesions	New/worse	0	1	1	2	1	1	2
	Improved	0	0	0	0	0	0	0
Training non-finishers (N=11 participants, 22 knees)								
Meniscal tears	New/worse	0	0	0	0	0	0	0
	Improved	0	0	0	0	0	0	0
Cartilage lesions	New/worse	0	3	0	3	3	0	3
	Improved	0	0	0	0	0	0	0
BME lesions	New/worse	0	1	1	2	1	1	2
	Improved	0	0	3	3	0	3	3
Tendon lesions	New/worse	1	0	0	1	1	1	2
	Improved	0	0	0	0	0	0	0
Iliotibial band signal	New/worse	0	1	0	1	1	0	1
	Improved	0	0	0	0	0	0	0
Ligament lesions	New/worse	0	0	0	0	0	0	0
	Improved	0	0	0	0	0	0	0

BME, bone marrow edema; Post-M, post-marathon.

4.3.6 Associations between MRI findings and participant characteristics

In terms of demographics and post-marathon MRI findings, the development of articular cartilage and/or BME lesions was more common in participants aged over 40 years old (88% and 72%, respectively), with more than half of them being women (65% and 56%, respectively). This was also confirmed in the case of post-marathon lesions of tendons (89% aged ≥40, 78% female), iliotibial band (89% aged ≥40, 75% female), ligaments (50% aged ≥40, 100% female) and other findings. By contrary, improvement in the extent of lesions was seen in 90% men, irrespective of their age. No associations between post-marathon BMI changes and MRI findings were made.

4.3.7. Double-reporting consensus

There was excellent agreement between the findings reported by the 2 radiologists, given that the assigned scores were identical in almost all cases (kappa 0.927). The differences found between few scores were discussed and final consensus scores were obtained.

4.3.8. KOOS results

Out of the 82 study participants, 70 completed KOOS questionnaires at both of the two time points: 65/71 marathon finishers and 5/11 training non-finishers. In the marathon finishers' group, there were no significant differences between the pre-marathon and post-marathon KOOS scores, for each type of questionnaire item: pain ($p=0.121$), other symptoms ($p=0.981$), daily activity ($p=0.303$), sports and recreational activities ($p=0.133$), knee-related quality of life ($p=0.096$). No significant changes between the two time points were reported for training non-finishers either: pain ($p=0.250$), symptoms ($p=0.375$), daily activity ($p>0.999$), sports and recreational activities ($p>0.999$), knee-related quality of life ($p=0.250$).

4.4 DISCUSSION AND CONCLUSIONS

Overall, our study showed that marathon running and the preceding beginner training programme had different effects on the 3.0T MRI scans of the knee joint structures of asymptomatic first-time marathon runners. The patellofemoral compartment and few tendons involved in knee stabilisation appeared to have an increase in the number and

extent of abnormalities after the marathon (lateral patellar cartilage: p=0.0005; semimembranosus tendon: p=0.016; iliotibial band: p=0.004). The knees with pre-existing cartilage defects or BME, respectively, were more likely to progress further or develop new lesions in other knee regions after the marathon than those knees without pre-existing lesions to develop new ones. Secondly, the subchondral bone marrow of the tibiofemoral compartment showed significant improvement i.e. reduction in the extent of edema following the run (medial tibia: p=0.011). Also, for the first time, we showed that meniscal tears - including complex and bucket-handle tears – did not prevent individuals from completing the training for the marathon and the marathon itself. Only 27% of the initial number of participants who registered for the race discontinued their training and did not run, which is lower than the predicted range of 30-50% [319–321]. Training non-finishers showed some similarity to marathon finishers in their results, however there were no statistically significant changes (increase/decrease) in this group of participants.

4.4.1. Study strengths

The key strengths of our study are the following: 1) Firstly, this is the largest MRI study to date evaluating the impact of marathon running on the knee joints of runners (82 participants, 164 knees). The sample size of previous marathon studies did not exceed 22 participants (22 knees) in any MRI trial. [43,223,225–228,318,322]Therefore the large sample size in our study provides increased reliability; 2) We used the high-resolution 3.0 T MRI technique which, in comparison to the widely used 1.5 T MRI, gives unprecedented diagnostic confidence for detailed analysis of knee pathologies, even subtle ones or early signs of lesions; 3) Our cohort included middle-aged physically inactive participants who participated in their first marathon ever as part of our study and had 3.0 T MRI scans of both knees before and after the marathon run – this is the first study of its kind; 4) The study is also the first one to include an assessment of the impact of both the training for the marathon and the marathon race itself, instead of focusing on the impact of marathon running only; previous studies included short-term intervals for the MRI scans in relation to the marathon i.e. 30 min-4 weeks before the marathon and 3 min-3 days after the marathon. The MRI scans in our study were conducted firstly 6 months before the marathon (2 months before starting the training - to capture any potential MRI changes during training), and then 2 weeks after the marathon; 5) Also, this study provides the most robust and comprehensive analysis of all knee features –

including internal knee structures and processes, per knee compartments and subregions, based on MRI-based scoring systems.

4.4.2. Study limitations

Our study has a couple of limitations to account for: 1) The activity levels at baseline and following the marathon were self-reported, therefore it is difficult to conclude with certainty that the changes seen 2 weeks after the marathon were solely caused by the run. Also, other pre-study lifestyle details were not recorded so could not be commented on; 2) The KOOS questionnaire is considered to be a reliable tool for participants to report on their perceived knee condition, however the nature of questionnaires may still involve a level of bias; 3) MRI reporting may involve a certain degree of subjectivity, therefore we tried to minimise this issue by including 2 musculoskeletal radiologists in the analysis of images; they reported the findings from a subset of scans independently and then discussed any disagreements between them to achieve optimal consensus scores; 4) The precise individual time points when each of the participants dropped out during training (from the group of training non-finishers) varied and were not recorded, so could not be analysed; 5) No internal quality controls of non-runners were included in this study. However, training non-finishers from the initial cohort were involved in our study analysis; nevertheless, the sample size was much smaller than that of marathon finishers and direct comparisons could not be made between the 2 groups of participants to clarify whether training alone or training plus the marathon run induce different effects on the knees; 6) Having measured a number of datasets and parameters with multiple simultaneous statistical tests may affect the reliability of the results. Therefore, a multiple comparisons problem might be involved which needs to be taken into account; 7) It can be argued that the 2 weeks post-marathon follow-up may not reflect the very immediate impact of the marathon and that a shorter interval of few days after the marathon could have been considered, or also that a short-term pre-race additional MRI scanning session should have been considered to better differentiate between the changes occurring during the training for the marathon versus the ones during the race; however we selected these based on participants' availability and research group's resources. Also, currently there is no consensus on the most appropriate scanning interval; 8) Longer-term follow-up studies are needed to understand whether the lesions that immediately appeared, or worsened from pre-existing ones, after the marathon run are reversible over time.

4.4.3. Comparison with previous studies

Meniscal tears did not progress further apart from one case in which a horizontal tear developed in a healthy knee subsequent to the marathon run. Also, the pre-existing meniscal signal abnormalities were all unchanged immediately after the marathon. In agreement with our findings, Schueller-Weidekamm *et al* [225] showed that only 1 of the 22 non-professional runners' knees scanned had an increase in intrameniscal high signal after the marathon. Moreover, Shellock *et* al [322] concluded that the prevalence of meniscal tears and meniscal signal abnormalities (the latter being indicative of meniscal degeneration) in asymptomatic marathon runners is no different than that of non-athletes/sedentary persons.

Before the marathon, articular cartilage lesions were found in 92 (63%) knees of those runners who then went on to finish the training for/and the marathon run. Following the marathon run, 8 lesions presented worsening after running and 17 new lesions appeared in knees without previous cartilage lesion. The patellofemoral compartment was most affected (21 lesions), especially on the lateral patellar facet (p=0.0005; 12 lesions). Unlike these results, in Schueller-Weidekamm *et al*'s study [225] only 4 (18%) out of 22 knees had cartilage lesions before the run and there were no new lesions or worsening of the existing ones after the run. However, in the latter study the sample size was much smaller, included experienced long-distance runners and the field strength was two times lower (1.5T MRI scanner) and most probably subtle changes were not reported (smaller cartilage lesions are better detected with 3.0T [323]). Moreover, in a more recent study using 3.0 T MRI, Luke *et al* [227] showed that 2 (20%) of 10 knees of runners who were scanned before a marathon run had asymptomatic high-grade cartilage abnormalities, involving the patella and the medial femoral condyle, but no changes in their extent were seen 2 days nor 3 months after the run.

Subchondral BME was identified in 58 knees (41%) prior to the marathon. Post-marathon, 4 lesions presented worsening and 22 new lesions appeared in knees without pre-existing bone edema. Similarly to the cartilage, the patellofemoral joint was most affected (19 lesions). Also, very interestingly, 21 lesions of the tibiofemoral compartment got better from baseline with the majority (19 lesions) completely resolving subsequent to the run – statistically significant improvement was seen in the medial tibia (p=0.082; 10 lesions). In accordance with some of our findings, Stahl *et al* [226] reported BME

pattern using 3.0 T MRI in 5 (50%) out of 10 marathon runners' knees and 1 (8.3%) out of 12 controls' knees before the marathon, and 3 days after the event day there was an increase in the extent of edema in 2 out of the 5 knees. By contrast, other studies [43,225,227] did not show any changes in the bone marrow from the pre- to the post-marathon scans. However, no study so far showed any indication of subchondral bone improvement from baseline immediately after a marathon run. This is the first study to report this. The improvement was seen from the pre-training to the post-marathon scans, and other studies did not include pre-training analysis and maybe this is why such changes were not captured.

In terms of ligaments, signal alterations were mainly seen in the ACL (61 knees, 43%) before the marathon, with very few abnormalities in the collateral ligaments and no abnormalities in the PCL. In other studies [225,318], ACL was reported in very few cases (up to 9%). In agreement with our study, no changes were seen in the ACL following the run. However, 2 additional abnormalities of the collateral ligaments were found to be developing after the run. Nevertheless, these results suggest that marathon running does not have much noticeable effects on the ligaments.

In terms of tendons, pre-marathon patellar tendon injuries were most prevalent (60 knees, 42%) and 13 lesions appeared after running. This is in agreement with another study [318] that found that signal alterations of the patellar tendon were present in 4 (50%) out of 8 knees of asymptomatic runners, however the signal remained almost unchanged following the run. As we might have expected with running [17], the incidence of iliotibial band signal was 2% before the marathon and then increased by 5 times after the marathon ($p=0.004$). However, this was not painful irritation of the band, but actually an asymptomatic non-specific finding which is common in asymptomatic runners and non-runners, as confirmed by other previous studies [243,324–326]. Therefore, it was not considered clinically concerning.

Finally, other knee features such as joint effusions and synovial collections were also assessed. Joint effusions were present in 74 knees (52%) based on the initial MRI scan and no changes were seen at the post-marathon scan. This was confirmed by previous studies,[225] whereby effusion was found in more than 50% knees of individuals with only a slight increase after the run. Also, pre-marathon, there was a relatively high incidence of prepatellar bursitis, Baker's cyst and pes anserine bursitis which slightly

increased after the run – these knee processes were not analysed much in the running literature for direct comparisons.

4.4.4. Clinical significance and future work

The reported reductions in the extent of subchondral BME in the tibiofemoral compartment may suggest that marathon running and/or the preceding training with gradual increase in mileage could have potential protective effects on the knee joint. The tibiofemoral compartment is essential for the appropriate functioning of knee joints and is the one responsible for weight-bearing. Therefore, it is the area of the knee most commonly affected by OA. The increased improvement seen in the medial tibiofemoral compartment might have occurred due to muscle strengthening during training which prevented compartment overload, and helped in supporting the knee and improving flexibility. According to other studies, the improvement in the medial tibiofemoral compartment may occur as a result of strengthening of lateral muscle knee chain which may have decreased the load on the medial compartment; this most probably happened during the gradual knee adaptation as part of the training programme for the marathon. However, the study results need to be interpreted with great caution. Further research and longer follow-ups are required to understand what are the potential implications of these findings and whether the supposedly beneficial effects of running are sustained over time. Since subchondral bone marrow defects are usually associated with early stages of OA [296–298], and exercise may be prescribed in patients with OA, it is crucial to understand what is the optimal duration of exercise in order to make evidence-based recommendations to patients related to their physical activity and prevent or delay the progression of OA. Despite the fact that pain and functional issues may restrict patients to a limited range of physical activities, regular movement may be of certain importance for managing OA.

With regard to the patellofemoral compartment, the increased number of abnormalities after the marathon in this knee region is not very surprising. The kneecap is subjected to forces up to 8 times bodyweight during running, which implies a great amount of stress being placed on the kneecap. Moreover, imbalance in any of these forces due to weakness or tightness of the quadriceps and hamstring muscles may lead to overload of the cartilage under the kneecap. Specific strengthening exercises should target this region of the knee during training and after the run. Moreover, despite the immediate MRI changes, the reversibility of these lesions over time needs to be investigated. The clinical significance

is unclear, especially because there were not much changes in symptoms or any complaints of pain or functional limitation after the run.

Also, there was a high prevalence of pre-marathon asymptomatic meniscal tears, such as bucket-handle and complex ones. Post-marathon, no progression of pre-existing ones was observed; also no development of new ones, except in one case. Therefore, this supports the importance of generally considering conservative methods in the treatment of meniscal tears (non-surgical procedures), especially if no symptoms are present.

Chapter 5 – Knee study

Analysing the impact of marathon running on the knee joints of novice marathon runners

(medium-term post-marathon data)

Work presented in this chapter has been published[1]

[1]Horga LM, Henckel J, Fotiadou A, Hirschmann AC, Di Laura A, Torlasco C, D'Silva A, Sharma S, Moon JC, Hart AJ. Is the immediate effect of marathon running on novice runners' knee joints sustained within 6 months after the run? A follow-up 3.0 T MRI study. *Skeletal Radiol* 2020;49(8):1221–1229. doi:10.1007/s00256-020-03391-2

5.1 INTRODUCTION

Despite the increasing uptake of long-distance running, little is known about the longer-term repercussions of marathon running and preceding training on knee joint health.

Previous studies demonstrated no major short-term damage after the completion of a marathon run (minutes to few weeks after the marathon) on the internal structures of the knee, where no significant pre-existing injuries were reported in the first place [43,225–228]. However, very little research was done on the medium-term impact of marathon running on the knees (2-3 months follow-up) - both morphologic and biochemical MRI analysis. The existing evidence showed that short-term post-marathon MRI changes reverse back to the pre-marathon state over time in healthy individuals, specifically within 3 months after the run [176,227,228,318]. Some biochemical analysis showed sustained compositional changes of the cartilage at 2-3 months after the marathon, however the clinical significance of those findings or whether a longer time is required for complete resolution of the changes is yet unknown [227,228].

The only long-term follow-up work to our knowledge was a 10 year longitudinal study confirming that marathon running is not associated with permanent knee damage and even suggesting a protective value on the joint [224]; however the limited resolution of the 1.0 T MRI scanner in this study made the accuracy of lesion scoring, and thus the research results, questionable. Moreover, all moderate to long-term studies up to this point were conducted with a very small population (up to 13 participants; 1 knee scanned only) and included only experienced long-distance runners, making it difficult to firmly clarify the impact of marathon running on the knee. Moderate and longer-term studies with improved study design are needed to clarify the lasting effect of marathon running on the knee joints over time.

5.1.1 Motivation

There is a necessity to understand how the marathon run and preceding 4-month training affects the knees of previously inexperienced novice marathon runners over time, and whether short-term post-marathon changes are temporary and disappear within 6 months after the run, or whether they progress further. It is also important to clarify whether new lesions may appear after this medium-term period of time after the marathon, as a delayed response to the impact of running on the joints. This will help to clarify how much of and

which types of changes are sustained or resolve over time, or whether longer time is required for complete resolution; this will support the development of strategies to impede or reduce the risk of injuries.

5.1.2 Aim

To compare between the knee outcomes of novice marathon runners shortly after completing the marathon run and then 6 months later.

5.1.3 Objectives

To better understand the continued effect of marathon running and preceding training on the knee joints of novice marathon runners over time using morphological high-resolution 3.0 T MRI, MRI-based knee scoring systems and self-reported questionnaires; to evaluate the reversibility of immediate post-marathon MRI changes to baseline levels at a 6 months follow-up.

5.2 MATERIALS AND METHODS

I was responsible for communicating with the study participants (via emails, phone and in person) and managing the organisation of the follow-up scans, reviewing the relevant literature and collecting the data. The musculoskeletal radiologists used the same MRI protocol and scoring systems for reporting the MRI findings. The Chief investigator and the other PhD supervisors were involved in supervising the project to ensure the smooth organisation of the study.

5.2.1 Study design and participants

As described in Chapters 3, 115 novice marathon runners who registered for the 2017 London Marathon were recruited at the beginning of our study. MRI scans of both knees of these runners were conducted 2 months before starting their 4-month training for the marathon. Then 82 out of these returned for a 2nd MRI scan at 2 weeks after the marathon: 71 marathon finishers and 11 training non-finishers (Chapter 4). Here, it is described the 3rd phase of our study whereby the 82 participants who attended the previous MRI scanning sessions were invited to a 6 months follow-up MRI study.

In this part of the study I assessed and compared the knee outcomes of novice marathoners (both marathon finishers and training non-finishers) at three distinct time points: time point 1 (6 months pre-marathon), time point 2 (2 weeks post-marathon), time point 3 (6 months follow-up). A particular emphasis was placed on the changes seen between the post-marathon results and the 6 months follow-up ones.

5.2.2 MRI protocol

The same methodology as in our previous studies (Chapters 3 and 4) was used here for ensuring optimal comparability, including the MRI technique and specific parameters. MRI scans of both knees of returning participants were conducted 6 months after the marathon. The complete protocol is available in Chapter 3.

5.2.3 Image analysis

All MRI scans were reviewed and compared at each time point on a PACS system by a musculoskeletal radiologist. The same subset of participants whose scans were double-reported by another radiologist in the previous phases of the study, were also analysed similarly at this MRI scanning time point. All details were described in the Methods section of Chapter 3.

In case of disagreement between radiologists regarding the assigned scores for each type of lesion and level of severity, consensus scores were established after a further discussion.

5.2.4 Quantification of MRI findings

The same validated scoring systems used in the assessment of all knee features and related lesions in the previous parts of the study were applied here as well. Each individual knee area was given corresponding scores based on their observed lesion status by the radiologists. The full description of these scoring systems, including the specific grading scales and regional subdivisions of each knee structure, can be found in Chapter 3.

5.2.5 KOOS questionnaire

All 44 participants were given KOOS questionnaires to fill in on the day when they had the MRI scan. The KOOS questionnaire description and calculation are summarised in Chapter 3. The objective was to evaluate the self-reported knee condition of the

participants 6 months after the marathon and compare these results with the 2 weeks post-marathon KOOS results, to understand whether any changes occurred in this period of time.

5.2.6 Statistical analysis

In the analysis of MRI findings, each individual knee of each study participant was evaluated and treated independently. The participant demographics, including age and BMI, were evaluated using unpaired *t* test to identify if there were any significant differences between marathon finishers and training non-finishers. Chi-squared test was performed to compare differences in gender between the two groups of participants, as well as differences between the prevalence of abnormalities at the 2 weeks post-marathon and 6 months follow-up MRI scans in these participants. The KOOS scores at these two time points were compared with Wilcoxon matched-pairs signed rank test and paired *t* test. Kappa scores were calculated to quantify interreader agreement. In all analyses, if the resulting p-values were < 0.05, the results were considered to be statistically significant (GraphPad Prism, version 6.0c).

5.3 RESULTS

I was involved in synthesising and analysing all the data including the scores reported by radiologists and participants' self-reported questionnaires, conducting statistical tests, writing the manuscript and disseminating the study findings. The interpretation of the findings was discussed with the radiologists. The supervisors evaluated the analysis and write-up.

5.3.1 Participant characteristics

There were 44/82 study participants who agreed to attend the third phase of the study and undergo bilateral MRI scans 6 months after the marathon. Our final cohort of 44 participants comprised of: 37 marathon finishers (who completed both the training programme for the marathon and the marathon run) and 7 training non-finishers (who did not finish the training nor ran the race). The remaining participants did not attend the follow-up MRI (drop-outs) due to reasons of unavailability on the specific scanning dates or personal reasons i.e. many runners were not London-based, being located across the UK. No complaints of knee injuries or other running-related issues were reported. The 7

training non-finishers who attended the 6 months follow-up stopped their training for the London Marathon and did not attempt to run on the race day due to the following reasons: 1 bradycardia, 1 bronchitis, 1 calf issue and 4 personal. The participant characteristics and study design are summarised in Table 5.1. and Figure 5.1, respectively.

Regarding participant demographics, I found no statistically significant differences between marathon finishers and training non-finishers, particularly in terms of age (p=0.922), BMI (p=0.238) and gender (p=0.273).

Out of 37 marathon finishers, the majority were aged ≥ 40 years old (68%; n=30) and the remaining ones (32%; n=7) were younger than 40 years old (range: 28-69 years old). All 7 training non-finishers were aged ≥ 40 years old (range: 41-54 years old). Regarding BMI, more than half of all marathon finishers (64%; n=28) fit in the normal BMI range category, while the rest had BMI ≥25 kg/m^2 at baseline but post-marathon reduction occurred as described in Chapter 4 (range: 19.6-33.9 kg/m^2). Similarly, the majority of training non-finishers had normal BMI (71%; n=5), and the range was: 21.3-25.1 kg/m^2 (see Table 5.1).

Table 5.1. Demographics of study participants

Characteristics	Marathon finishers (n=37)	Training non-finishers (n=7)
Age (years)	46.2 ± 9.3	46.6 ± 4.4
Male : Female ratio	13 : 24	4 : 3
BMI (kg/m^2)	24.5 ± 3.4	23.2 ± 1.5

Values are reported as mean ± standard deviation for age and BMI. BMI, body mass index.

There was great variety in the amount of physical activity in the period of time between the 2 weeks post-marathon MRI to the 6 months follow-up MRI: marathon finishers (mean 3 h/week [0–10]); training non-finishers (mean: 2 h/week [0–7]). The participants continued to run but did not train for any upcoming marathon running event in the period of time leading to the 6 months follow-up. No other exercise-related details were reported.

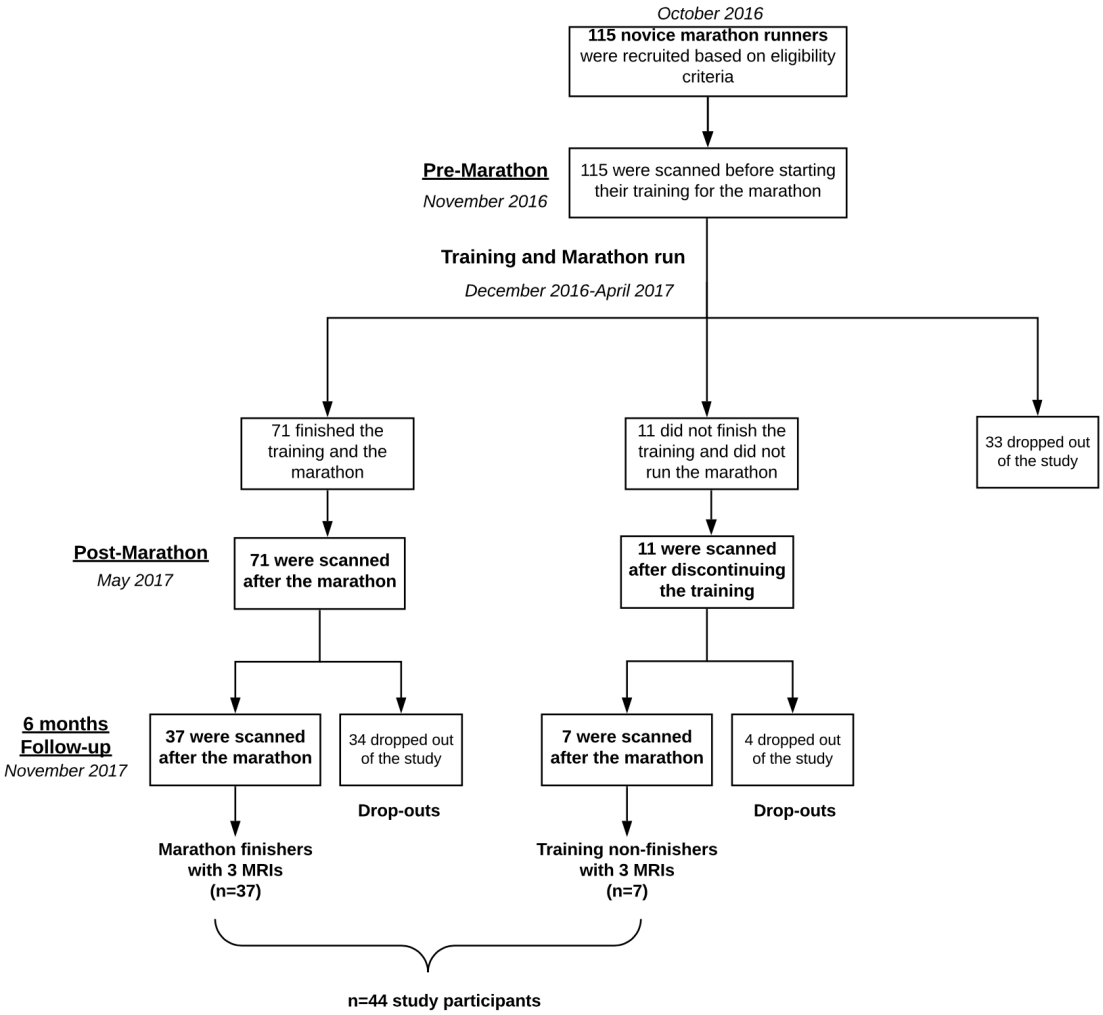


Figure 5.1. Study design

5.3.2 MRI findings

Articular cartilage

Improvement of pre-marathon abnormalities

There were 2 pre-marathon cartilage abnormalities which improved in their level of severity on the post-marathon MRI - in 2 knees of marathon finishers. One of these abnormalities was located in the patellofemoral compartment, and the other one in the tibiofemoral compartment (see Chapter 4).

Six months later, we scanned again both knees with these lesions and showed that this improvement was sustained on the MRI scans (Table 5.2). No worsening or reversibility to the pre-marathon grading status was reported. The specific grades are available in Appendix A.1.2)

Table 5.2. Status of marathon related changes at the 6 months follow-up in different structures, in 74 knees of 37 marathon finishers and 14 knees of 7 training non-finishers: 1) improved pre-marathon lesions at the 2 weeks post-marathon scan which had sustained improvement at the 6 months follow-up; 2) post-marathon lesions (new/worsened from the pre-marathon condition) which showed reversibility in extent at the 6 months follow-up; and 3) newly improved pre-marathon lesions at the 6 months follow-up. "Improvement" was defined as reduction in the extent of lesion (score/grade of severity) between MRI scans.

Knee abnormalities per structure	Marathon finishers (n=74 knees)					Training non-finishers (n=14 knees)				
	Sustained improvement		Reversibility of damage		New Improvements at 6 months FU	Sustained improvement		Reversibility of damage		New Improvements at 6 months FU
	Improved at Post-M	Sustained at 6 months FU	New/ Worse at Post-M	Reversed at 6 months FU		Improved at Post-M	Sustained at 6 months FU	New/ Worse at Post-M	Reversed at 6 months FU	
Cartilage lesions	2	2	21	3	3	0	0	4	0	3
Patellofemoral	1	1	17	3	3	0	0	3	0	3
Medial tibiofemoral	1	1	1	0	0	0	0	1	0	0
Lateral tibiofemoral	0	0	3	0	0	0	0	0	0	0
BME lesions	3	3	18	10	5	0	0	3	1	0
Patellofemoral	0	0	15	8	4	0	0	3	1	0
Medial tibiofemoral	1	1	2	1	0	0	0	0	0	0
Lateral tibiofemoral	2	2	1	1	1	0	0	0	0	0
Tendon lesions	0	0	6	1	0	0	0	2	1	0
Iliotibial band signal	0	0	9	5	0	0	0	1	1	0
Ligament lesions	2	2	2	2	0	0	0	0	0	0

All abnormalities were recorded including Grade 1 abnormalities (all grades different from 0 were defined as "lesions"). BME, bone marrow edema; Post-M, post-marathon; FU, follow-up.

Moreover, few new improvements in the extent of pre-existing pre-marathon lesions (which were unchanged at the post-marathon scan) were found at the 6 months follow-up. Specifically, there were 3/87 (3%) pre-marathon abnormalities in 3/48 (6%) knees of marathon finishers which showed a lower grade of severity at the 6 months follow-up MRI, and thus reached an improved state in comparison to the pre-marathon state. Out of the initial sum of 87 abnormalities - 62 in the patellofemoral compartment and 25 in the tibiofemoral one – the 3 improved cases were seen in the patellofemoral compartment at the follow-up (Appendix A.1.2).

Also, there were 3/11 (27%) reported pre-marathon lesions (with unchanged status after the training) in 2/7 (29%) knees of training non-finishers which improved in their extent at the 6 months follow-up (Table 5.2, Appendix A.1.2).

Reversibility of post-marathon abnormalities

Post-marathon, there were 25 cartilage abnormalities in total developing in 20 knees of marathon finishers. Six months later, we scanned 21/25 (84%) lesions of 16 knees of those marathon finishers who attended the follow-up MRI. These included 13 new abnormalities and 8 pre-existing abnormalities which worsened in their grading status from the pre-marathon to the post-marathon scans. Most of these abnormalities were found in the patellofemoral compartment (17/21; 81%), out of which half were new abnormalities. At the 6 months follow-up, 3/21 (14%) cartilage lesions in 3 individual knees of marathon finishers returned to the pre-marathon grading status (Figure 5.2). Further details on the specific changes in lesion grade can be found in Appendix A.1.2.

In the training non-finishers' group, 4 abnormalities in 3 knees of participants were reported shortly after training discontinuation. The majority of findings were located in the patellofemoral compartment (3/4; 75%), and none were new lesions, but increased in extent between the pre-marathon to the post-marathon time point. At the 6 months follow-up, all training non-finishers presenting with these lesions returned for a scan; no changes were reported at the follow-up, neither reversibility or worsening of those lesions.

No new lesions or further lesions progressing in extent from the post-marathon scan were reported at the 6-months follow-up.

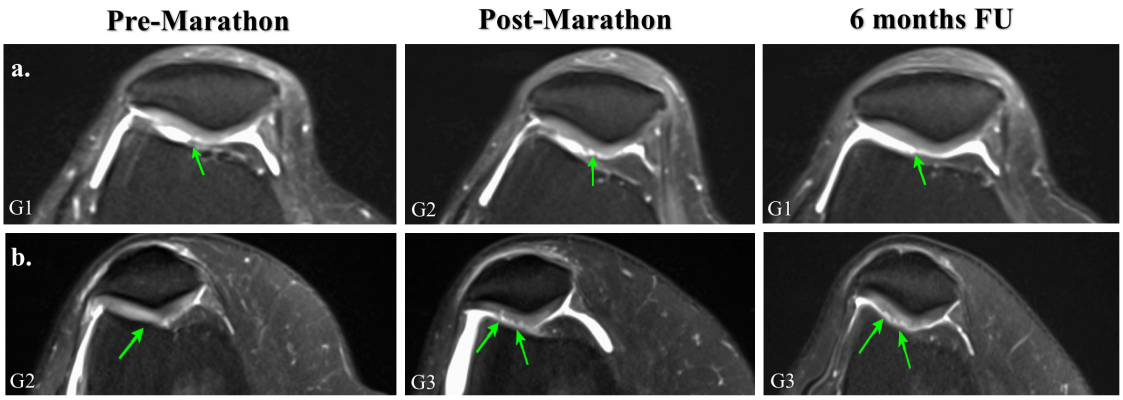


Figure 5.2. Axial proton-density fat-saturated MR images of two different knees with changes in the extent of chondral lesions of the patella: A) resolution at 6 months follow-up of a lesion that previously developed from the pre-marathon scan to the 2 weeks post-marathon scan, in the right knee of a 67-year-old woman; B) smaller lesion at the 6 months follow-up in comparison to the post-marathon state. The extent of lesion falls within the same grade parameters; however, it is slightly smaller showing signs of reversibility, in the right knee of a 51-year-old woman. Cartilage abnormalities are indicated by arrows and the lesion grade (G) is included in the left bottom corner and is defined in the new modified Noyes scoring system.

Bone marrow

Improvement of pre-marathon BME

Shortly post-marathon, there were 23 lesions in total (in 16 knees) which reduced in extent in comparison to their pre-marathon condition, mostly in the tibiofemoral compartment (see Chapter 4). Six months later, we captured 3/23 (13%) lesions on the MRI scans of 2 knees (all in the tibiofemoral compartment) of the returning participants at the follow-up. The improvement observed after the marathon was sustained at the 6 months follow-up (Table 5.2, Figure 5.3), and did not go back to the increased grading status reported before the marathon.

In the training non-finishers group, there were 3 improved lesions (one each in 3 knees, respectively), all in the tibiofemoral knee compartment, after training discontinuation. One of these lesions (33%) was scanned 6 months later and sustained improvement was reported as well over the respective period of time (Table 5.2, Appendix A.1.2).

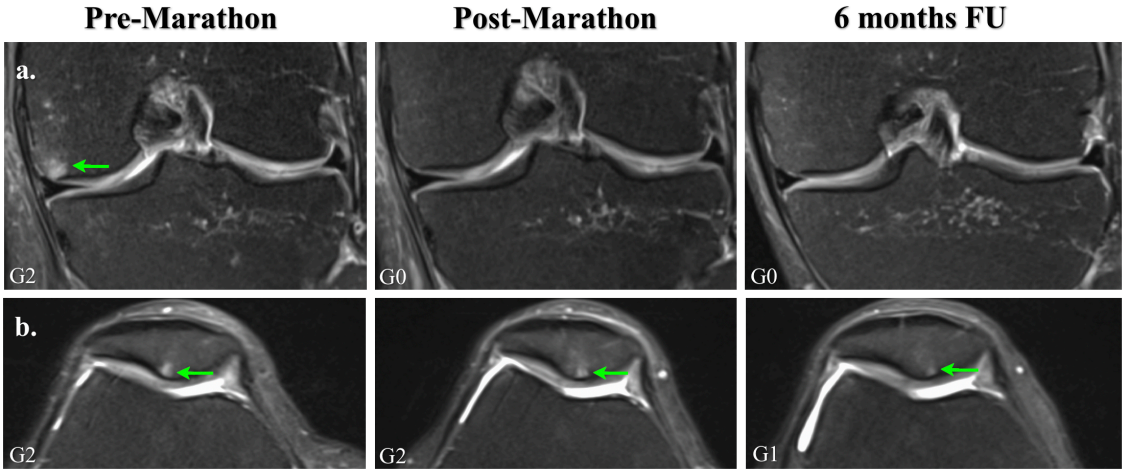


Figure 5.3. Coronal and axial proton-density fat-saturated MR images of two different knees with changes in the extent of subchondral BME: a) sustained improvement at the 6 months follow-up of a previous pre-marathon lesion that reduced in extent 2 weeks post-marathon, in the femur of the left knee of a 54-year-old man; b) new improvement at the 6 months follow-up in a pre-marathon lesion that remained unchanged from pre- to post-marathon, in the patella of the right knee of a 48-year-old woman. BME is indicated by arrows and the lesion grade (G) is included in the left bottom corner and is defined in KOSS, Knee Osteoarthritis Scoring System; BME, bone marrow edema.

Also, there were new improvements at the 6 months follow-up in the pre-marathon abnormalities which were unchanged from the pre-marathon to the post-marathon MRI scans (Figure 5.3, Appendix A.1.2). Overall, 46 such abnormalities (in 27 knees) were estimated in our final cohort of marathon finishers, out of which 33 were found in the patellofemoral compartment and 13 in the tibiofemoral one. At the 6 months follow-up, 5/46 (11%) abnormalities reduced in their extent– specifically 4/33 (12%) in the patellofemoral compartment and 1/13 (8%) in the tibiofemoral one (Table 5.2). The reduction was seen in the corresponding 4/27 (15%) knees.

Reversibility of post-marathon BME

Overall, there were 26 lesions (24 knees) which were acquired shortly post-marathon (see Chapter 4). Six months later, we scanned 18/26 (69%) lesions in 16 knees of the returning follow-up cohort of marathon finishers, specifically 16 new lesions and 2 which progressed from the pre-marathon state. The majority of these lesions were located in the patellofemoral compartment (15/18; 83%; 13 were new lesions). The 6 months follow-up scans showed reversibility in 10/18 (56%) BME-like lesions, in 10/16 (63%) knees (Table 5.3, Figure 5.4, Appendix A.1.2). Out of the 10 improved lesions, 8 returned completely to the pre-marathon condition, while the remaining 2 lesions reduced in their extent over time but not to the baseline status.

In the training non-finishers' group, 3 lesions developed in 2 knees after training discontinuation (knees), in the patellofemoral compartment (see Chapter 4). All lesions were scanned at the 6 months follow-up and reversibility was detected in 1/3 (33%), so in one of the knees of a participant (Table 5.2)

There were no new abnormalities or further lesions progressing in extent at the 6-months follow-up.

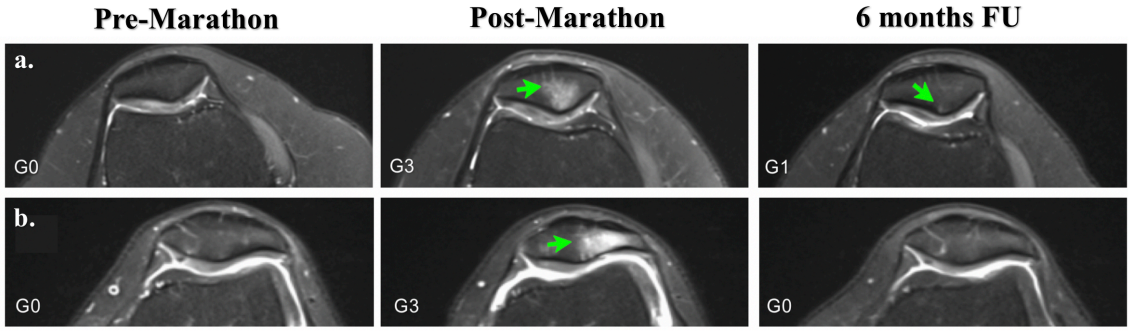


Figure 5.4. Axial proton-density fat-saturated MR images of two different knees that showed reversibility at 6-month follow-up in the extent of subchondral BME of the patella that previously developed from the pre-marathon scan to the 2 weeks post-marathon scan: a) reversibility but not to the pre-marathon grading status, in the right knee of a 31-year old woman; b) complete resolution to the pre-marathon grading status, in the left knee of a 34-year-old woman. BME is indicated by arrows and the lesion grade (G) is included in the left bottom corner and is defined in KOSS, Knee Osteoarthritis Scoring System.

Subchondral cysts

Additionally, shortly post-marathon, 2 pre-existing patellofemoral lesions improved in extent (in 2 knees of marathon finishers) and one of those knees was scanned 6 months later and showed sustained improvement. Also, 4 cysts (1 patellofemoral and 3 tibiofemoral) that developed following the run were all re-scanned at the 6 months follow-up and one of those (25%) resolved in the tibiofemoral compartment. Also, 2 training non-finishers each had a new lesion in one of their knees at the post-marathon scan but those participants were unable to attend the follow-up scan. No changes or new lesions appeared at this time point in any of the knees of the returning participants.

Tendons

Post-marathon, 13 tendon abnormalities were identified in 11 knees (see Chapter 4). At the 6 months follow-up, we scanned 6/13 (46%) tendon lesions (6 knees): 4 semimembranosus, 1 patellar, 1 gracilis. One semimembranosus tendon abnormality showed reversibility (1/6; 17%), while the rest remained unchanged on the MRI scans.

Two pre-marathon lesions improved in extent on the post-marathon scans, but we could not scan those participants' knees to assess if the improvement was sustained over time.
There were 2 post-marathon tendon abnormalities in 2 knees of one training non-finisher. We scanned both knees 6 months later and showed that one of them reversed while the other one was the same as before.
Also, 12 cases of post-marathon iliotibial band signal (in 12 knees) were identified on the MRI scans shortly after the marathon; 9/12 were scanned at the 6 months follow-up and 5/9 (56%) reversed. One abnormality was identified in a training non-finisher and this reversed 6 months later (Table 5.2, Appendix A.1.2)
There were no findings of new lesions or progression of post-marathon abnormalities on the follow-up scans.

Ligaments

Post-marathon, 2 pre-marathon abnormalities of the MCL disappeared – we scanned both abnormalities in two separate knees of marathon finishers after 6 months and both reported sustained improvement (Table 5.2, Appendix A.1.2). Also, there were 2 pre-marathon abnormalities of the LCL which worsened in their level of severity in 2 knees of separate runners shortly after the marathon. Both were scanned 6 months later and showed reversibility.
Training non-finishers showed no post-marathon abnormalities nor any changes at the follow-up.
No new lesions were identified on the 6 months follow-up MRIs.

There were no other changes to report on the MRI scans.

5.3.3. Associations between different MRI findings

No associations were found between the appearance of different types of MRI findings at the 6 months follow-up.

5.3.4 Distribution of MRI findings in participants and per knee side

There was no tendency towards one specific knee side to encounter certain changes. The number of participants and distribution of MRI changes per knee side at the 6 months follow-up, in both marathon finishers and training non-finishers, is summarised in the table below.

Table 5.3. Number of participants with both knees or single knees showing post-marathon MRI changes, either sustained improvement or reversibility of damage from the post-marathon status, in the articular cartilage, bone marrow, tendons, iliotibial band tendon and ligaments.

Key knee abnormalities	Type of changes at 6 months FU from the Post-M findings	No. of participants with changes from the Post-M condition in both knees	No. of participants changing from the Post-M condition in single knee sides		Total no. of participants with changes in either knee	Total no. of knees with Post-M changes		
			Right knee	Left knee		Right knee	Left knee	All knees
Marathon finishers (N=37 participants, 74 knees)								
Cartilage lesions	Sustained improvement	0/0	1/1	1/1	2/2	1/1	1/2	2/2
	Reversibility of damage	0/3	0/4	3/6	3/13	0/7	0/9	0/16
BME lesions	Sustained improvement	0/0	2/2	0/0	2/2	2/2	0/0	2/2
	Reversibility of damage	5*/6	2/4	0/0	7/10	5/10	5/6	10/16
Tendon lesions	Sustained improvement	0/0	0/0	0/0	0/0	0/0	0/0	0/0
	Reversibility of damage	0/0	1/4	0/2	1/6	1/4	0/2	1/6
Iliotibial band signal	Sustained improvement	0/0	0/0	0/0	0/0	0/0	0/0	0/0
	Reversibility of damage	2**/2	1/2	1/3	4/7	3/4	2/5	5/9
Ligament lesions	Sustained improvement	0/0	0/0	2/2	2/2	0/0	2/2	2/2
	Reversibility of damage	0/0	1/1	1/1	2/2	1/1	1/1	2/2
Training non-finishers (N=7 participants, 14 knees)								
Cartilage lesions	Sustained improvement	0/0	0/0	0/0	0/0	0/0	0/0	0/0
	Reversibility of damage	0/0	0/3	0/0	0/3	0/3	0/0	0/3
BME lesions	Sustained improvement	0/0	0	1/1	1/1	0	1/1	1/1
	Reversibility of damage	0/0	1/1	0/1	1/2	1/1	0/1	1/2
Tendon lesions	Sustained improvement	0/0	0/0	0/0	0/0	0/0	0/0	0/0
	Reversibility of damage	1**/1	0/0	0/0	1/1	1/1	0/1	1/2
Iliotibial band signal	Sustained improvement	0/0	0/0	0/0	0/0	0/0	0/0	0/0
	Reversibility of damage	0/0	1/1	0/0	1/1	1/1	0/0	1/1
Ligament lesions	Sustained improvement	0/0	0/0	0/0	0/0	0/0	0/0	0/0
	Reversibility of damage	0/0	0/0	0/0	0/0	0/0	0/0	0/0

The number of cases which underwent a specific type of change at 6 months follow-up in comparison to the post-marathon condition was separated by '/' from the total number of tested cases showing post-marathon damage or improvement. *In 2 out of 5 participants with post-marathon changes in both their knees, only one of the knees of each participant changed further (sustained post-marathon improvement or reversed post-marathon damage) at the 6 months follow-up, respectively. The remaining 3 participants had changes in both knees;**Only one of the knees changed in one participant (not both knees); BME, bone marrow edema; Post-M, post-marathon.

No other findings were noticed apart from the ones presented in the table and few subchondral cysts changes. One subchondral cyst in the right knee of a marathon finisher, which improved in extent from the pre-marathon to the post-marathon status, showed sustained improvement 6 months later. Also, there were 4 cysts that developed shortly after the run and were located in the right knees of 4 different marathon finishers, and one of them resolved at the 6 months follow-up.

Additionally, new improvements at the 6 months follow-up were seen in the extent of pre-existing cartilage lesions (in both knees of one marathon finisher, and in the right knee of another marathon finisher) and BME (in 4 right knees of each 4 marathon finishers). Also, new improvements in pre-existing cartilage lesions were found in 2 left knees of 2 individual training non-finishers.

5.3.5 Associations between MRI findings and participant characteristics

There were no associations between the MRI results at the 6 months follow-up and any of the known participant characteristics or physical activity levels.

5.3.6 Double-reporting consensus

There was very good agreement between the radiologists' scores for the double-reported sample (kappa 0.810).

5.3.7 KOOS

Based on the KOOS scores, no significant differences were found in our study participants' perceived knee condition between the 2 weeks post-marathon and the 6 months follow-up MRI scanning time points, in marathon finishers: pain (p=0.532), other symptoms (p=0.683), daily activity (p=0.586), sports and recreational activities (p=0.594), knee-related quality of life (p=0.417); and training non-finishers: pain (p=0.500), other symptoms (p>0.999), daily activity (p=0.500), sports and recreational activities (p>0.999), knee-related quality of life (p>0.999).

5.4 DISCUSSION AND CONCLUSIONS

This study showed that marathon running and preceding training may have differential effects on the knees of novice marathoners in terms of type and location of 3.0 T MRI changes at a 6 months interval after the marathon. Firstly, the beneficial effects of marathon running particularly in reducing the extent of pre-marathon BME, and in some cases, of cartilage lesions, were sustained 6 months later; this suggests that the improvement seen shortly after the marathon run may be maintained over time. Secondly, the abnormalities that spontaneously appeared in some of the knee structures on MRI shortly after the run, especially in the patellofemoral joint, showed signs of reversibility within 6 months after the marathon: more than half of all BME-like lesions showed

reversibility to the pre-marathon state, cartilage lesions resolved in 14% cases, subchondral cysts reversed in 25% cases (out of a small number of post-marathon cysts), tendon abnormalities in 17% (most of the remaining ones had mild post-marathon increases in tendon signal only), iliotibial band signal in 56%, and all ligamentous abnormalities showed reversibility; this means that immediate post-marathon insult to the soft tissues may be temporary, however the amount of time needed for complete resolution of the remaining lesions is yet unclear. No new lesions or progression of pre-existing ones was observed at the 6 months follow-up. Also, few new improvements in the status of pre-marathon lesions which were unchanged shortly after the run were reported in 3% cartilage lesions and 11% BME cases.

5.4.1 Study strengths

Our study adds to the existing peer-reviewed literature due to a number of reasons: 1)This is the largest study to date to evaluate the lasting impact of intense running over time and included the longest medium-term follow-up of 6 months after the run, using bilateral high-resolution 3.0 T MRI. Other MRI studies did not include more than 13 runners and the follow-up periods were not longer than 3 months. We selected a 6 months medium-term follow-up to allow more time for the knee joints to potentially adapt to the immediate impact of a marathon run and observe any changes occurring over time; 2) This study assessed the impact of both a single marathon run and the training for the marathon on the knees, whereas the existing literature to date conducted the MRI scans shortly before and after the marathon running event, yet not prior to the start of the training; 3) This was the most comprehensive follow-up assessment of all knee features of runners, including knee joint compartments, regions and subregions; while some previous studies looked at specific structures of interest only, or did not use reliable validated MRI-based scoring systems; 4) 3.0 T MRI is a highly sensitive equipment that was used in this study for its increased resolution in comparison to the commonly used 1.0 T and 1.5 T MRI and better detection of even subtle signs of lesions in the internal structures; 5) The study cohort included previously untrained physically inactive, first-time marathon runners, with no running experience, while in previous studies the participants were generally experienced long-distance runners. This is the first MRI study of this kind.

5.4.2 Study limitations

I acknowledge few limitations of the study, including the following: 1) the physical activity levels during the period of time leading to the 6 months follow-up varied among participants and were self-reported, not giving full details. The participants confirmed that they were not training for a second marathon race, however it was not reported whether they were training for a different type of race, such as half-marathon or shorter/longer-distance races. Also, the participants could have altered the amount of self-reported physical activity, which might have resulted in the recovery of some abnormalities faster than others; however, close monitoring of the physical activity over a relatively long period of time is challenging and some level of bias or lack of reporting cannot be avoided; 2) Internal quality controls of non-runners were not included, so I could not compare the results from our cohort to the MRI findings of a group of participants whose knees were not exposed to any training for the marathon; however training non-finishers were included as part of our analysis; 3) MRI analysis involves a certain degree of bias, but we included two radiologists in our research to improve the reliability of our results; 4) the precise times when training non-finishers stopped their training plan were not recorded, so could not be analysed or commented on; 5) Slightly more than half of the total number of participants who were scanned shortly after the marathon returned to the 6 months follow-up; therefore the MRI status of all knees could not be checked over time (including post-marathon new lesions or improved ones in drop-outs). The drop-out rate/loss to follow-up may cause bias and affect the interpretation of our results [327]; 6) longer-term follow-up studies (e.g. 2 years after the marathon or longer) are required to clarify whether the improvement seen after the marathon is sustained over a longer period of time or how it changes later on depending on participant characteristics, and whether complete reversibility of the remaining post-marathon abnormalities occurs over time as the clinical significance of the results is currently uncertain.

5.4.3 Comparison with previous studies

Despite the increasing participation in long-distance running of novice runners and the reported risks of injuries, there is limited evidence on the lasting effect of marathon running on the knee joints of inexperienced long-distance runners. Most studies only analysed the short-term impact of marathon running and included non-professional yet regular long-distance runners with previous running experience, demonstrating no major knee MRI abnormalities after a marathon [43,223,225–228]. Moreover, only very few

investigated further whether a marathon run induces any permanent knee changes over a longer period of convalescence: ≤3 months; and one study did a 10-year follow-up; none suggested permanent running-related knee damage [58,176,227,228].

Firstly, Krampla *et al* [58] analysed the knees of 8 recreational long-distance runners with 1.0 T MRI before the Vienna City Marathon, 24 hours after the competition and then 2 months later. In accordance with our study, increased MRI signal in the bone marrow was identified immediately after the marathon and then the signal decreased back to baseline in the following two months. In a 10-year follow-up study, the same group confirmed no long-term knee damage being associated with running [224]. However, our study showed decrease in only half of the post-marathon lesions at a 6 months follow-up. Possible explanations for the differences in the study results are the following: 1) MRI equipment - we used high-resolution 3.0 T MRI and a multichannel coil for increased sensitivity therefore all MRI changes were detected, including subtle ones which might have been omitted with low-resolution 1.0 T MRI [193,288]; 2) different participant characteristics – we included older (mean age: 44 years), previously sedentary individuals before the training for the marathon, with no long-distance running experience, who ran their first marathon and were exposed to high physical stress over 4 months, while in Krampla's study the participants were regular runners, younger than our cohort (mean: 37 years), with a long history of long-distance running of 5-20 years. So perhaps the knees of novice, older marathoners are more vulnerable to intense exercise and it might take longer for them to recover after a run [269,328]. Moreover, traumatic BME has been reported to resolve within 3 months - 2 years [12,13,235,329–331]. Also, studies have suggested that the knees of trained runners could potentially develop adaptation mechanisms which may decrease the rate of impact and reduce the risk of injury, and that adaptation mechanisms differ significantly among runners [43,71,110–112,332]; 3) large sample size - we included 5 times more participants and scanned both their knees.

Secondly, using 3.0 T MRI, few recent medium-term follow-up studies analysed the biochemical changes in the knee cartilage for signs of degeneration, apart from morphological changes [176,227,228]. Morphological defects in the cartilage are thought to be preceded by early degradation of the biological matrix [164,166–168]. Luke *et al* [227], Stehling *et al* [228] and Hesper *et al* [176] conducted MRI analyses immediately before and after (48-72 hours) the marathon, as well as 2-3 months later. None of them found any morphologically evident damage on MRI throughout the scanning period,

however biochemical changes were detected shortly after the marathon in the cartilage. Some of these biochemical changes reversed within 2-3 months after the run, while some others remained persistent; yet further investigations are required to clarify the significance of these results [176,227,228]. Contrary to these findings, our morphological assessment revealed a number of MRI abnormalities in the articular cartilage two weeks after the marathon, out of which only 14% showed reversibility 6 months after the marathon. However the biochemical fluid changes demonstrated in the above mentioned studies suggest that the cartilage is a complex structure to analyse and the mechanisms of pathogenesis are still unclear. The cartilage may be able to adapt to loads caused by repeated loading during running and recover from post-marathon changes over time [223,229], but the time of recovery may vary [229]. The cartilage does not have a blood supply, therefore injuries to this structure may take a longer time to heal in comparison to other structures [2], so further investigations including longer follow-ups are required. Moreover, as mentioned before, the differences in study designs and participant characteristics may also account for the conflicting results. The other studies included younger (mean age: 31 years), more experienced regular long-distance runners and the sample size was <13 participants [176,227,228]. Also, there is evidence to suggest that cartilage abnormalities are generally more common in individuals aged ≥40 years old [269].

In addition, previous running studies focused on the effects of marathon running on the knees while excluding the impact of training for the marathon; perhaps because those participants had previous long-distance running experience and might not have been at their first training for a marathon or long-distance running event when the study was conducted [43,58,166,176,224,227,228]. Only one study resembled our study by assessing the effect of a single marathon training programme followed by the marathon itself on the knees of first-time marathon runners [229]. However the participants had more previous running experience before their training (average: 34 months) than our study participants who were previously sedentary. Similarly to our study, cartilage deformation was observed the day after the marathon in comparison to the pre-training status, however the clinical significance was uncertain and no follow-up study was conducted.

5.4.4 Clinical significance and future work

Firstly, from a clinical perspective, the sustained beneficial impact of marathon running and preceding training on the knee joints at the 6 months follow-up suggests that running

may contribute to improving knee outcomes and even potentially decrease the risks of getting OA over time. Also, the new improvements seen in the extent of pre-existing BME (lesions that were unchanged shortly after the marathon) at the 6 months follow-up further emphasise that running may benefit the health of knees also later on after the marathon was finished. This hypothesis is also supported by other research studies which imply that running may have a protective effect against developing knee OA [124,333–335], and this needs to be investigated further in long-term studies.

Secondly, our findings suggest that, for asymptomatic inexperienced runners, with a 4-month pre-marathon training only, a marathon run may be more demanding on the patellofemoral knee compartment, particularly the patellar bone marrow and cartilage, but there is significant reversibility in the extent of BME over time which may indicate a transitory effect of the post-marathon insult to the knee. According to the existing literature, post-traumatic bone marrow bruising (symptomatic or asymptomatic) deriving from various types of trauma are common, but the natural history of these lesions has not been well investigated; however, spontaneous bone marrow edema healing has been reported in several studies, within a range of 3 months - 2 years [12,13,235,329–331]. Therefore, the remaining BME developing or progressing in extent after the marathon run is expected to reverse and disappear on the MRI scans within 2 years, and follow-up scans will be required to demonstrate this. Moreover, the cartilage may also have the ability to adapt to running related-loads exerted on the knee joint, but the time needed for full recovery may vary [223,229]. While the bone marrow is relatively simple to visualise in order to quantify the effect of exercise on the structure, the cartilage is a more complicated structure to radiologically grade and study. Cartilage analysis is more complex given the differences between the morphological measurements and the biochemical analysis demonstrated using 3.0 T MRI in recent studies [176,227,228], also given the difficulties in grading the cartilage, as being acknowledged in the literature [336]; therefore the impact of marathon running needs to be investigated further. Since subchondral bone marrow and cartilage defects are linked with the onset of OA [296–298,337], it is crucial to understand what is the optimal duration of exercise in order to make evidence-based recommendations to patients related to their physical activity and prevent or delay the progression of OA.

Further research is required to clarify whether more time is needed for the complete recovery of post-marathon BME, cartilage lesions and other structural changes, in those cases that did not reverse back to pre-marathon levels at the 6 months follow-up.

Chapter 6 – Hip study

Assessing the prevalence of MRI abnormalities in asymptomatic hip joints of novice and experienced marathon runners before marathon running

(pre-marathon data)

Work presented in this chapter has been submitted for publication

6.1 INTRODUCTION

There has been a steady growth in the popularity of long-distance running over the last decades, particularly marathons and ultramarathons (distances longer than a marathon) as ultimate challenges and running goals [338]. The increasing participation in both recreational running events and competitive races has showed to be prevalent in individuals of all ages. Female participation has increased significantly, with over 40% women taking up running. Despite the myriad of health benefits associated with running (e.g. cardiovascular protection, overall wellbeing), long-distance running has been controversially linked with a rise in the number of injuries affecting the lower limb extremities, including the hip joints [65].

So far, the knee has been the most studied human body joint in running research since it is considered to be a common area of running-related complaints. However, there is extremely little research investigating the impact of long-distance running on the hip joints of runners. Furthermore, the optimal duration of running for ensuring healthy hips is not clear yet. The reported prevalence of injuries ranged between 3 and 12% [61,65,113,339]; the discrepancies in the reported numbers may result from the use of various definitions of injury, different types of runners being included in studies, with distinct levels of experience and types of training plans, diagnostic tools and imaging techniques.

Limited diagnostic tools and management interventions were available in the past for injuries of the hips of either athletes or non-athletes [340,341]. The progress in hip surgical procedures and recent advances in high-resolution MRI, particularly 3.0 T MRI technology have led to improvements in the diagnosis and treatment of nonarthritic hips [340].

Research evidence on the prevalence of asymptomatic hip abnormalities on MRI in the population is very scarce [342–346]. Moreover, there is one study only that assessed the hips of runners using MRI. But this was not a baseline study, but an analysis of the MRI changes appearing after a marathon run; also a small sample size was included (n=8), specifically of experienced long-distance runners only, and low-resolution unilateral MRI technique instead of a high-resolution bilateral one was used. Therefore, there is a need for providing evidence-based recommendations on the appropriate duration of running for the hip joints, by conducting reliable running studies using high-resolution MRI in different types of runners.

6.1.1 Motivation

It is essential to analyse the prevalence, types, levels of severity and locations of existing asymptomatic abnormalities in the hip joints of both non-marathon runners and experienced marathon/ultrarunners, to gain a better understanding of the hip health status of individuals with various exercise and running experiences, and to learn how to prevent and minimise the risk of hip injuries. In comparison to the knee project described in previous Chapters, apart from the analysis of intraarticular hip joint features, we hereby provide an additional analysis of hip muscles.

6.1.2 Aim

To investigate the hip condition of asymptomatic non-marathon runners, who never ran a marathon, and experienced marathon/ultrarunners.

6.1.3 Objectives

To assess the prevalence and type of hip joint abnormalities in asymptomatic non-marathon runners and experienced marathon/ultrarunners and to compare between the outcomes of the 2 groups, using morphological high-resolution 3.0 T MRI, validated MRI-based hip scoring systems and self-reported questionnaires.

6.2 MATERIALS AND METHODS

I was involved in preparing the ethics application and obtaining ethics approval, helping with conceptualising the study design along with the research team, recruiting participants, organising the study, reviewing the relevant literature and collecting the data. The musculoskeletal radiologists were responsible for designing the MRI protocol, helping in selecting the appropriate scoring systems and for reporting the MRI findings. The Chief investigator and the other members of the research team were involved in supervising me and ensuring that the study was organised appropriately.

6.2.1 Study design and participants

I recruited participants in our study from the wide community of runners in Greater London, by contacting organisers of local running events and by word of mouth. The volunteers who expressed interest in our study were selected based on our inclusion and

exclusion criteria. Then they were given information sheets with further details about their involvement via email. Once they agreed to all the conditions of their participation, the volunteers signed consent forms and completed the recruitment process.

Inclusion criteria were the following ones: individuals with healthy asymptomatic hip joints, with no known hip conditions, or history of hip injuries or surgical interventions. Volunteers with varying levels of physical activity and running experience were included in the study and there were no restrictions on the dose of exercise limit. The range of volunteers varied from 'couch potatoes' (physically inactive individuals) to occasional runners, marathon runners and ultrarunners. I differentiated between 2 main groups of volunteers by considering the participation in at least one marathon event as a reference point. The groups of volunteers were classified into: 1)'Non-marathoners' (<Marathon group'), whose physical activity levels were below a marathon running distance; 2)'Marathoners+' (≥Marathon group), who ran at least one marathon race or longer distances in the past (≥42 km).

There were a number of exclusion criteria which were considered: present or past hip injuries or pathologies, age <18 years old, pregnancy or breastfeeding, MRI contraindications (e.g. history of claustrophobia, panic attacks or anxiety).

6.2.2 MRI protocol

All participants underwent MRI scans of both hips (bilateral scanning). The MRI protocol included the use of a Siemens Magnetom VidaHealthineers 3.0 T MRI scanner (produced in Erlangen, Germany) and a 18-channel ultraflex coil. The MRI sequences chosen for this morphological evaluation were in 3 planes, with specifically designed parameters (TR/TE; measured in ms): coronal PD FS TSE sequences (4190/44), with image size/acquisition matrix: 512x512 pixels; sagittal bilateral planes PD FS TSE (4420/35), with image size: 320x320 pixels; axial T_1 TSE (27/10); coronal PD TSE (3290/39); axial PD TSE (4400/36); with image size: 384x384 pixels. Moreover, Dixon axial sequences were used in 4 phases (4220/45); and T_1 volumetric interpolated breath-hold examination (VIBE) 3D coronal (0.1/4.92). The Dixon sequences included as part of the protocol were in 4 phases: in-phase, out-of-phase, water phase, fat phase. Slice thickness was 3 mm. Both hips of each participant underwent MRI scanning (bilateral scans) and the total scanning duration was 25 minutes per participant. The protocol was designed and optimised by a senior musculoskeletal radiologist.

6.2.3 Image analysis

The images were viewed on PACS and analysis was done further on an image processing software (OsiriX MD v.9.0, Pixmeo Sarl 2016). All MRI scans were reported by a senior musculoskeletal radiologist with 10 years of experience in musculoskeletal imaging. The scans from 20% of participants (10 randomly-selected volunteers) were co-reported independently by a second musculoskeletal radiologist with 9 years of experience in radiology, to confirm the accuracy of MRI reporting. The participants were randomly selected. The two radiologists were blinded to participant characteristics and other details about their physical activity.

In case the radiologists' reports showed disagreement, consensus reading was done in a second meeting where the 2 radiologists discussed and came to an agreement about the presence or extent of a specific finding.

6.2.4 Quantification of MRI findings

MRI-based semi-quantitative validated scoring systems were used for reporting the findings, including both the presence of lesions and their severity levels for each individual hip joint feature. The main hip joint structures that were evaluated are the following: labrum, articular cartilage, bone marrow, tendons, ligaments, and muscles [260–262]. The presence of other additional findings or joint processes, including trochanteric bursitis and effusion, were reported (Table 6.1). These scoring systems were selected by the research team after discussions with the radiologists, based on their expertise, the existing literature and common medical practice in radiology.

SHOMRI system was used for the analysis of most of the structures of interest, including the labrum, articular cartilage, bone marrow and ligaments. For tendon and muscle analysis, the radiologists used reliable classification systems described by Chi *et al* [261] and Goutallier *et al* [262], respectively. All abnormalities with scores/grades>0 were counted.

The anatomical divisions for each internal hip structure were defined by the specific scoring system assessing those structures. The labrum was divided into 4 subregions: anterior, posterior, anterosuperior, superior. The articular cartilage and bone marrow were separated into main 2 regions: acetabular region (with 4 further subregions: anterior, posterior, superolateral, superomedial) and femoral region (with 6 further subregions: anterior, posterior, lateral, superolateral, superomedial, inferior).

Table 6.1. Hip joint scoring systems

Hip feature	Scale of grading system		Reference
Labrum	0=normal variant such as aplasia or hypoplasia 1=abnormal signal and/or fraying 2=simple tear 3=labrocartilage separation 4=complex tear 5=maceration		**SHOMRI** [260]
Articular cartilage (acetabular, femoral)	0=no loss 1=partial thickness 2=full thickness loss 2=full thickness loss		**SHOMRI** [260]
Bone marrow (acetabular, femoral)	**Subchondral BME** 0=no lesion is present 1=≤0.5 cm in size 2=>0.5 cm but ≤1.5 cm 3=>1.5 cm in size	**Subchondral cyst** 0=absent lesion 1=≤ 0.5 cm in size 2=>0.5 cm in size	**SHOMRI** [260]
Tendons	0=normal 1=tendinosis (intermediate signal, not fluid) 2=low-grade partial thickness tear (<50% tendon fluid signal) 3=High grade partial thickness tear (>=50% tendon fluid signal) 4=Full thickness tear (complete fluid signal) 4=Full thickness tear (complete fluid signal)		**Chi *et al*** [261]
Ligaments (ligamentum teres)	0=normal 1=signal abnormalities or fraying 2=partial tear 3=complete tear.0=normal3=complete tear.		**SHOMRI** [260]
Muscles	0=normal muscle (no fat) 1=some fatty streaks (for minimal atrophy) 2=less than 50% fatty muscle atrophy (for mild atrophy - fat infiltration less than muscle) 3=50% fatty muscle atrophy (for moderate atrophy - fat infiltration equal to muscle) 4=greater than 50% fatty muscle atrophy (for marked atrophy - fat infiltration greater than muscle)		**Goutallier *et al*** [262]
Other findings	Binary (present/absent)		-

SHOMRI, Scoring hip osteoarthritis with MRI; BME, bone marrow edema.

6.2.5 Hip Disability and Osteoarthritis Outcome Score (HOOS) questionnaire

HOOS questionnaire aimed to evaluate the self-reported hip health status of the study participants. The main questionnaire items were the following: pain (questions P1-P10), other symptoms (questions S1-S5), function in daily living (questions A1-A17), function in sports and recreational activities (questions Sp1-Sp4) and knee-related quality of life

(questions Q1-Q4). The HOOS questionnaires were completed by participants on the same day when the MRI scanning session took place. The role of this questionnaire was to confirm that all participants had asymptomatic hips and to compare between the HOOS scores and the MRI scores assigned by radiologists based on the scoring systems used.

The HOOS questionnaire takes around 10 minutes to complete and can be found below (Figure 6.1).

HOOS HIP SURVEY

Today's date: _____/_____/_____ Date of birth: _____/_____/_____

Name: _____

INSTRUCTIONS: This survey asks for your view about your hip. This information will help us keep track of how you feel about your hip and how well you are able to do your usual activities.
Answer every question by ticking the appropriate box, only one box for each question. If you are uncertain about how to answer a question, please give the best answer you can.

Symptoms

These questions should be answered thinking of your hip symptoms and difficulties during the **last week**.

S1. Do you feel grinding, hear clicking or any other type of noise from your hip?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S2. Difficulties spreading legs wide apart

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

S3. Difficulties to stride out when walking

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Stiffness

The following questions concern the amount of joint stiffness you have experienced during the **last week** in your hip. Stiffness is a sensation of restriction or slowness in the ease with which you move your hip joint.

S4. How severe is your hip joint stiffness after first wakening in the morning?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

S5. How severe is your hip stiffness after sitting, lying or resting **later in the day**?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Pain

P1. How often is your hip painful?

Never	Monthly	Weekly	Daily	Always
☐	☐	☐	☐	☐

What amount of hip pain have you experienced the **last week** during the following activities?

P2. Straightening your hip fully

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

What amount of hip pain have you experienced the **last week** during the following activities?

P3. Bending your hip fully

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P4. Walking on a flat surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P5. Going up or down stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P6. At night while in bed

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P7. Sitting or lying

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P8. Standing upright

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P9. Walking on a hard surface (asphalt, concrete, etc.)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P10. Walking on an uneven surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, daily living

The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your hip.

A1. Descending stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A2. Ascending stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A3. Rising from sitting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A4. Standing

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your hip.

A5. Bending to the floor/pick up an object

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A6. Walking on a flat surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A7. Getting in/out of car

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A8. Going shopping

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A9. Putting on socks/stockings

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A10. Rising from bed

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A11. Taking off socks/stockings

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A12. Lying in bed (turning over, maintaining hip position)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A13. Getting in/out of bath

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A14. Sitting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A15. Getting on/off toilet

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A16. Heavy domestic duties (moving heavy boxes, scrubbing floors, etc)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A17. Light domestic duties (cooking, dusting, etc)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, sports and recreational activities

The following questions concern your physical function when being active on a higher level. The questions should be answered thinking of what degree of difficulty you have experienced during the **last week** due to your hip.

SP1. Squatting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP2. Running

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP3. Twisting/pivoting on loaded leg

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP4. Walking on uneven surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Quality of Life

Q1. How often are you aware of your hip problem?

Never	Monthly	Weekly	Daily	Constantly
☐	☐	☐	☐	☐

Q2. Have you modified your life style to avoid activities potentially damaging to your hip?

Not at all	Mildly	Moderately	Severely	Totally
☐	☐	☐	☐	☐

Q3. How much are you troubled with lack of confidence in your hip?

Not at all	Mildly	Moderately	Severely	Extremely
☐	☐	☐	☐	☐

Q4. In general, how much difficulty do you have with your hip?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Thank you very much for completing all the questions in this questionnaire.

Figure 6.1. HOOS questionnaire (reproduced from pramodachan.co.uk).

HOOS score calculation

The HOOS score is calculated in a similar way to the KOOS score for each individual questionnaire item (see Chapter 3). The resulting score can range from 0 to 100, with 0=worst hip outcomes, and 100=no hip problems. Below is a summary of the calculations:

6. PAIN: $100 - \frac{Mean\ score\ (P1-P10)x100}{4} = HOOS\ Pain$

7. SYMPTOMS: $100 - \frac{Mean\ score\ (S1-S5)\ x\ 100}{4} = HOOS\ Symptoms$

8. ADL: $100 - \frac{Mean\ score\ (A1-A17)\ x\ 100}{4} = HOOS\ ADL$

9. SPORT/REC: $100 - \frac{Mean\ score\ (Sp1-Sp4)\ x\ 100}{4} = HOOS\ Sport/Rec$

10. QOL: $100 - \frac{Mean\ score\ (Q1-Q4)\ x\ 100}{4} = HOOS\ QOL$

6.2.6 Statistical analysis

Comparative analyses between two groups of participants were performed using the unpaired *t* test or Mann–Whitney *U* test. Also, ANOVA or Kruskal-Wallis statistical test was conducted when >2 groups or subgroups of participants were compared. Gender differences between groups or subgroups of participants were calculated based on Chi-squared test. Any associations between participant demographics and the presence of different types of MRI findings were evaluated by performing Chi-squared test. Estimations of OR with 95% CI were done for calculating potential associations. In the case of double-reporting, interobserver agreement was measured based on the calculation of kappa values. The evaluation of MRI findings was done by treating each hip individually in the statistical analysis. Statistically significant results were indicated by $p<0.05$ (GraphPad Prism, V.6.0 c).

6.3 RESULTS

I was involved in synthesising and analysing all the data including the questionnaires and radiological scores provided by radiologists, doing statistical analyses, writing the manuscript and disseminating the research. The results were discussed and interpreted with the help of radiologists. The supervisors assessed the analysis and write-up and made comments/edits.

6.3.1 Participant characteristics

I included 52 volunteers in our final study cohort who met all the inclusion criteria, and were divided into 2 main categories: 'non-marathoners' and 'marathoners+'. Thirty-six volunteers fell into the category of 'non-marathoners': 8 'couch potatoes' (sedentary physically inactive) and 28 'recreational/occasional runners' [n=5 completed 10 km races, while n=23 completed 21 km races as longest distance; running ≥2 times/week (median: 3; range: 2-4 times/week), for 3-4 hours running/week overall (all sessions/week)]. The second group of volunteers that I recruited is called 'marathoners+', comprising of 16 individuals: 10 'marathon runners' (who ran ≥3 marathons), and 6 'ultramarathoners' [who ran races longer than a marathon distance (>42 km); n=2 ran 50 km distances, n=1 ran 60 km and n=3 completed 100 km running distances; running ≥4 times/week (median: 4; range: 4-7 times/week); for a median of 6 hours (range: 4-10 hours) of running/week (all running sessions).

The vast majority of participants (95%) had white ethnicity: Welsh/English/Scottish/Northern Irish/British. Among the non-marathoners group 53% were males and 47% females, while in the marathoners+ group there were 75% males and 25% females. There were 6/36 (17%) non-marathoners aged ≥40 years old and 6/16 (38%) marathoners+ aged ≥40 years old, while the rest were aged <40 years old. The age range for non-marathoners was 18-58 years old, while the range for marathoners+ was 21-59 years old. Also, 4/16 (25%) non-marathoners and 8/28 (29%) marathoners+ had BMI ≥25 kg/m^2, respectively; the rest had BMI <25 kg/m^2. The BMI range for non-marathoners was 17.5-27.7 kg/m^2, while for marathoners+ was 19.3-33.3 kg/m^2. The characteristics and demographics of the two groups of participants are listed in Table 6.2.

No significant differences were found between non-marathoners and marathoners+ regarding demographics, specifically for age (p=0.080), gender (p=0.132), BMI

(p=0.623). Moreover, there were no statistically significant differences between the characteristics of the subgroups making up the non-marathoner group (couch potatoes and recreational runners), as well as the subgroups making up the marathoners+ group (marathon runners and ultramarathoners).

Table 6.2. Baseline characteristics of study participants

Characteristics	Non-marathoners (n=36)	Marathoners+ (n=16)
Age (years)	30.0 ± 8.0	36.0 ± 10.0
Male : Female	19 : 17	12 : 4
BMI (kg/m^2)	23.0 ± 2.3	23.8 ± 3.5

Values are reported as mean ± standard deviation for age and BMI. BMI, body mass index.

6.3.2 MRI findings

We analysed the 3.0 T MRI findings from 104 asymptomatic hips (bilateral scans of 52 participants) and found 50-60% of them having at least one type of hip abnormality or joint process, specifically 51% hips of non-marathoners and 63% hips of marathoners+. A number of abnormalities were identified in the following intraarticular structures: labrum, articular cartilage, bone marrow, ligament, tendons; and also muscles. The prevalence of abnormalities was generally higher for most structures in non-marathoners than in marathoners+, except for bone marrow cysts and tendinosis. This was an assessment of both hips of study participants, as an overview of all abnormalities, so the reporting of findings was done per hips and not per individual participants.

No significant differences were found between the MRI scores of couch potatoes and recreational runners (among the group of non-marathoners), as well as no significant differences between marathon runners and ultramarathoners (within the group of marathoners+).

Labrum abnormalities: prevalence, location, type

There were labrum abnormalities in 13/72 (18%) hips of non-marathoners and 5/32 (16%) hips of marathoners+ (Table 6.3). No significant differences were found between the groups of participants (p=0.718).

Considering the different levels of severity, the 13 hips of non-marathoners presented with the following grades on MRI: 8 hips with labrum signal and/or fraying (grade 1), 2 hips with simple tear (grade 2), 3 hips with labrocartilage separation (grade 3).

Meanwhile, the 5 hips of marathoners+ showed the following grades: 3 hips with grade 1 abnormalities, 1 hip with grade 2 abnormality and 1 hip with grade 4 abnormality/complex tear (Table 6.3, Figure 6.2).

Table 6.3. Prevalence of labrum abnormalities in the hips of non-marathoners (72 hips) and marathoners+ (32 hips)

Labrum	Number (%) of hips with labral abnormalities*															
	Non-marathoners n=72 hips								Marathoners+ n=32 hips							
	0	1	2	3	4	5	Any tear (at least 1)	Any grade ≥1	0	1	2	3	4	5	Any tear (at least 1)	Any grade ≥1
anterior	70 (97%)	2 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (3%)	32 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
posterior	71 (99%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)	32 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
anterosuperior	61 (85%)	7 (10%)	2 (3%)	2 (3%)	0 (0%)	0 (0%)	4 (6%)	11 (15%)	28 (87%)	2 (6%)	1 (3%)	0 (0%)	1 (3%)	0 (0%)	2 (6%)	4 (13%)
superior	69 (96%)	1 (1%)	1 (1%)	1 (1%)	0 (0%)	0 (0%)	2 (3%)	3 (4%)	30 (94%)	1 (3%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	2 (6%)
Any location	59 (82%)	8 (11%)	2 (3%)	3 (4%)	0 (0%)	0 (0%)	5 (7%)	13 (18%)	27 (84%)	3 (9%)	1 (3%)	0 (0%)	1 (3%)	0 (0%)	2 (6%)	5 (16%)

*Grades were defined according to SHOMRI scoring system [260]. SHOMRI, Scoring Hip Osteoarthritis with MRI. Some numbers may not add to the total number referred to as ′ Any location′ because some hips had abnormalities in more than one subregion of the labrum.

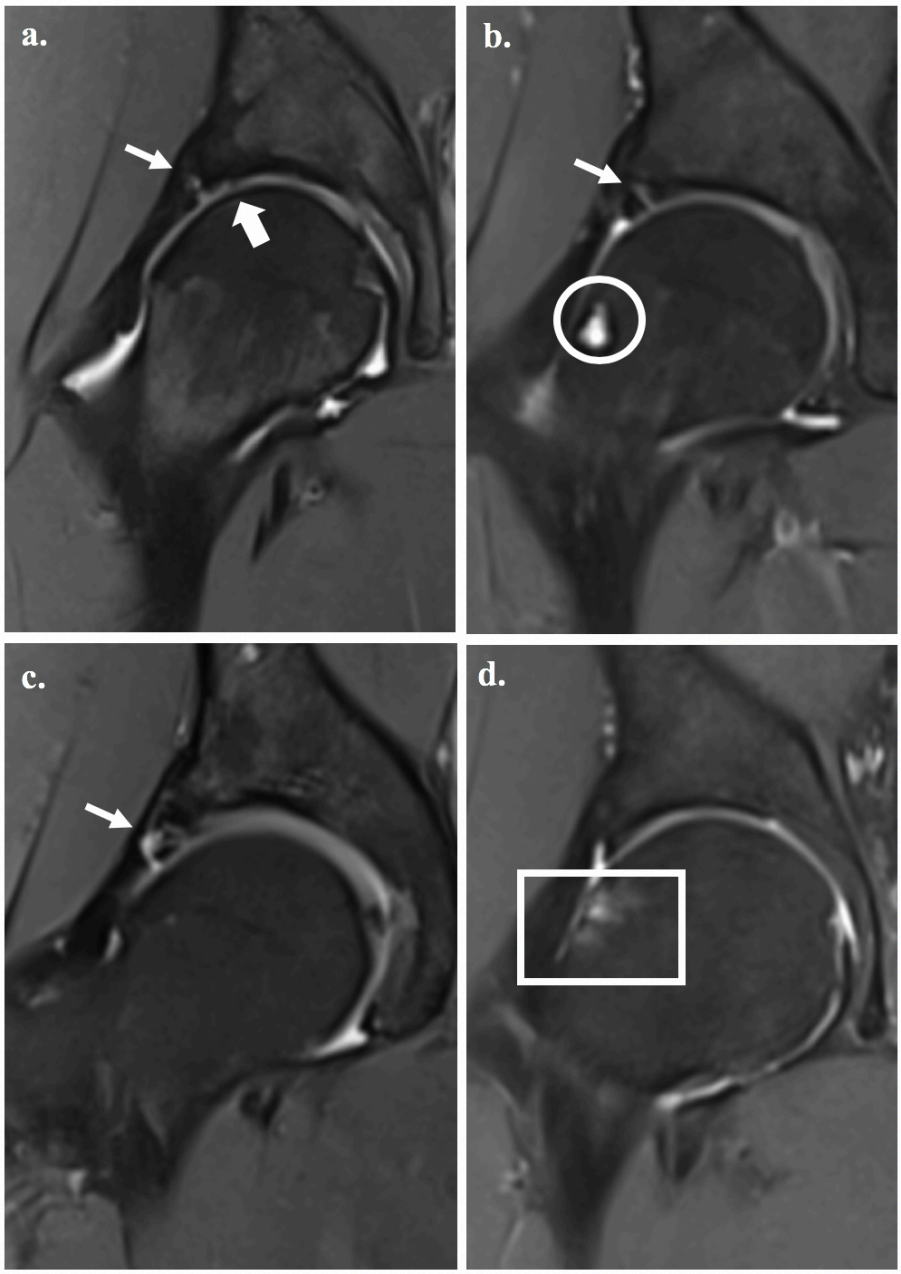


Figure 6.2. Coronal Dixon MR images showing intraarticular abnormalities in 4 volunteers, in 'in-phase' MRI sequences: a) Non-marathoner 1 with labrocartilage separation (small arrow) and full thickness cartilage defect (big arrow); b) Non-marathoner 2 with simple labral tear (small arrow) and subcortical cyst (circle); c) Marathoner+ 1 with complex labral tear (small arrow); d) Non-marathoner 3 with subchondral BME (square); SHOMRI grading system [208] was used in the assessment of labrum, cartilage, bone marrow; SHOMRI, Scoring Hip Osteoarthritis with MRI; BME, bone marrow edema.

Labrum abnormalities were most commonly detected in the following subregions, in the group of non-marathoners' hips: 11 anterosuperior, 3 superior, 2 anterior, 1 posterior, whereas in the group of marathoners+ the abnormalities were distributed in the anterosuperior (4 hips) and superior areas (2 hips), and no findings were present in other subregions of the labrum.
In addition to this, paralabral cysts were found in 4/72 (6%) hips of non-marathoners and 3/32 (9%) hips of marathoners+ (p=0.673).

Articular cartilage abnormalities: prevalence, severity, location

Acetabular cartilage abnormalities were detected in 3/72 (4%) hips of non-marathoners on the MRI scans. No femoral cartilage abnormalities were identified. Also, no cartilage lesions were found in the hips of marathoners+. The differences between the 2 groups of participants were not statistically significant (p=0.551).
With regard to severity levels, the 3 hips of non-marathoners showed the following grades: 2 hips with partial thickness defect (grade 1), 1 hip with full thickness defect (grade 2; see Figure 6.2, Table 6.4).

Table 6.4. Prevalence of articular cartilage and bone marrow abnormalities in the hips of non-marathoners (72 hips) and marathoners+ (32 hips)

Anatomical structure	Number (%) of hips graded per structure*											
	Non-marathoners n=72 hips						Marathoners+ n=32 hips					
	0	1	2	3	4	Any grade≥1	0	1	2	3	4	Any grade≥1
Cartilage	Cartilage abnormalities											
Acetabular	69 (96%)	2 (3%)	1 (1%)	-	-	3 (4%)	32 (100%)	0 (0%)	0 (0%)	-	-	0 (0%)
Femoral	72 (100%)	0 (0%)	0 (0%)	-	-	0 (0%)	32 (100%)	0 (0%)	0 (0%)	-	-	0 (0%)
Any subregion	69 (96%)	2 (3%)	1 (1%)	-	-	3 (4%)	32 (100%)	0 (0%)	0 (0%)	-	-	0 (0%)
Bone marrow	BME											
Acetabular	68 (94%)	2 (3%)	1 (1%)	1 (1%)	-	4 (6%)	32 (100%)	0 (0%)	0 (0%)	0 (0%)	-	0 (0%)
Femoral	69 (96%)	3 (4%)	0 (0%)	0 (0%)	-	3 (4%)	32 (100%)	0 (0%)	0 (0%)	0 (0%)	-	0 (0%)
Any subregion	65 (90%)	5 (7%)	1 (1%)	1 (1%)	-	7 (10%)	32 (100%)	0 (0%)	0 (0%)	0 (0%)	-	0 (0%)

*Grades were defined according to SHOMRI scoring system [260]. SHOMRI, Scoring Hip Osteoarthritis with MRI; BME, bone marrow edema.

Bone marrow

There were 7/72 (9%) hips of non-marathoners with BME (see Figure 6.2, Table 6.4). There were no such abnormalities in the group of marathoners+; no significant differences were found between the 2 groups of participants (p=0.098).

The extent of edema varied among the 7 lesioned hips of non-marathoners. Specifically, there were 5 hips with edema of ≤0.5 cm in size (grade 1), 1 hip with edema >0.5 cm but ≤1.5 cm in size (grade 2) and 1 hip with edema size >1.5 cm (grade 3). In terms of specific subregions being affected, 4 of these edema-like lesions were detected in the femoral bone marrow and 3 in the acetabular area.

In addition to this, 2/72 (3%) hips of non-marathoners and 6/32 (19%) hips of marathoners+ presented with subchondral cysts – all acetabular in non-marathoners, while half acetabular and half femoral in marathoners+; the differences between groups was statistically significant (p=0.008), however the cysts were very small (<0.5 cm in size).

Tendons

There were 9/72 (13%) hips of non-marathoners with tendinosis (grade 1 intermediate signal) and 9/32 (28%) hips of marathoners+ with tendinosis. The differences between these participants were still not statistically significant (p=0.052).

Only grade 1 tendon lesions were reported by radiologists – no higher grades of severity were observed.

The 9 cases of tendinosis were identified in different types of tendons: 1 gluteus medius, 2 gluteus minimus, 4 psoas, 2 hamstring (Table 6.5, Figure 6.3).

Table 6.5. Prevalence of tendon and ligament abnormalities in the hips of non-marathoners (72 hips) and marathoners+ (32 hips)

Anatomical structure	Number (%) of hips graded per structure*											
	Non-marathoners n=72 hips						Marathoners+ n=32 hips					
	0	1	2	3	4	Any grade≥1	0	1	2	3	4	Any grade≥1
Tendons	Tendon abnormalities											
Gluteus medius	71 (99%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	30 (94%)	2 (6%)	0 (0%)	0 (0%)	0 (0%)	2 (6%)
Gluteus minimus	70 (97%)	2 (3%)	0 (0%)	0 (0%)	0 (0%)	2 (3%)	32 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Gluteus maximus	72 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	32 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Psoas	68 (94%)	4 (6%)	0 (0%)	0 (0%)	0 (0%)	4 (6%)	29 (91%)	3 (9%)	0 (0%)	0 (0%)	0 (0%)	3 (9%)
Hamstring	70 (97%)	2 (3%)	0 (0%)	0 (0%)	0 (0%)	2 (3%)	27 (84%)	5 (16%)	0 (0%)	0 (0%)	0 (0%)	5 (16%)
Any tendon	63 (87%)	9 (13%)	0 (0%)	0 (0%)	0 (0%)	9 (13%)	23 (72%)	9 (28%)	0 (0%)	0 (0%)	0 (0%)	9 (28%)
Ligamentum teres	66 (92%)	6 (8%)	0 (0%)	0 (0%)	-	6 (8%)	30 (94%)	2 (6%)	0 (0%)	0 (0%)	0 (0%)	2 (6%)
Muscles	Muscle abnormalities											
Gluteus medius	54 (75%)	18 (25%)	0 (0%)	0 (0%)	-	18 (25%)	26 (81%)	6 (19%)	0 (0%)	0 (0%)	-	6 (19%)
Gluteus minimus	48 (67%)	20 (27%)	4 (6%)	0 (0%)	-	24 (33%)	26 (81%)	6 (19%)	0 (0%)	0 (0%)	-	6 (19%)
Gluteus maximus	18 (25%)	45 (63%)	9 (12%)	0 (0%)	-	54 (75%)	16 (50%)	12 (38%)	2 (6%)	2 (6%)	-	16 (50%)
TFL	30 (42%)	26 (36%)	16 (22%)	0 (0%)	-	42 (58%)	20 (63%)	10 (31%)	2 (6%)	0 (0%)	-	12 (38%)
Quadratus femoris	71 (99%)	1 (1%)	0 (0%)	0 (0%)	-	1 (1%)	30 (94%)	2 (6%)	0 (0%)	0 (0%)	-	2 (6%)
Hamstring	71 (99%)	1 (1%)	0 (0%)	0 (0%)	-	1 (1%)	30 (94%)	0 (0%)	2 (6%)	0 (0%)	-	2 (6%)
Any muscle	16 (22%)	56 (78%)	23 (32%)	0 (0%)	-	56 (78%)	12 (38%)	18 (56%)	6 (19%)	2 (6%)	-	20 (62%)

*Grades were defined according to Chi *et al* [261] (tendons), SHOMRI scoring system [260] (ligaments) and Goutallier *et al* [262] (muscles). SHOMRI, Scoring Hip Osteoarthritis with MRI. Not all percentages add up to 100% because some different grades of lesions may be present in the same hips.

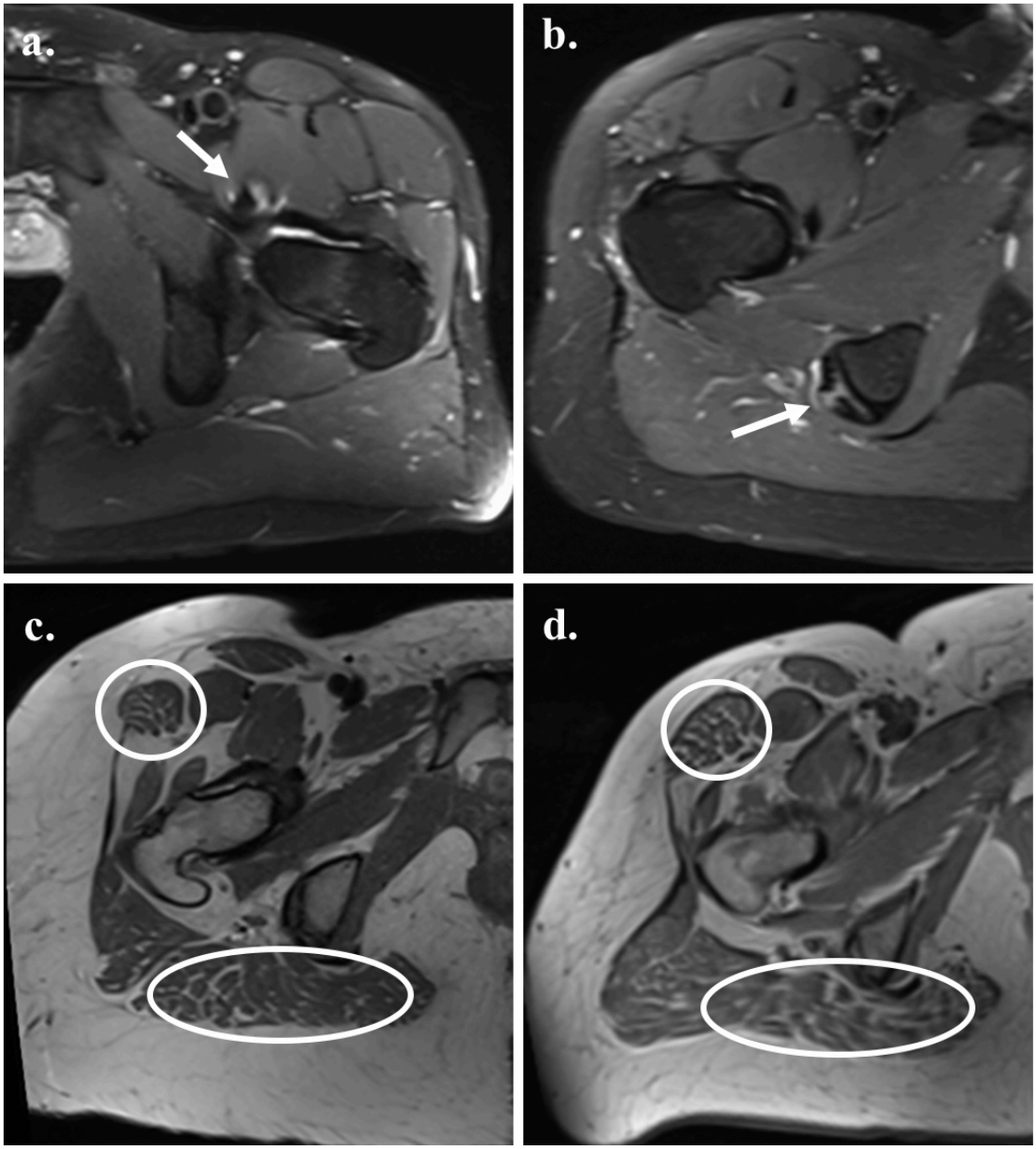


Figure 6.3. Axial Dixon MR images showing tendinosis, in 'water phase' sequences (a, b) and fatty muscle atrophy, in 'in phase' sequences (c, d), in 4 runners, respectively: a) Non-marathoner 1 with psoas tendinosis (arrow); b) Marathoner+ 1 with hamstring tendinosis (arrow); c) Non-marathoner 2 with gluteus maximus mild atrophy (big oval) and tensor fascia latae mild atrophy (small circle); d) Marathoner+ 2 with gluteus maximus mild to moderate atrophy (big oval) and tensor fascia latae mild atrophy (small circle). The grading systems developed by Chi *et al* [261] and Goutallier *et al* [262] were used in the assessment of tendons and muscles, respectively.

Ligaments

There were 6/72 (8%) hips of non-marathoners and in 2/32 (6%) hips of marathoners+ with abnormal ligament signal (grade 1) on the MRI scans (Table 6.5; $p>0.999$).

Only grade 1 severity levels were found.

Muscles

Fatty infiltration in muscles was found in 56/72 (78%) hips of non-marathoners and 20/32 (62%) hips of marathoners+, in different amounts (Table 6.5, Figure 6.3).

In terms of the extent of fatty infiltration, out of the 56 affected hips of non-marathoners, all had grade 1 (minimal atrophy) and 25 of them also had grade 2 (mild atrophy) in other muscles of the same hips. In marathoners+, the majority of reported abnormalities were of grade 1 severity; out of the 20 affected hips, there were 18 hips with grade 1, 6 with grade 2 and 2 with grade 3 (moderate atrophy) – whereby 2 hips presented with grade 1, 2 and 3 in different muscles simultaneously, while 2 other hips had both grade 1 and 2 fatty infiltration. No grade 4 marked atrophy was detected. There were significantly more hips with grade 2 atrophy in non-marathoners than in marathoners+ ($p=0.020$).

Most fatty streaks were detected in gluteus maximus muscles, followed by tensor fascia latae, gluteus minimus and medius, hamstring and quadratus femoris muscles.

Other findings

There were 3/72 (9%) hips of marathoners+ with small hip joint effusion. Moreover, trochanteric bursitis was present in 8/72 (11%) hips of non-marathoners and 5/32 (16%) hips of marathoners+. No statistically significant differences were found between these groups ($p=0.750$).

6.3.3 Associations between different MRI findings

The presence of tendinosis was associated with an increased prevalence of mild fatty muscle atrophy in non-marathoners' hips (95% CI, OR=5.2, 1.2–23.1; $p=0.021$). No other associations were found between the presence of different types of findings in the same hips, in either non-marathoners or marathoners+.

6.3.4 Distribution of MRI findings in participants and per hip side

Cartilage abnormalities were found exclusively in the right hip of non-marathoners, while BME was slightly more prevalent in the left hip than the right one. However, the numbers were too small to draw conclusions or make associations. Only fatty infiltration in muscles showed clear distribution in both hips of participants in all the affected cases. Table 6.6 presents the number of participants with specific abnormalities in the main hip structures and the distribution per hip sides.

Few other findings were not listed in the table: paralabral cysts (in 3 non-marathoners – 2 left hips, 1 both; in 3 marathoners+, in 3 individual right hips), subchondral cysts (in 1 non-marathoner – both hips; in 4 non-marathoners – 1 right, 1 left, 2 both), effusion (in 2 marathoner+ - 1 right, 1 both) and trochanteric bursitis (in 7 non-marathoners – 1 right, 5 left, 1 both; in 3 marathoners+ – 1 left, 2 both).

Table 6.6. Number of participants with both hips or single hips showing abnormalities on MRI, respectively, and total number of affected hips, in the labrum, articular cartilage, bone marrow, tendons and ligaments.

Key hip abnormalities	No. of participants (%) with abnormalities in both hips	No. of participants (%) with abnormalities in single hip sides		Total no. of participants (%) with abnormalities in hips	Total no. of hips (%) with abnormalities		
		Right hip	Left hip		Right hip	Left hip	All hips
Non-marathoners (N=36 participants, 72 hips)							
Labral tears	2 (67%)	1 (33%)	0 (0%)	3 (100%)	3 (60%)	2 (40%)	5 (100%)
Cartilage abnormalities	0 (0%)	3 (100%)	0 (0%)	3 (100%)	3 (100%)	0 (0%)	3 (100%)
BME	1 (17%)	2 (33%)	3 (50%)	6 (100%)	3 (43%)	4 (57%)	7 (100%)
Tendon abnormalities	2 (29%)	3 (42%)	2 (29%)	7 (100%)	5 (56%)	4 (44%)	9 (100%)
Ligament abnormalities	2 (50%)	2 (50%)	0 (0%)	4 (100%)	4 (67%)	2 (33%)	6 (100%)
Muscle abnormalities	28 (100%)	0 (0%)	0 (0%)	28 (100%)	28 (50%)	28 (50%)	56 (100%)
Marathoners+ (N=16 participants, 32 hips)							
Labral tears	0 (0%)	2 (100%)	0 (0%)	2 (100%)	2 (100%)	0 (0%)	2 (100%)
Cartilage abnormalities	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
BME	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Tendon abnormalities	1 (12%)	5 (63%)	2 (25%)	8 (100%)	6 (67%)	3 (33%)	9 (100%)
Ligament abnormalities	0 (0%)	1 (50%)	1 (50%)	2 (100%)	1 (50%)	1 (50%)	2 (100%)
Muscle abnormalities	10 (100%)	0 (0%)	0 (0%)	10 (100%)	10 (50%)	10 (50%)	20 (100%)

BME, bone marrow edema.

6.3.5 Associations between MRI findings and participant characteristics

The number of lesions was not found to increase with older age in most cases. However, the mean age of non-marathoners presenting with tendinosis was greater than the mean age of non-marathoners without tendinosis [37.7 ± 12.1 years (n=7) vs 29.8 ± 6.9 (n=29)]. The odds of a participant from the group of non-marathoners and aged ≥ 40 years old to have tendinosis were 6.5 (95% CI, 1.0–44.2; p=0.038).

No significant differences were found between men and women when the prevalences of any type of MRI abnormality per gender group were counted and compared.
There were no significant differences between the BMI values of those participants with abnormalities on MRI and the BMI values of those participants without any abnormality. There was only one exception for tendinosis, in the group of non-marathoners (p=0.025) – the likelihood of an overweight non-marathon (BMI≥ 25 kg/m^2) to have tendinosis was 3.6 (95% CI, 0.6–21.4).

6.3.6 Double-reporting consensus

The agreement between the scores assigned by the 2 radiologists for the co-reported scans was very good (kappa 0.850).

6.3.7 HOOS results

The resulting mean HOOS scores were ≥ 90/100 in all participants for each questionnaire item. Specifically, in non-marathoners: symptoms (92.5 ± 11.2); pain (96.9 ± 5.0); function in daily living (99.3 ± 2.3); function in sport and recreation (98.5 ± 2.8) and knee-related quality of life (96.9 ± 7.6); while in marathoners+: symptoms (92.5 ± 11.2); pain (97.3 ± 4.8); function in daily living (99.3 ± 2.3); function in sport and recreation (98.8 ± 2.6) and knee-related quality of life (96.9 ± 7.6).

6.4 DISCUSSION AND CONCLUSIONS

This study evaluated, for the first time, the prevalence of hip joint abnormalities in a large cohort of asymptomatic non-marathoners and experienced marathon/ultrarunners using 3.0 T MRI. A number of internal joint abnormalities were found in the labrum, articular cartilage, bone marrow, tendons and ligaments. The highest number of abnormalities were detected in the labrum and tendons, in both groups of participants. Also, there was minimal fatty infiltration in muscles in most hips, and only few mild ones and even less moderate cases.

In general, non-marathoners had a higher prevalence of MRI findings than marathoners+ in most of the assessed hip joint features. No chondral lesions or BME-like lesions, which are both key indicators of joint health, were present in marathoners+. Only small cysts and tendinosis (signal alteration, not tear) were more frequently encountered in the group

of marathoners+. However, these need to be investigated further since the prevalence of subchondral cysts in marathoners+ is similar to than in non-runners from previous studies so may not necessarily reflect running-related effects on the joint.

6.4.1 Study strengths

There are a number of strengths of our study which add value to the existing research on hip running: 1) This is the first study to evaluate particularly the baseline prevalence of hip joint abnormalities in a cohort of runners. It includes the largest sample size to date (104 hips), with only one other study (non-baseline one) previously assessing a much smaller number of 8 hips of runners; 2) The use of high-resolution 3.0 T MRI technology provides excellent resolution and sensitivity to detect all types of lesions, even minor ones and early signs of pathologies which may potentially develop in the future. The MRI protocol was optimised to have Dixon sequences in 4 phases [183] for increased visualisation of the hip joint structures, including muscles; 3) Also, non-contrast MRI techniques are included for increased safety since the dye may not be recommended in certain groups of people, while still providing great detail and MRI contrast of the internal structures of interest; 4) Moreover, the additional use of a multichannel coil provides further benefits of increased spatial resolution, reduced scanning time and better detection of lesions; 5) The study cohort included 2 groups of participants; therefore this allowed us to compare for the first time between the hip outcomes of asymptomatic inexperienced and experienced long-distance runners; 6) This study provided a comprehensive detailed analysis of all internal hip joint structures and used validated scoring systems to grade all regions and subregions of the hip features. Moreover, this is the first study to include an additional analysis of runners' muscles and their amount of fatty infiltration.

6.4.2 Study limitations

I acknowledge the existence of some study limitations: 1) radiological reporting may have a risk of bias, therefore we included 2 senior musculoskeletal radiologists to double-report a subset of scans to improve the accuracy of reporting the study findings. 2) However, only one of these radiologists evaluated the set of scans from the whole cohort. The second radiologist reported the bilateral scans from 20% of the cohort; we internally decided on this percentage after discussing with the radiologists. Other large-scale medical studies included MRI double-reporting analysis of 10% of the total cohort, so we used 20% for improved confidence. Moreover, the reports showed excellent agreement

between the scores assigned by the radiologists; this confirmed the reliability of our findings, in an attempt to optimise time and resources while ensuring highly accurate results; 3) The HOOS questionnaire and physical activity information were self-reported, therefore a degree of subjectivity needs to be considered; however, HOOS is considered to be a reliable validated diagnosis tool with successful clinical use. 4) Other co-founding factors may influence the results of our study, such as genetics, overall physical fitness, running surface, biomechanics, leg alignment. These details were not recorded and could not be analysed in this study, and can be the subject of many other future studies; 5) Long-term follow-up studies are needed to evaluate the clinical significance of the findings, by also comparing the MRI changes with the development of any symptoms or hip complaints over time; 6) Generally speaking, the ankle is thought to be more affected by running than the hip joint (i.e. higher injury rates), therefore it would have been good to study it in detail. However, we decided to evaluate the hip joint instead of other lower limb joints because the research group is planning further studies on the muscles around the hip joint (post-processing e.g. 3D segmentation) and the effects of exercise on them.

6.4.3 Comparison with previous studies

Our study findings revealed a lower number of hip joint abnormalities on MRI than in symptom-free non-runners as reported in previous studies [342–346]. In particular, the evidence from existing literature demonstrated a higher prevalence of labral tears in non-runners (39-86% hips), paralabral cysts (13-26%), articular cartilage abnormalities (24%), BME-like lesions (11%), subchondral cysts (16%) than the prevalence reported in both our study groups, of non-marathoners: labral tears (7% hips), paralabral cysts (6%) cartilage defects (4%), BME (10%), subchondral cysts (3%); and marathoners+: labral tears (6% hips), paralabral cysts (9%), no cartilage or bone marrow defects. Only subchondral cysts were slightly more prevalent in marathoners+ (19%) than in non-runners (16%), however the difference is insignificant. Also, our study included participants with a median age of 30 years old, while previous research groups included participants of various ages from 15 to 66 years old, yet the prevalences of abnormalities in our runners were smaller in comparison to those in other studies. This suggest that runners with no previous hip injuries had better outcomes than non-runners from the general population.

With regard to running research, only one previous study evaluated the hips of asymptomatic runners and used MRI tools in their analysis [43]. But this study investigated the MRI alterations occurring in both the hips and knees of runners after a marathon run, so the MRI scans were done before and after the race; this was not a baseline study conducting a detailed assessment of the general prevalence of symptom-free hip abnormalities on MRI, but instead was focused on the impact of a single marathon

run on the hips and knees. In disagreement with our study results, no lesions were seen before the marathon and, additionally, no changes occurred after the marathon. Some limitations of this study are the following: small cohort of subjects (n=8), the participation of experienced long-distance runners only (60-150 km/week) and no other types of low-dose runners, the use of unilateral low-resolution MRI scans. Also, according to a survey of 1212 runners [109], experienced long-distance runners may present with better joint health findings than less experienced runners,who may potentially be more predisposed to running-related abnormalities if they did not have sufficient training before a race. Therefore, this questionnaire-based study supported the results of our study whereby experienced marathoners and ultrarunners, with no present or history of hip injuries, had lower prevalences of MRI abnormalities than asymptomatic non-marathon runners, including both 'couch potatoes' and occasional runners. This may be explained by the fact that the joints of experienced long-distance runners could potentially have specific adaptation mechanisms developing gradually over time, as a result of a training on a regular basis. Thus, an appropriate level of running experience in individuals with no previous injuries is speculated to have a protective effect against developing hip injuries and other complaints [110–112,347].

Furthermore, tendon analysis of the hip joint was not conducted in any of the previous MRI studies of symptom-free individuals, despite the fact that tendon lesions are anecdotally reported as being a common reason for runners' complaints of hip pain [338]. Even though no symptoms were manifested in our study, the results showed that early signs of tendon abnormalities were frequent on the MRI scans, so this may require further analysis.

Also, minimal fatty infiltration in muscles (grade 1: very few traces of fatty streaks) was frequently seen on the hip MRIs, but this is considered to be within normal range (insignificant amounts) and a common finding in the general asymptomatic population [348]. There was a higher number of mild atrophy cases in non-marathoners than in experienced marathoners+, suggesting that running training experience may induce protective effects on muscles and attenuate disuse muscle atrophy, as confirmed in other previous studies [349–352]. The two isolated cases of moderate atrophy in experienced marathoners may indicate overtraining [353], yet those were still asymptomatic.

6.4.4 Clinical significance and future work

First of all, our study gives an MRI-based overview of the actual health status of asymptomatic hip joints in individuals of various exercise levels, from 'couch potatoes' and occasional runners to experienced long-distance runners (marathoners and ultramarathoners). Experienced marathoners appear to have higher prevalences of hip MRI abnormalities than less experienced runners and

individuals doing minimal physical effort, therefore a potential beneficial effect of regular running in trained individuals without previous injuries may be suggested. However, other confounding factors may affect the results so this remains unclear.

Secondly, the MRI results are very relevant in the context of developing better diagnosis and treatment interventions in individuals with hip complaints of pain and other symptoms. This is because a number of internal hip joint pathologies may be either symptomatic or asymptomatic [342,354], or asymptomatic ones may develop further in the future; this makes appropriate clinical decision-making challenging. In current clinical practice, hip arthroscopy may be recommended by physicians in case of symptomatic labral tears, chondral defects, BME-like lesions, ligamentum teres pathologies [355–358]. However, the actual source of pain or discomfort in the hip is often not easy or straightforward to identify out of all intraarticular joint structures. Associations between symptoms and labral tears or other specific lesions in the hip area may not be readily and accurately made. Therefore, the decision to perform a surgical procedure such as hip arthroscopy, with its inherent risks and potential post-operative complications, should be made very carefully and not only based on the identification of a labral abnormality or other findings on the MRI scans. Instead, a combination of symptoms evaluation, MRI analysis, thorough physical examination and other clinical assessments should be considered beforehand [345].

Future studies, including short-term and longer-term follow-ups, are required to provide a better understanding of which specific dose of exercise and running is beneficial or detrimental to the hip joint structures. Also, further investigations are needed to clarify whether any complaints of pain or other symptoms progress over time, alongside a potential development and extension in size of current MRI abnormalities, in both the group of experienced runners and the group of less experienced runners.

Chapter 7 – Hip study

Analysing the impact of marathon running on the hip joints of novice marathon runners

(short-term post-marathon data)

Work presented in this chapter has been submitted for publication

7.1 INTRODUCTION

The increasing global popularity of long-distance running, especially among less experienced runners signing up for marathon runs, has given rise to concerns about the risks of running-related injuries [359]. It is estimated that the forces acting on the knee joint may be up to 8 times the runner's body weight, while the forces acting on the hip joint may reach 5 times the body weight [119,360]. The repetitive stress exerted on the joints during a long-distance running event, such as a marathon run, may be anecdotally considered by some to trigger potential harmful effects on the internal joint structures, especially on the cartilaginous tissues and subchondral bone marrow, which can be linked to a higher risk of OA. However, the existing evidence is inconclusive [43,222,224–226,318,322,361–363]. Moreover, it has been suggested that the prevalence of arthritis may be more common in the non-running population than in active regular long-distance runners, according to a large-scale questionnaire-based study [108].

Since the advent of MRI technologies, it has become easier to study exercise-induced anatomical and functional alterations of the joints in excellent detail, while ensuring patient safety and great reliability of the findings. Previous MRI research on the impact of marathon running on the human body has been focused on the analysis of knee joints before and after a marathon run; thus there is evidence to suggest that the forces exerted during marathon running may be well-tolerated in knees with no previously reported lesions, given that no major changes were detected following the marathon run [43,226–228,347,364]. Nevertheless, there is extremely little knowledge on the impact of marathon running on hip joints. Only one study to date assessed the hips of asymptomatic runners before and after a marathon race, and identified no lesions at either time point [43]. But a number of limitations need to be considered: small cohort of runners (n=8), experienced long-distance runners instead of novice marathon runners, unilateral hip analysis, low-resolution MRI technique. Therefore, more studies including high-resolution 3.0 T MRI [190,191] and large sample size of less experienced runners are required to better analyse running-induced changes of the hip, with increased diagnostic precision and reliability.

7.1.1 Motivation

The main motivation of this study is to gain a better understanding of the changes occurring in the internal hip joint structures of novice marathon runners after completing

a standardised 4-month beginner training schedule for the marathon and also the marathon race. It is important to clarify which types of lesions develop and which specific hip areas and subregions are affected shortly after the run (2 weeks post-marathon), and inform injury prevention strategies.

7.1.2 Aim

To evaluate the differences between the hip joint outcomes of novice marathon runners prior to the start of the training plan in preparation for a marathon race and then immediately after finishing the race.

7.1.3 Objectives

To investigate the short-term impact of marathon running and preceding beginner training plan on the hip joints of novice marathon runners by performing morphological high-resolution 3.0 T MRI scans and using MRI-based hip scoring systems and self-reported questionnaires.

7.2 MATERIALS AND METHODS

I liaised with the participants to return for the second scan, organised the study, reviewed the relevant literature and collated all the data. The senior radiologists agreed to use the same MRI equipment and methodology that was approved in Chapter 6 to conduct the study and report the MRI scans. The Chief investigator and the other PhD supervisors were involved in managing me for the appropriate organisation of the study.

7.2.1 Study design and participants

My research team and I conducted a prospective cohort study. The participants provided written informed consent before joining the study.

In Chapter 6 I recruited a cohort of 52 asymptomatic volunteers of different levels of physical activity for a baseline hip study: 36 non-marathoners (8 couch potatoes and 28 recreational runners) and 16 marathon/ultrarunners. Here, I invited all the 28 recreational runners from the previous study to participate in a follow-up study in relation to a marathon run, Richmond Marathon 2019. All the 28 recreational runners already signed

up for participating in their first marathon ever, Richmond Marathon, before being recruited to the baseline study. More details about the pre-study physical activity and running levels of these volunteers are available in Chapter 6. The participants will be referred to as 'novice marathoners' in this Chapter.

The main inclusion criteria for this group of participants were the following: novice marathon runners (no previously attempted marathon runs; no past races longer than 21 km), asymptomatic joints, no present or past hip injuries or pathologies, no contraindications to MRI scanning. I excluded pregnant or actively breastfeeding women, volunteers aged under 18 years old, with known hip joint pathologies or a history of hip injuries/surgeries, with contraindications to MRI scanning (claustrophobia, anxiety, panic attacks).

All 28 participants had bilateral scans of both hips just before starting a formal 4-month beginner (standardised) training programme in preparation for the marathon. This training schedule involved gradual increase in the number of miles/week and can be accessed online on the Richmond Marathon website (www.richmondrunfest.co.uk; Appendix A.2.2).

Two weeks after completing the training for and the marathon run, all study participants were called to attend a 2nd MRI scan of both their hips. The MRI scans at the two different time points were assessed for any signal changes occurring during this period of time: time point 1 (4 months pre-marathon), time point 2 (2 weeks post-marathon).

7.2.2 MRI protocol

The same 3.0 T MRI scanner provided by Siemens Magnetom VidaHealthineers (Erlangen, Germany), including identical multichannel coil, imaging technique and specific parameters as in the baseline study described in Chapter 6, was used in this study. Bilateral MRI scans were conducted before and after the Richmond Marathon, and the scanning time was 25 minutes per participant. The protocol is fully presented in Chapter 6.

7.2.3 Image analysis

As in Chapter 6, a senior musculoskeletal radiologist was mainly responsible for the analysis of both the pre-marathon and post-marathon scans, using a PACS workstation. The images from 20% of the initial cohort of participants, at both MRI scanning time points, were co-reported independently by another senior musculoskeletal radiologist of

similar level of experience. In case of any discrepancies between the scores given by the two radiologists, a further discussion was organised between them to achieve consensus scores. More details were provided in Chapter 6.

7.2.4 Quantification of MRI findings

MRI-based semiquantitative scoring systems were used in the assessment of all hip joint structures and processes, including abnormalities of the labrum, articular cartilage, bone marrow, tendons, ligaments, muscles, trochanteric bursitis, joint effusion, other findings. Most of these hip joint features were evaluated based on SHOMRI [260], while tendon and muscle analyses were done according to Chi *et al* [261] and Goutallier *et al* [262], respectively. The anatomic divisions and regional subdivisions were described in the above mentioned scoring systems and scores were assigned for each individual region and subregion. The full description of these can be found in Chapter 6.

7.2.5 HOOS questionnaire

All participants were asked to fill in HOOS questionnaires at each visit, on the specific MRI scanning days – before the marathon and after the marathon. This was done to assess the self-reported changes in their perceived hip condition after the impact of training for and the marathon race. The questionnaire format, questions and score calculation were described in detail in Chapter 6.

7.2.6 Statistical analysis

The characteristics and demographics of the participants who completed the training for/and the marathon, and of those who did not finish their training were analysed and compared. Unpaired t-test was used in making comparisons between these groups of participants in terms of age and BMI, respectively. Chi-squared test was performed for gender analysis. Statistical differences between the BMI values of participants before and after the marathon were assessed using paired t-test. The scores given to each internal hip feature before and after the marathon by radiologists were compared with Wilcoxon test. Also, pre- and post-marathon HOOS scores for each questionnaire category were compared with Wilcoxon test. Each individual hip of each participant was treated separately in the statistical analysis of the changes in MRI scores after the marathon. Kappa statistics were used in the assessment of interreader agreement for the subset of

double-reported MRI scans. Any results showing a p-value<0.05 were considered to be statistically significant (GraphPad Prism, V.6.0 c).

7.3 RESULTS

I was responsible for all data analysis including the questionnaires and radiological scores, statistical tests, for writing the manuscript and for general dissemination. The findings were interpreted appropriately with the contribution of the experienced radiologists included in the study. The supervisors evaluated the whole analysis and write-up, as well as suggested ways of improvement if needed.

7.3.1 Participant characteristics

Out of the 28 novice marathon runners who signed up for the Richmond Marathon and started the 4-month beginner training plan, 21 completed the full programme while the remaining 7 participants stopped their training for the marathon due to a number of different reasons. All the 21 participants who completed the training entered and finished the marathon run (marathon finishers), while the 7 participants who discontinued the training did not attempt to run on the race day (training non-finishers).

After the marathon, both marathon finishers and training non-finishers were invited to attend a second hip MRI scanning session since the last one they had before starting the training. All marathon finishers and 4/7 training non-finishers agreed to attend the 2 weeks post-marathon session. Therefore, 25 participants returned and underwent 2 MRI scans in total (pre- and post-marathon) and completed the study. The 3 remaining training non-finishers could not return due to issues of availability or personal problems, therefore they dropped out of the study (see Table 7.1 and Figure 7.1 for participant characteristics and study design, respectively).

The 4 training non-finishers who attended both the pre- and post-marathon scans stopped their training as a result of 1) minor hip pain; 2) Achilles tendon injury; 3) illness unrelated to the training for the marathon; 4) foot injury unrelated to training (Table 7.2). Also the 3 training non-finishers who dropped out of the study discontinued the training due to the following reasons: 1) knee pain; 2) skin disease unrelated to training; 3) family bereavement (Table 7.3).

Table 7.1. Baseline characteristics of study participants

Characteristics	Marathon finishers (n=21)	Training non-finishers (n=4)
Age (years)	33.0 ± 9.5	30.0 ± 6.6
Male : Female	12 : 9	3 : 1
BMI (kg/m^2)	24.0 ± 1.9	20.8 ± 1.8

Values are reported as mean ± standard deviation for age and BMI. BMI, body mass index.

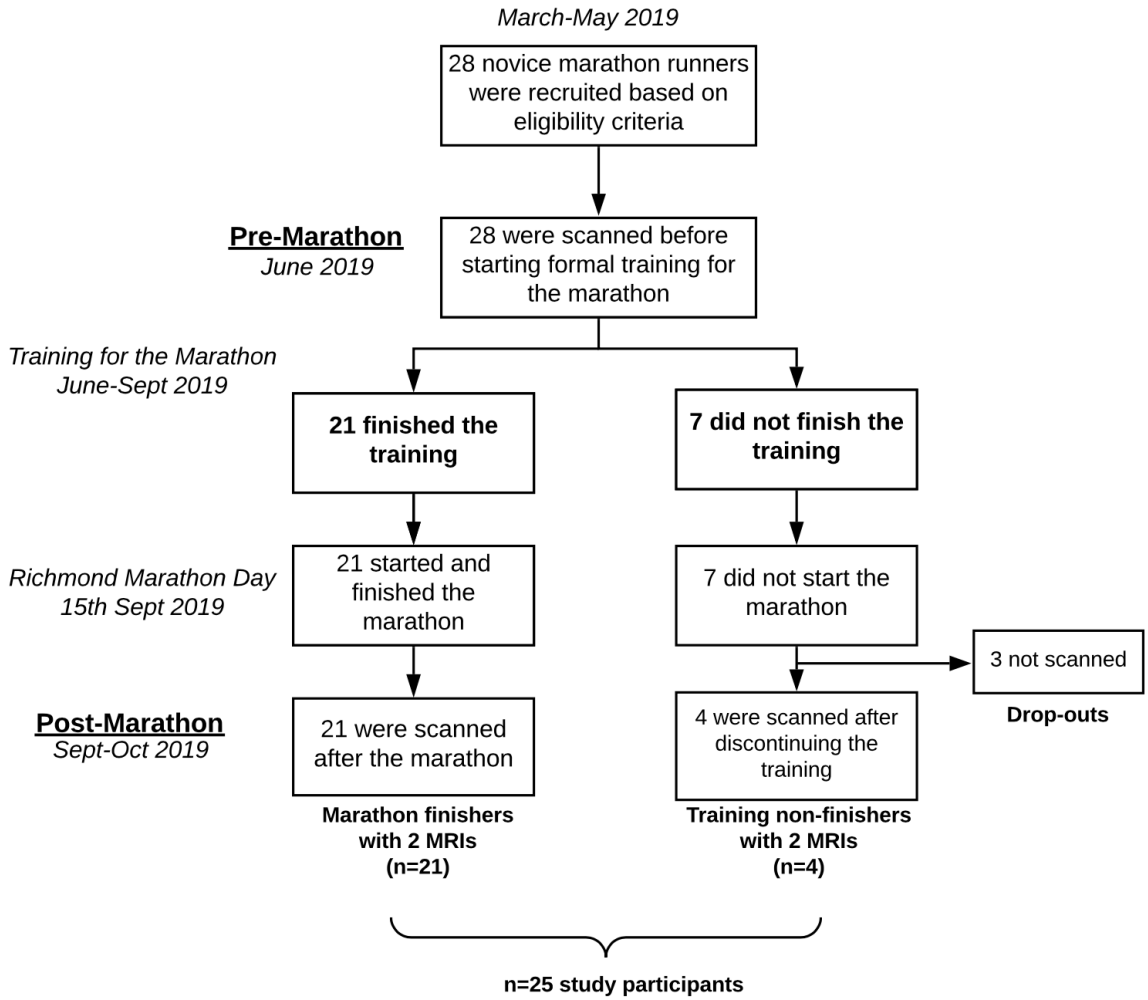


Figure 7.1. Study design

Only one of all training non-finishers withdrew from the running schedule as a consequence of hip pain. However, this participant was scanned at the two time points and no abnormal signal was detected in this hip (right one) on either MRI scan. The pain disappeared before the 2nd MRI scanning session, so no change in the HOOS scores between these time points was reported. Nevertheless, the pre-marathon scan showed a small area of BME in the contralateral (left) hip. Moreover, the participant suffered from

a torn ligament in the right ankle 6 years ago (previously unreported) which recovered long before the study recruitment stage, however this might have had an indirect effect on the right hip.

Table 7.2. Details on the training non-finishers who completed the study (n=4) i.e. attended both time point 1 and time point 2 MRIs, but did not finish the training for/and the marathon.

Participant (no.)	Reasons for stopping training	Amount of completed training before stopping (months)	Training-related symptoms resolved at time point 2 MRI	New lesions appearing on time point 2 MRI
1	Hip injury related to training	2 months	Yes	No
2	Ankle injury related to training	2 months	Yes	No
3	Illness unrelated to training	3 months	n/a	No
4	Foot injury unrelated to training	2.5 months	n/a	No

n/a, not applicable.

Table 7.3. Details on the training non-finishers who dropped-out of the study (n=3) i.e. attended time point 1 MRI, but not time point 2 MRI; and did not finish the training for/and the marathon**.** No lesions were observed at MRI 1.

Participant (no.)	Reasons for stopping training	Amount of completed training before stopping (month)	Training-related symptoms resolved after stopping training
1	Knee injury related to training	2 months	Yes
2	Skin disease unrelated to training	3.5 months	n/a
3	Family bereavement	3 months	n/a

n/a, not applicable.

No statistically significant differences in baseline demographics were found between marathon finishers and training non-finishers: age (p=0.413), gender (p=0.238), BMI (p=0.255).

Out of 21 marathon finishers, the majority were aged <40 years old (16/21; 76%) and had BMI in the normal range <25 kg/m^2 (15/21; 71%). The age range was 18-58 years old, while the range for BMI values was 20.3-27.4 kg/m^2. Similarly, out of 7 training non-finishers, all were aged <40 years old (16/21; 76%) and the majority had BMI <25 kg/m^2 at baseline (6/7; 86%; Table 7.1). The age range in this group was 23-39 years old, while the BMI range was 20.5-27.4 kg/m^2.

The BMI values after the marathon run were not significantly different from the BMI values before the run, in both marathon finishers (p=0.641) and training non-finishers (p=0.391).

7.3.2 MRI findings

The MRI findings were evaluated from a total of 50 hips (25 returning participants) in relation to the training for and/or a marathon run, including both marathon finishers and training non-finishers. Pre-marathon, I found a number of pre-existing abnormalities in key structures of the hip joint. However, the post-marathon MRI scans showed that only 2 abnormalities of the bone marrow developed after the run but were not associated with symptoms or other hip complaints of limited function.

Labrum

Before the marathon, 12/42 (29%) hips of marathon finishers had asymptomatic labrum abnormalities: 7 with abnormal signal (grade 1), 2 with simple tear (grade 2) and 3 with labrocartilage separation. Paralabral cysts were found in 4/42 (10%) hips. After the marathon, no changes were noticed on the MRI scans (grade 3; Figure 7.2; Figure 7.3.c-d). Training non-finishers showed no MRI findings at neither of the two scanning time points.

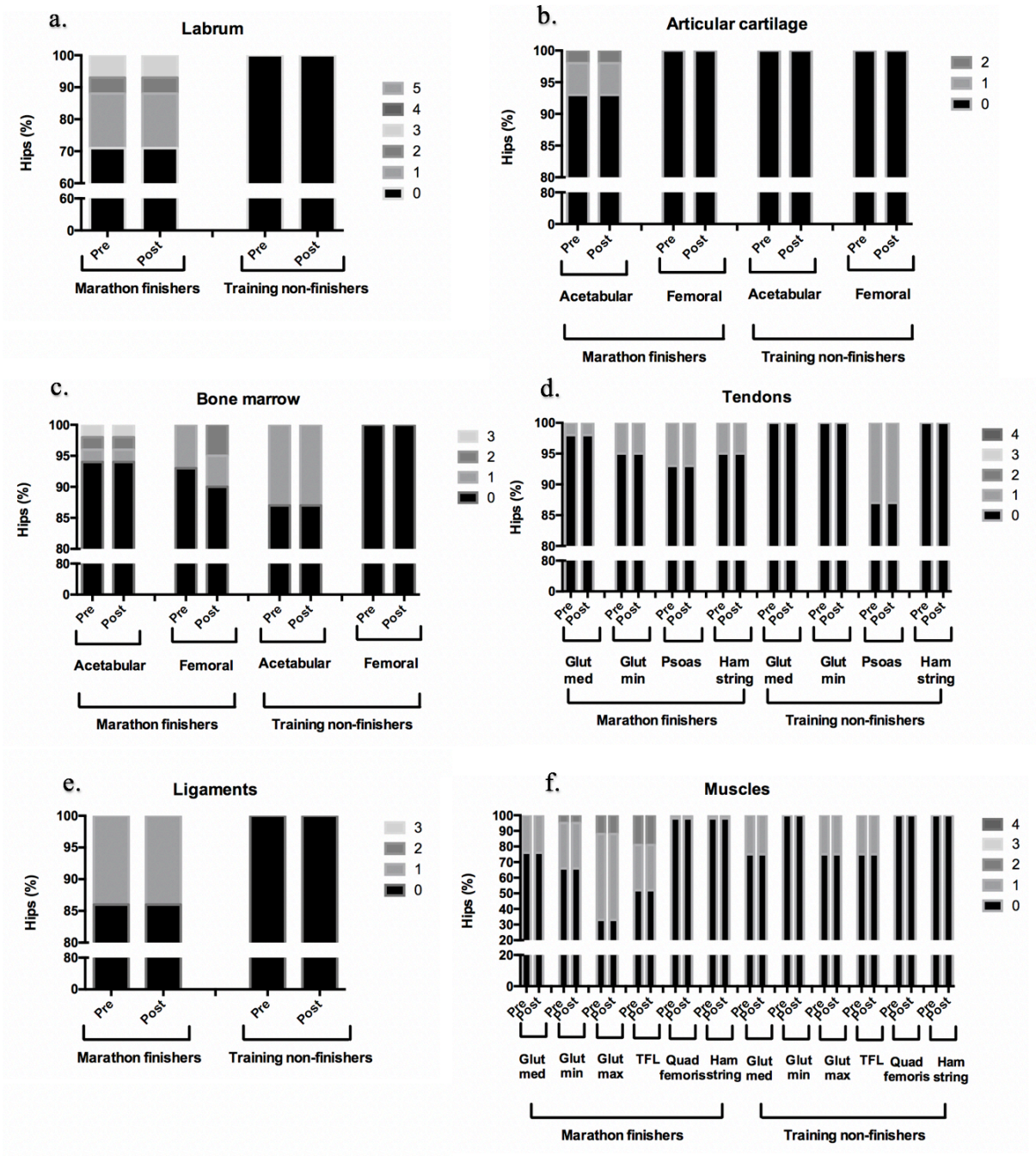


Figure 7.2. MRI findings in the key hip joint structures – labrum, articular cartilage, bone marrow, tendons, ligaments; and muscles (a-f) at two time points: Pre-marathon and Post-marathon, in the hips of both marathon finishers (n=21, 42 hips) and training non-finishers (n=4, 8 hips). Bone marrow findings refer to BME-like lesions; BME, bone marrow edema; Glut, Gluteus; med, medius; min, minimus; TFL, tensor fascia latae; Quad, quadriceps.

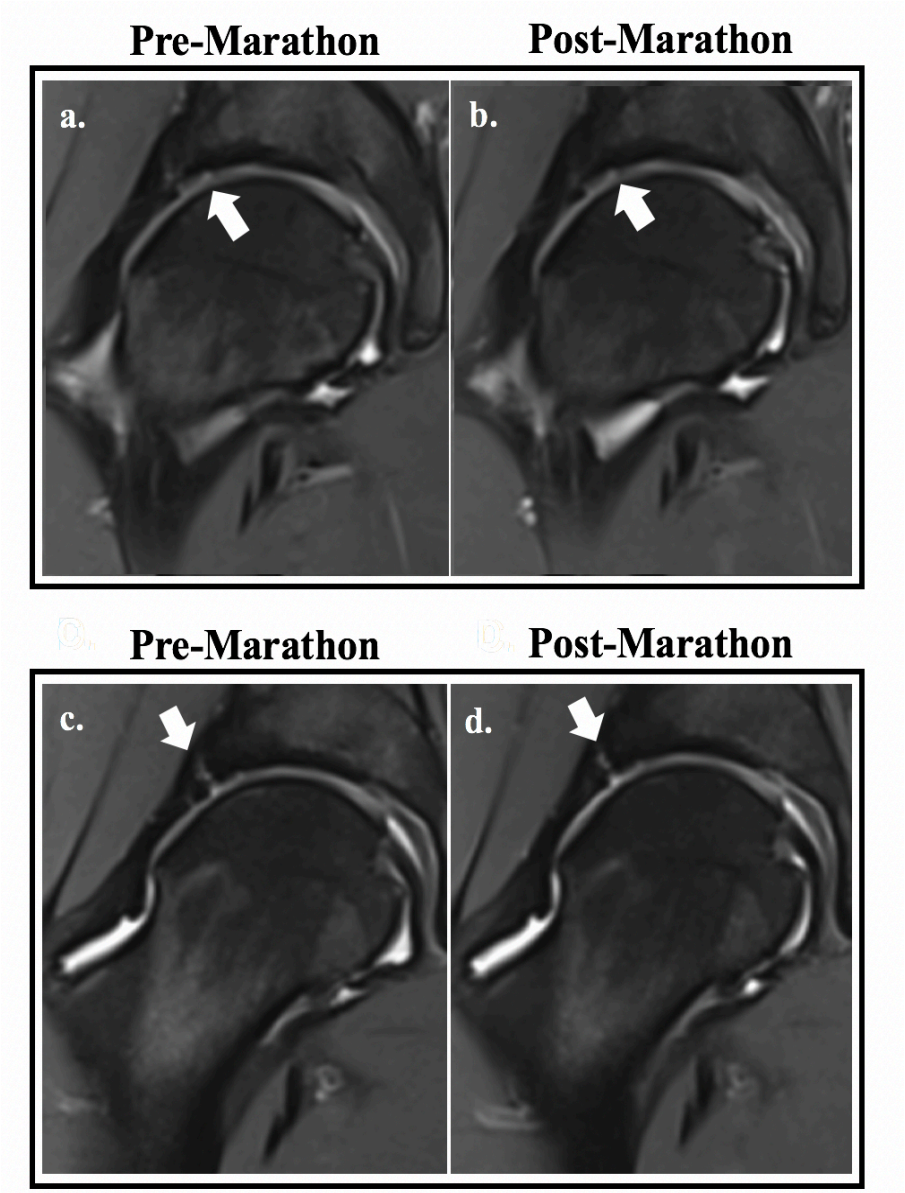


Figure 7.3. Coronal Dixon MR images of 2 participants showing damage before the marathon and no worsening after the marathon. Participant 1 (a - pre-marathon; b – post-marathon) had a full thickness acetabular cartilage defect (arrowed). Participant 2 (c - pre-marathon; d – post-marathon) had a labrocartilage separation (arrowed). SHOMRI grading system was used; SHOMRI, Scoring hip osteoarthritis with MRI.

Articular cartilage

Pre-marathon, 3/42 (7%) hips of marathon finishers presented with acetabular cartilage abnormalities: 2 had partial thickness defect (grade 1) and 1 had full thickness defect (grade 2). No progression or other changes were seen after the marathon (Figure 7.2, Figure 7.3.a-b). No MRI signal was detected in training non-finishers at either time point.

Bone marrow

Before the marathon, there were 6/42 (14%) hips of marathon finishers with BME in either the acetabular or femoral area: 4 with size ≤0.5 cm (grade 1), 1 with size ranging from >0.5 cm to 1.5 cm (grade 2) and 1 with size >1.5 cm (grade 3). After the marathon, 2 small areas of BME developed in the femoral heads of 2 left hips of male runners, one spontaneously appeared from grade 0 to grade 2, and the other one increased in extent slightly from grade 1 to grade 2 (p=0.684; Figure 7.2, Figure 7.4). These findings were both located in the non-weight bearing region of the hip joint; they were asymptomatic and no physical discomfort was reported by the participants. In the first one of these two cases, a concomitant pre-existing partial thickness loss of the cartilage was found in the respective runner in exactly the same hip, in the acetabular region (which was detected on the pre-marathon MRI but did not develop further on the post-marathon MRI). No other associations could be made between the presence of these findings and other known participants' characteristics.

In the group of training non-finishers, 1/8 hips (13%) had pre-marathon grade 1 BME. Also, 2/8 (25%) hips had pre-marathon subchondral cysts. None of these changed over time.

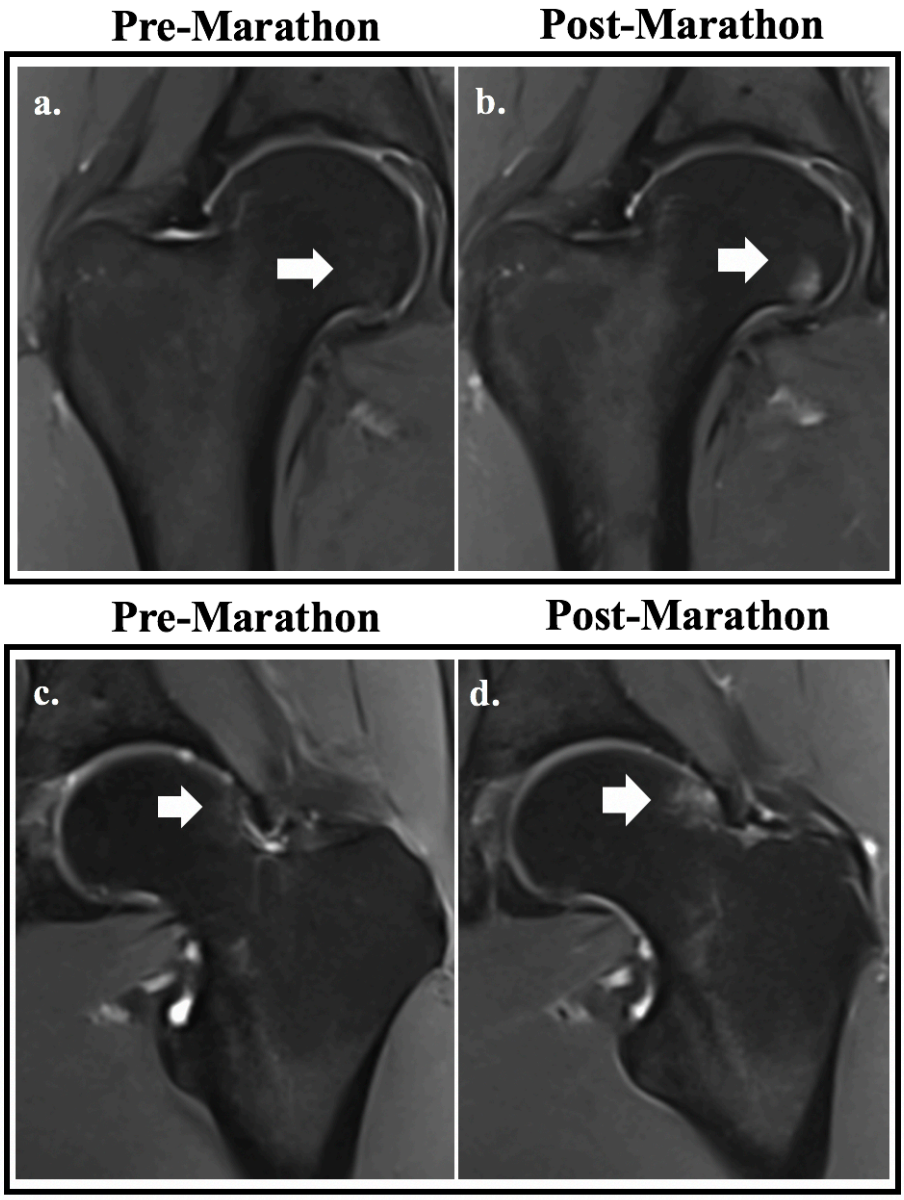


Figure 7.4. Coronal Dixon MR images of 2 participants showing all subchondral BME changes after the marathon: Participant 1 had no edema before the marathon (a) and mild edema appeared after the marathon (b; grade 2, size between 0.5-1.5 cm); Participant 2 had little edema before the marathon (c; grade 1, <0.5 cm in size) which slightly extended after the marathon (d; grade 2, size between 0.5-1.5 cm). SHOMRI grading system was used; SHOMRI, Scoring hip osteoarthritis with MRI; BME, bone marrow edema.

Tendons

Pre-marathon, tendinosis (grade 1) was present in 7/42 (17%) hips of marathon finishers; particularly the gluteal, psoas and hamstring tendons were affected. No changes occurred after the marathon. Also, one hip of a training non-finisher (13%) had psoas tendinosis before the training for the marathon and no progress in its extent was seen at the 2nd MRI scanning time point (Figure 7.2, Figure 7.5).

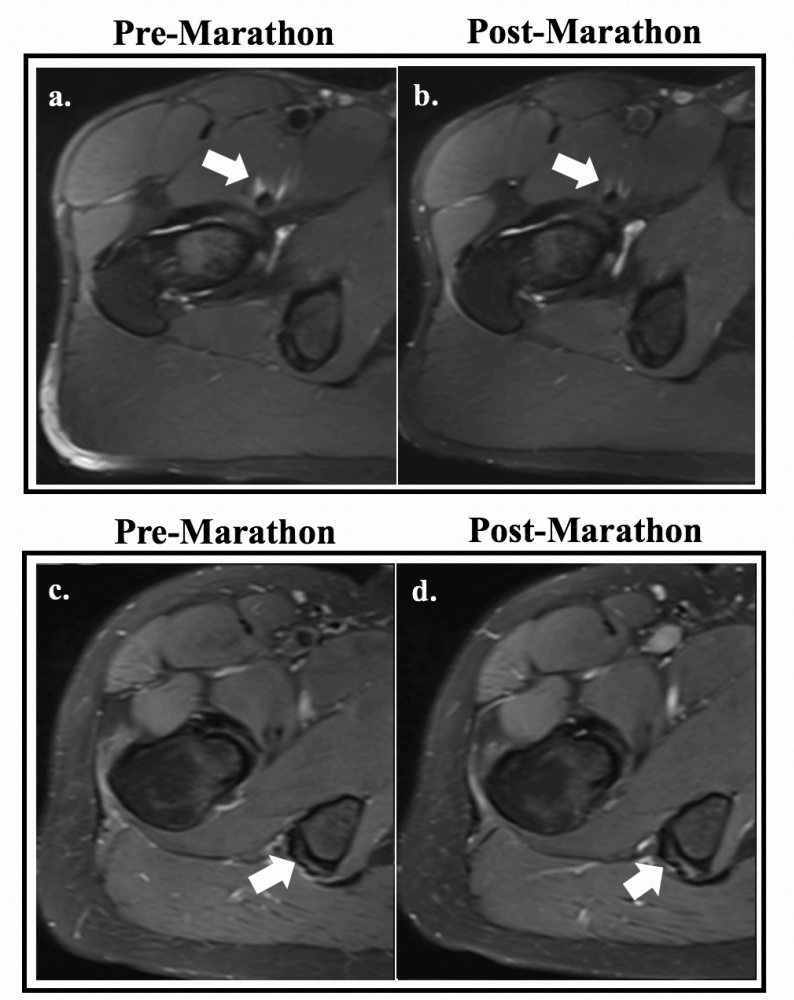


Figure 7.5. Axial Dixon MR images of 2 participants showing tendinosis before the marathon and no worsening after the marathon. Participant 1 (a – pre-marathon; b – post-marathon) had psoas tendinosis (arrowed). Participant 2 (c – pre-marathon; d – post-marathon) had hamstring tendinosis (arrowed). SHOMRI grading system was used; SHOMRI, Scoring hip osteoarthritis with MRI.

Ligaments

Pre-marathon abnormal ligament signal (grade 1) was detected in 6/42 (14%) hips of marathon finishers, and none in training non-finishers. There were no post-marathon changes (Figure 7.2).

Muscles

Pre-marathon fatty infiltration was found in minimal extent in 30/42 (71%) hips (grade 1) and in mild extent in 13/42 (31%) hips (grade 2) of marathon finishers. Those hips with grade 2 muscle fatty atrophy had simultaneous grade 1 atrophy in other muscles. No post-marathon changes were seen. Four hips of training non-finishers had both pre-marathon grade 1 and grade 2 abnormalities, in different muscles (50% hips). There were no changes at the second scan (Figure 7.2).

Other findings

Before the marathon, we reported 2/42 (5%) hips with joint effusion and 3/42 (7%) hips with trochanteric bursitis in marathon finishers, and 3/8 (38%) hips with trochanteric bursitis in training non-finishers. No changes were reported after the marathon.

7.3.3 Marathon finishing times

The estimated mean of marathon finishing times was 4 hours 23 minutes ± 42 minutes. The varying pre-training physical activity and running experience among study participants did not have an impact on marathon finishing times (p=0.686) nor other post-run findings. The marathon finishing times of participants with labral lesions were not significantly different from the finishing times of those participants without labral lesions (p=0.310; see Figure 7.6). Also, marathon finishing times were not affected by the existence of any other type of MRI abnormality, such as abnormalities of the articular cartilage (p=0.214), BME (p=0.975), abnormal ligament signal (p=0.433), tendinosis (p=0.802), muscle abnormality (p=0.521), effusion/bursitis/cysts (p=0.378).

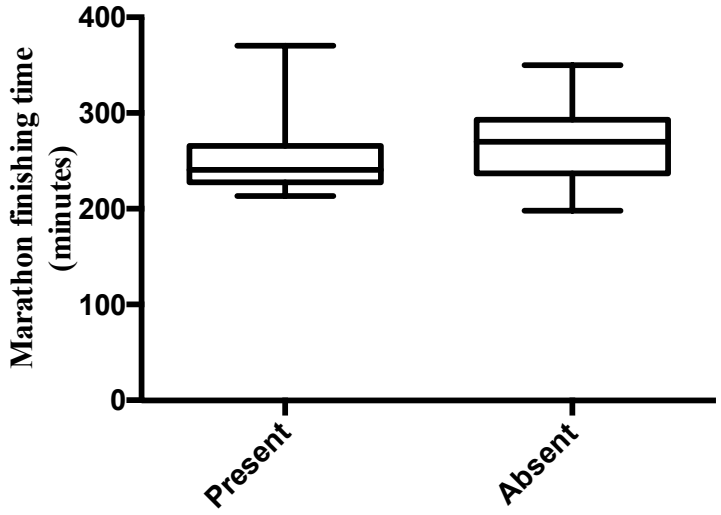


Figure 7.6. Marathon finishing times of participants, divided into 2 groups, based on: presence or absence of pre-marathon labral tears or labrocartilage separation; 21 participants entered and finished the marathon, with labrum abnormalities (n=8) or normal labrum (n=13).

7.3.4 Double-reporting consensus

There was excellent agreement between the radiologists scores in terms of the changes seen after the marathon (kappa 1.000).

7.3.5 HOOS results

The post-marathon HOOS scores were similar to the pre-marathon scores, for each questionnaire section, in marathon finishers: symptoms (p=0.780), pain (p=0.445), daily activity (p=0.227), sports and recreational activities (p=0.992), quality of life (p=0.565); and also in training non-finishers (too small sample for calculating statistical significances).The HOOS scores of the two participants who developed small areas of post-marathon BME did not change over time, thus reflecting no alterations in their perceived hip condition.

7.4 DISCUSSION AND CONCLUSIONS

Overall, this study showed that marathon running did not damage the hips of first-time marathon runners. The pre-existing damage in the participants' asymptomatic hips did not prevent them from completing the training programme nor finishing the race, and did not progress further after the marathon. Marathon finishing times were unaffected by the

presence of pre-marathon abnormalities. This included labral tears which are frequently recommended hip surgery. There were very minor alterations on the MRI scans from the pre-marathon time point to the post-marathon time point. In particular, only 2/42 hips of marathon finishers developed small areas of BME in the non-weight-bearing hip region. Moreover, no complaints of pain, poor function or other symptoms were reported by these participants so no associations could be made. Also, only 25% of the initial cohort that signed up for the marathon stopped their training and did not run the race – this is actually lower than the expected range 30-50% [319–321]. Only one of them did so due to hip pain but those symptoms disappear over time, before the 2nd MRI scan. The MRI results were similar between marathon finishers and training non-finishers in terms of prevalences and levels of damage – the pre-marathon findings were slightly higher in marathon finishers, yet no major differences. Also, the sample size of training non-finishers was much smaller than that of marathon finishers, so direct comparisons could not be made.

7.4.1 Study strengths

There are a number of strengths related to the design and specific characteristics of this study: 1) Firstly, this is the first study to use high-resolution 3.0 T MRI to evaluate the effects of marathon running and preceding training for the marathon on the hips joints of novice marathon runners; 2) This study included the largest cohort of runners being assessed so far and did a complete analysis of both hips of runners; 3) The cohort of runners selected as study participants involved first-time marathon runners only, rather than including experienced long-distance runners who previously completed at least one marathon. This was done to analyse the impact of a single marathon run (and training for it) on the hip joints of less experienced runners; 4) The participants followed a standardised 4-month beginner training plan in preparation for the race to minimise the impact of past exercise/running experience among participants; 5) The employed equipment was optimised to include a high-resolution 3.0 T MRI scanner for high sensitivity and specificity in detecting post-marathon changes, as well as providing safety advantages being a non-invasive technique, and not using contrast agents to avoid any potential allergic reactions associated with them; 6) The percentage of participants who dropped out of the study was not higher than expected, but in fact it was lower than predicted estimations from other marathons; 25% of the initial cohort did not finish the training plan and did not enter the marathon, therefore I included a comparison between these participants and those who finished the marathon; 7) This study provided a

comprehensive analysis of all intraarticular hip joint features, plus hip muscles, by using semi-quantitative validated scoring systems and 2 senior radiologists for co-reporting a subset of scans. This is the first study to evaluate the hip muscles of runners before and after a run using MRI.

7.4.2 Study limitations

A couple of study limitations need to be taken into account: 1) There is an inherent risk of bias and error when it comes to radiological reporting in general. Therefore, we aimed to minimise this risk by including 2 musculoskeletal radiologists in our investigation. One of the radiologists reviewed all images, while a second radiologist co-reported the images from 20% of the same cohort of runners. 2) However, not all images from the whole cohort were double-reported by the 2 radiologists, which may question the accuracy of all the assigned scores. The size of the double-reported subset of scans was decided based on an internal discussion, as well as the evidence from existing literature for maximising resources (as explained in Chapter 6). Moreover, the interreader agreement was excellent, therefore we considered that the single-reporting of the rest of the scans was reliable; 3) There were 3 participants who discontinued the training and could not be scanned again after that because of reasons of unavailability; this would have been beneficial for the analysis of any MRI changes that might have occurred between the pre-training and post-training scanning time points. Nevertheless, none of these reported hip complaints. Only one of them showed symptoms of knee pain during training which resolved after discontinuing the training, whereas the remaining 2 participants did not stop due to running-specific reasons; 4) No internal controls (i.e. non-runner group) were included in the study; this would have helped to better understand the marathon-related outcomes; 5) Self-reported symptoms may involve some subjectivity. A reliable HOOS questionnaire was used to minimise this, but a level of bias is unavoidable; 6) There was a long period of time between the pre-training and post-marathon scans (4.5 months), thus no scans were conducted immediately (hours to few days) before and after the race day. This could have helped in understanding the impact of the marathon run alone on the hips. However, the aim was to to capture any changes that might have occurred over the course of training (which would have been missed otherwise) and not only during the marathon race. Ideally, such additional scans would have provided more data for analysis, but we had limited resources as a research group. The 2 weeks post-marathon session was selected based on the availability of most participants; 7) Medium-term and longer-term follow-up studies are required to evaluate whether the 2 cases of post-marathon BME

development resolve over time, and whether any new MRI changes or hip symptoms/complaints appear over a longer period of time.

7.4.3 Comparison with previous studies

There is extremely little literature on the impact of marathon running on hip joints. Most of the existing literature on marathon running focused on its effects on the knee joints instead of the hip joints, demonstrating no permanent significant alterations on MRI following the run [43,227,228,230,318].

Only one previous MRI study conducted by Hohmann *et al* [43] investigated the MRI changes occurring in the hips of 8 asymptomatic runners, particularly 6 recreational and 2 semi-professional long-distance runners. These participants underwent unilateral hip MRI scans shortly (24 hours) before and after a marathon run, and no abnormalities were detected on the MRI scan at either time point. By contrast, the results of our study showed that before the marathon there were a number of asymptomatic abnormalities in the hips of those participants who then went on to finish the marathon, specifically labral abnormalities (29%), articular cartilage defects (7%), BME (14%), tendinosis (17%), abnormal ligament signal (14%). Nevertheless, there were several differences between these research works in terms of study design. Firstly, the number of participants in our study was three times bigger compared to the number of participants in Hohmann *et al*'s study, plus we scanned both hips of runners so the sample size was much larger (25 runners, 50 hips versus 8 runners, 8 hips). Secondly, the types of runners were different in these studies - we included novice marathon runners, while the other study included experienced long-distance runners who were achieving 60-150 km/week. Moreover, we performed high-resolution MRI versus low-resolution MRI as in the previous study, to identify even small abnormal MRI signal and early signs of pathologies. However, in agreement with Hohmann *et al*, our post-marathon results showed no significant changes in comparison to the pre-marathon findings.

7.4.4 Clinical significance and future work

Our study indicates that marathon running and the preceding training for the marathon do not have detrimental effects on the internal hip joints structures of novice marathon runners, with no pre-existing symptomatic hip lesions or past surgeries. This evidence has important implications on our understanding of long-distance running, considering that there are increasing concerns regarding running-related hip injuries and risks of developing OA [361–363], despite the paucity of research studies supporting these. The results of our study suggest that running a marathon does not increase the risk of

developing hip joint pathologies, thus confirming the current lack of evidence linking long-distance running with hip OA. However, I acknowledge the fact that no evidence of existence does not necessarily mean no proof of absence. This study was not tailored primarily with the aim of evaluating OA development over time, but to assess the immediate impact of running in relation to joint health in asymptomatic adults. Longer-term follow-up studies are required to closely monitor the progression of MRI abnormalities and/or symptoms over time.

Moreover, there are studies – including our research presented in Chapters 4 and 5 - demonstrating a beneficial impact of marathon running on knee joint health [347,364]. This may potentially support the stability of the hip joint as well, given that the knee and hip joints are interconnected and depend on each other for maintaining co-ordinated movement and good functioning of the lower limbs. Also, other research work indicated that participating in a higher number of marathon runs, and thus acquiring increased long-distance running experience, may be associated with lower risk of joint pain in previously non-injured runners [108]. The explanation for this may be that training for a running event involves gradual muscle strengthening which may result in a decreased load impact on the joints. Therefore, the high-impact forces exerted during running may become well-tolerated, and also protective adaptive mechanisms may develop in the joints over time [347,364].

Additionally, a multitude of cofounding factors may need to be taken into consideration, such as running surface, running style, shoes, nutrition. These aspects may have an important impact on reducing the repetitive running-related stress on the cartilaginous tissues, subchondral bone and other soft tissues surrounding the joints. The development of adaptation mechanisms may prevent overloading and therefore reduce the risk of getting injured [110–112,347,364,365].

Future long-term studies are needed to further investigate the impact of marathon running and confirm that no gross morphologic changes occur over time.

The presence of asymptomatic pre-marathon labral tears (including complex ones) and other abnormalities of the hip joint did not affect marathon running performance. All marathon entrants completed the race and no significant differences between the finishing times of runners with tears and of those without tears were found. There was no progression in the extent of labral tears or development of new ones. This emphasises the importance of reconsidering the utility of hip arthroscopy for repairing labral tears on a case by case basis. As in the case of meniscal tears and the frequent use of meniscectomy, clinical decisions to perform arthroscopy should be based on a number of factors,

including: clinical evaluation, symptoms assessment, MRI results; yet not solely on the MRI results [345,355–358].

Chapter 8 – Conclusions from the knee and hip studies and future work

Long-distance running is an extremely popular physical activity all around the world. Apart from the multiple benefits associated with running, including cardiovascular and aerobic fitness, it is a convenient and inexpensive type of exercise which requires very little equipment [48-53]. Therefore, it is preferred by people of all ages and fitness levels, with different training goals from recreational to competitive races. The ultimate challenge for many runners is to complete a marathon race (42 km), which requires significant preparation of several months prior to the race. In fact, an increasing number of beginner or inexperienced runners has been reported to participate in marathon runs. The majority of them are aged over 30 years old; moreover elderly runners (aged over 40-50 years old), often beginner ones, are on the rise nowadays [58]. This has given rise to concerns as to whether marathon running may have a negative impact on their joints, especially given their lack of experience and/or age. Moreover, long-distance races such as marathon runs have controversially been associated with overuse injuries of the lower limb joints, presumably due to the high-impact repetitive motion of the joints during running [55]. The knees and hips are considered two of the most commonly affected sites. However, the prevalence of reported running-related injuries varies significantly from 18% and 92% [64-66]. This wide range is most probably explained by differences in the definition of injuries, numerous confounding factors, diagnostic tools, participant characteristics, unclear clinical relevance [77]. Therefore, it is yet clear what is the exact impact of marathon running on the knee and hip joints.

Imaging techniques have revolutionised medical healthcare and orthopaedic research, enabling the identification of early signs of lesions in internal structures, even before the manifestation of physical symptoms. The MRI technology gives unprecedented benefits of safety, sensitivity and specificity, with high-quality contrast-detection of all soft tissues surrounding the joints [198,199]. Moreover, the relatively recent development of high-resolution 3.0 T MRI provides benefits of higher accuracy for excellent visualisation of intraarticular features and related pathologies [189-197]. 3.0 T offers better resolution in comparison to 1.5 T for a number of structures, including: chondral surfaces, tendons, ligaments, menisci. For example, while 1.5 T can diagnose high-grade cartilage lesions well (large size which is equivalent to high severity level), including partial and complete thickness defects, there is less accuracy in detecting lower-grade lesions such as surface fibrillation and small-sized abnormalities [193,194]. This is important to consider because lower-grade lesions may indicate early signs of pathologies which need to be identified and then monitored further. Although low-grade lesions may appear to be less

severe than high-grade lesions, the first ones can develop over time and become high-grade lesions, in certain conditions, therefore careful long-term monitoring is required.

Also, there is very little scientific evidence, particularly based on MRI analysis, on the impact of marathon running on the knee and hip joints, respectively. Most of these focused on knee joint analysis, while only one study investigated the hip joints of runners. Furthermore, the existing evidence is characterised by a number of study design limitations, including: low-resolution MRI, small sample size, experienced runners instead of inexperienced ones, impact of training not taken into account, short follow-ups.

The aim of this thesis was to assess the impact of marathon running, including the training before the run, on the knee joints and hip joints, respectively, of asymptomatic novice marathon runners, with no history of known injuries. My research team and I designed 2 separate research projects, one on knee analysis and another one on hip analysis. We conducted bilateral 3.0 T MRI scans of each joint, respectively, before the training for the marathon and then shortly after the marathon run, including the largest cohorts of runners to date among MRI running studies, and specifically inexperienced, first-time marathoners. Also, an additional medium-term follow-up was organised as part of the knee project. Moreover we did a baseline assessment of the hips of less experienced long-distance runners versus experienced marathon/ultrarunners, before participants from the first group of runners went on to train for their first marathon and run the race, then attend the post-marathon hip study mentioned above. These are the first research projects of these kind, with unique study designs which overcome several limitations of previous studies.

From the knee MRI analysis, the main conclusions were the following: 1) Pre-marathon, there was a high prevalence of asymptomatic abnormalities in most internal knee joint structures (increasing with age), including meniscal tears, articular cartilage and bone marrow defects (from small to high-grade lesions), tendon and ligament abnormalities; the patellofemoral compartment was most affected; 2) Shortly post-marathon, 3 main findings were highlighted. Firstly, there was a significant increase in the prevalence and grades of patellofemoral articular cartilage abnormalities from the pre-marathon status. Secondly, there was a significant decrease in the prevalence and grades of tibiofemoral (weight-bearing) BME from the pre-marathon grade. Meanwhile, a number of patellofemoral edema-like lesions developed after the run, but not statistically significant;

the perceived knee condition of these participants was not significantly altered during this time. Also, the knees with pre-existing abnormalities were more likely to have those extended after the marathon or develop new ones in other regions of the same knees (the latter was more common) than the knees without pre-existing abnormalities to develop new ones. Thirdly, marathon performance was not influenced by the presence of pre-marathon abnormalities; 3) Six months later, the changes seen on MRI were the following: Firstly, those cartilage abnormalities that developed shortly after the run showed reversibility in 14% of cases. Secondly, the reduction seen in the extent of tibiofemoral BME was sustained over time and few new improvements appeared at this follow-up. Also, more than half of those BME-like lesions that developed after the marathon reversed over time. Moreover, no progress of any pre-existing lesions or new ones appeared at this stage.

These results suggest that training for a marathon and running the race may have counterbalanced implications on the knee joints of novice marathoners. On one hand, there might be potential beneficial effects on the weight-bearing bone region of the knee which is most commonly associated with OA; this is speculated to be due to muscle strengthening during training, as a result of gradual adjustment of the joint to increased load – however this needs careful further investigations before drawing conclusions. On the other hand, the patellofemoral compartment – especially the articular cartilage - was more vulnerable to the impact of running, which may not be surprising given the fact that the kneecap is under great pressure during running. Therefore, specific exercises during training should better target this area of the knee to minimise impact. However, the clinical significance of these findings is uncertain considering that participants' symptoms were almost unchanged after the run. Moreover, the reversibility of some lesions at the 6 months follow-up suggests that these effects may be temporary and, perhaps, more time is required for complete resolution. Future long-term follow-up studies need to investigate any changes in symptoms over time, the status of bone marrow improvement, cartilage lesions reversibility, and thus clarify the clinical significance of the two different post-marathon findings in both cases.

From the hip MRI analysis, the main conclusions were the following: 1) Pre-marathon, both non-marathoners (less experienced runners who never ran a marathon) and marathoners+ (experienced marathon/ultrarunners) had asymptomatic abnormalities in their hips. Prevalences were higher in non-marathoners than in marathoners+ in most cases (labral tears, cartilage defects, BME, abnormal ligament signal), but lower than the

estimated prevalences in the population of sedentary non-runners (when compared to previous studies); this suggests that running experience may be an important factor in preventing running-related injuries; 2) Post-marathon, participants from the group of non-marathoners, who started their training for their first marathon after the baseline assessment, showed extremely little change on their MRI scans. Only 2 cases of BME increased in grade from the pre-existing ones, however there were no symptoms or other hip complaints to associate them with. All other pre-marathon abnormalities remained unchanged and did not not affect marathon running performance, indicating that preparing for a marathon and running it do not damage the hip joints. Medium-term and long-term follow-ups are required to assess the reversibility of the 2 post-marathon edema appearances over time, as well as any potential delayed responses of marathon running, new MRI signal appearances or potential improvements in pre-existing lesions, or changes in symptoms.

Based on the findings from these two 3.0 T MRI research studies, the main common conclusion that can be drawn is that marathon running does not damage the knee and hip joints of novice marathoners with no previous symptomatic injuries, as it is commonly (and mostly anecdotally) perceived. Despite the changes seen on MRI after the marathon, there were not much changes in symptoms or complaints of functional limitations (based on self-reported questionnaire scores), therefore the clinical significance is yet to be established. Longer-term follow-up studies are required to clarify this over time. Also, an important consideration from the pre-marathon findings is the presence of asymptomatic meniscal and labral tears, respectively, particularly of complex patterns which are not commonly found in asymptomatic joints and are usually treated operatively, using arthroscopy. Moreover, these tears were unchanged after the run; this supports the reconsideration of using arthroscopy based on imaging findings only, but to take also other factors into account such as clinical examinations and symptoms.

In both research projects, the rate of pre-race drop-outs or so called ‘training non-finishers’ was actually lower than the expected one, estimated by other marathon studies. All participants who completed the training and entered the race also finished it, except for one case only in the knee study cohort. The presence of pre-training MRI abnormalities did not prevent runners from completing the marathon run. Generally, training non-finishers showed a reduced number of pre-marathon and post-marathon changes than marathon finishers (although there was similarity in the specific regions being affected), and did not show any significant improvement or worsening after the

marathon. However, no significant differences were found between training non-finishers and marathon finishers in either study, especially because the sample size was much smaller so direct comparisons could not be made. Therefore, it cannot be concluded whether the training for the marathon or the marathon itself had a bigger impact on the joints, but it is suggested that the training and race together led to these results.

In terms of participant characteristics, no significant differences were found between marathon finishers and training non-finishers. The prevalence of pre-marathon MRI abnormalities increased with older age in knees but not in hips. Pre-marathon tendon abnormalities of both knees and hips were more common in overweight participants. Also, the increase in post-marathon knee abnormalities seemed to be more common in older women aged ≥40, while the reduction in the extent of lesions was prevalent in men irrespective of their age.

Planned future work involves conducting a medium-term follow-up study on the hips of novice marathoners to check the status of those 2 cases of post-marathon edema (which are predicted to resolve over time, as in the medium-term follow-up knee study), as well as to check any MRI alterations in the state of pre-existing lesions or changes in symptoms. Also, future work will involve long-term follow-up studies (2 years after the run and even longer ones) to monitor the hips of our participants and the status of their MRI abnormalities over time. Other future studies could focus on compositional analysis of cartilaginous tissues for an in-depth characterisation of the biological processes and changes occurring in relation to running. Potential MRI-based studies could include specific sequences which have been developed for cartilage biochemical analysis, such as T_{1rho}, T_2, T_{2*} or dGEMRIC [74-76,165,167,171,172,173]. Also, MR spectroscopy enables tissue evaluation for the presence of various metabolites and their specific amounts. This metabolic information is important in lesion characterisation and assessment of changes after running [366]. Infrared spectroscopy is another method that can be employed for molecular assessment purposes. Based on this technique, molecular characterisation of a sample is enabled according to the interactions between infrared radiation and matter (e.g. fourier transform infrared spectroscopy) [367].

Regarding potential biological explanations of the phenomena seen on MRI with regards to cartilage lesions and bone marrow edema, respectively, the following details need to be considered: 1) First of all, cartilage consists mainly of extracellular matrix (water, collagen, proteoglycans, non-collagenous proteins) with a distribution of specialised cells

called chondrocytes [2]. Excessive mechanical forces may lead to cartilage matrix deterioration, such as formation of matrix fragments, resulting in overstimulation of chondrocytes through the activation of signalling pathways, including production of reactive oxygen species. This results in the formation of an increased number of inflammatory mediators: cytokines, chemokines; also proteolytic enzymes [368]. The catabolic activity of chondrocytes aims to remove the damaged matrix. However, the chondrocytes' insufficient response to the stimulation of growth factors and thus unbalanced catabolic and anabolic activity leads to continuous deterioration of the matrix [368]. On MRI scans, this appears in the form of areas of MRI signal hyperintensity within the cartilage and in certain cases may progress to loss of chondral thickness, superficial chondral fraying and fissuring, which at the latest stage can breach subchondral bone. In our study, such cartilage lesions of different grades of severity were seen before the marathon, from potential past traumatic events, mechanical stress or aging, and further progression was seen immediately after the run. All biochemical changes were clearly reflected on the 3.0 T MRI findings. Secondly, it is known that cartilage lesion reversibility can occur once a balance between catabolic and anabolic processes is established for cartilage turnover. The conditions for cartilage reversibility are yet unclear, but few strategies can include weight control, physical activity instead of sedentary lifestyle (the optimal dose of exercise is still debatable though), appropriate rest time after exercise [369-371]. In our study, reversibility of 14% cartilage lesions was seen on follow-up MRIs after a period of rest following the marathon; 2) Bone marrow edema can be caused by various factors, including excessive mechanical stress or previous trauma. It is characterised by inflammation which is indicated by an increased vascularity and cellularity, mainly including cells of the immune system (T cells, B cells, macrophages). The development of edema increases the diffusion distance for oxygen and other nutrients, which may be detrimental for cellular metabolism in the respective tissue [372,373]. In the study, bone marrow edema was seen as areas of hyperintensity within the bone marrow of the joint reflecting the process summarised above i.e. this was detected before the marathon, and in some cases there was bone marrow edema progression after the marathon run. Next, speaking about bone marrow edema reversibility, bone remodelling is thought to be based on the activation of bone remodelling units of osteoclasts (which remove the damaged bone) and osteoblasts (which help in replacing the damaged bone with new healthy bone) which are recruited at the area of bone lesion and result in increased cell-mediated bone remodelling process [374,375]. Bone marrow edema formation and reversibility are very complex processes which still

need to be better understood and studied further. Gradual increase in exercise involving leg muscles, especially around the body area affected by bone marrow edema, may contribute in pumping the excess fluid back towards the heart. This will stimulate the activity of osteoclasts and osteoblasts and thus may help in reducing inflammation [376-377]. In our study, we detected complete or partial resolution of bone marrow hyperintensity at the follow-up scans in relation to the marathon i.e. in one situation, there was significant reduction in the extent of bone marrow edema immediately after the marathon run (in the weight-bearing compartments), while in another situation there were some cases of edema which developed immediately after the run and then 6 months later reversed in extent in more than half of those cases (patellofemoral compartment).

Having said these, there are a number of limitations related to these studies and room for improvement. First of all, an ideal study design would have involved MRI scans of both knees and hips of the same cohort of novice marathoners on the same research project; or perhaps even including ankle MRIs, to provide an overview of the overall condition of asymptomatic lower limb joints before running and then monitoring any changes occurring after the training for the marathon and completing the race. Lower limb joints are interconnected, therefore analysing them all together would have provided an even better understanding of the dynamics and potential links between findings. However, this would have been a very complex and demanding project for both participants and research team, and requiring extensive resources. Moreover, a comparative analysis of the joints of both novice marathoners and experienced marathoners before and after running a marathon, would have been helpful in confirming the hypothesis (suggested in our baseline hip study and other previous studies) that the increased level of running experience or the gradual increase in running volume over time during training for long-distance running events (as in the case of the novice marathoners in our studies) may provide a protective effect on the joints.

Another limitation is that an MRI analysis of the muscles around the knee joint was not conducted. The MRI protocol was designed to capture the intraarticular knee joint structures but not the muscles, which could have given important information in relation to running. However, the study provided an analysis of hip muscles in the hip project. Also, a potential future study could include manual or automated 3D muscle segmentation tools to quantify the muscle-to-fat ratio from the MRI scans, and then compare the

findings with the scores reported by radiologists. This can help in checking levels of agreement and the reliability of radiological reporting.

Furthermore, there are several confounding factors that might have impacted the results of our studies, but could not be taken into account or properly analysed. Such risk factors for running-related injuries can vary significantly among individuals and include (but are not limited to) the following: leg-length discrepancies, leg alignment, biomechanics, running shoes, running style, running surface, running posture, rest time, additional physical activities apart from the standardised training, unreported changes to the standardised marathon training plan (e.g. adjusted weekly running volume from), nutrition, health and lifestyle habits, unreported accidents or joint-related traumatic events. For example, repetitively running on hard surfaces, such as road running (i.e. as in the London Marathon) may involve increased impact forces and biomechanical stress. Mixing the surfaces to include grass, bark or treadmill during training could potentially benefit the joints, but this would depend on other confounding factors of the individual and there are no clear guidelines or physio advice on the best approach. Also, choosing the best-fitting shoes based on the individual's running mechanics and running stride to provide support and cushioning is important. Future studies need to investigate these further. However, it is extremely challenging in one study to analyse all or even a part of these factors in sufficient detail. Given the complexity and multifactorial nature of running-related injuries, there is still considerable lack of knowledge on the impact of long-distance running on the joints and how important certain factors are over others. But this research project took a major step forward in addressing this subject by means of high-resolution MRI and increased our understanding of the implications of marathon running and its preceding training on the internal knee and hip structures, with promising evidence of non-clinically significant damage.

Appendix A

Ethical approvals and further study details

A.1. Studies described in Chapters 3-5 (Knee project)

A.1.1 Ethical approval (with amendments)

NHS
Health Research Authority

London - Queen Square Research Ethics Committee

HRA NRES Centre Manchester
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

Tel: 0207 104 8009

24 October 2016

Professor Sanjay Sharma
Department of Cardiovascular Sciences
St George's University of London
Cranmer Terrance, London
SW17 0RE

Dear Professor Sharma

Study title:	**Increased left ventricular trabeculation in athletes – a marker of left ventricular non-compaction or a physiological epiphenomenon of increased cardiac preload?**
REC reference:	**15/LO/0086**
Amendment number:	**6**
Amendment date:	**20 October 2016**
IRAS project ID:	**156948**

Addition of validated KOOS questionnaire. Updated patient documents to reflect this.

The above amendment was reviewed at the meeting of the Sub-Committee held on 25 October 2016 by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

There were no ethical issues raised.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering letter on headed paper		
Notice of Substantial Amendment (non-CTIMP)	6	20 October 2016

Participant consent form	11	20 October 2016
Participant information sheet (PIS)	14	20 October 2016
Research protocol or project proposal	13	20 October 2016
Validated questionnaire [KOOS]		

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

15/LO/0086:	**Please quote this number on all correspondence**

Yours sincerely

[redacted]

Signed on behalf
of the Alternate
Vice-Chair
Ms Danielle Wilson

E-mail: nrescommittee.london-queensquare@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Ms Debbie Rolfe, St. George's Joint Research Office*

London - Queen Square Research Ethics Committee

Attendance at Sub-Committee of the REC meeting on 25 October 2016

Committee Members:

Name	*Profession*	*Present*	*Notes*
Mrs Jenny Johnson	Charity Trustee	Yes	
Ms Danielle Wilson	Clinical Trials Facility Manager	Yes	Chaired Meeting

Also in attendance:

Name	*Position (or reason for attending)*
Miss Amber Ecclestone	REC Manager
Miss Jenna Woodburn	REC Assistant

NHS
Health Research Authority

London - Queen Square Research Ethics Committee

HRA NRES Centre Manchester
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

Tel: 0207 104 8009

14 September 2016

Professor Sanjay Sharma
Department of Cardiovascular Sciences
St George's University of London
Cranmer Terrance, London
SW17 0RE

Dear Professor Sharma

Study title:	**Increased left ventricular trabeculation in athletes – a marker of left ventricular non-compaction or a physiological epiphenomenon of increased cardiac preload?**
REC reference:	**15/LO/0086**
Amendment number:	**5 13/08/16**
Amendment date:	**13 August 2016**
IRAS project ID:	**156948**

In order to investigate the effects of marathon training on knees amendment proposes to perform a non-contrast MRI scan of each participant's knees, which will take approximately 30 minutes to perform. This would be performed in the same department as the cardiac MRI scans.

The above amendment was reviewed at the meeting of the Sub-Committee held on 02 September 2016 by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

The Sub-Committee requested that a clause should be added into the Informed Consent Form with regards to the MRI scan of the knee. In addition to this the Sub-Committee questioned whether the Researcher proposes to perform MRI's of the knee on participants who have already consented or just new participants.

The Researchers noted this and supplied an updated Informed Consent Form. The Researcher also confirmed that the knee MRI's will only take place on new participants.

The Sub-Committee noted the Researcher response and was happy to issue a Favourable Opinion.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering letter on headed paper		
Notice of Substantial Amendment (non-CTIMP)	5Ï¾ 13/08/16	13 August 2016
Participant consent form	11	13 September 2016
Participant information sheet (PIS)	13	16 August 2016
Research protocol or project proposal	12	16 August 2016

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

15/LO/0086:	**Please quote this number on all correspondence**

Yours sincerely

[redacted]

Signed on behalf of
Dr Eamonn Walsh
Chair

E-mail: nrescommittee.london-queensquare@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Ms Lucy Parker, St George's, University of London*

London - Queen Square Research Ethics Committee

Attendance at Sub-Committee of the REC meeting on 02 September 2016

Committee Members:

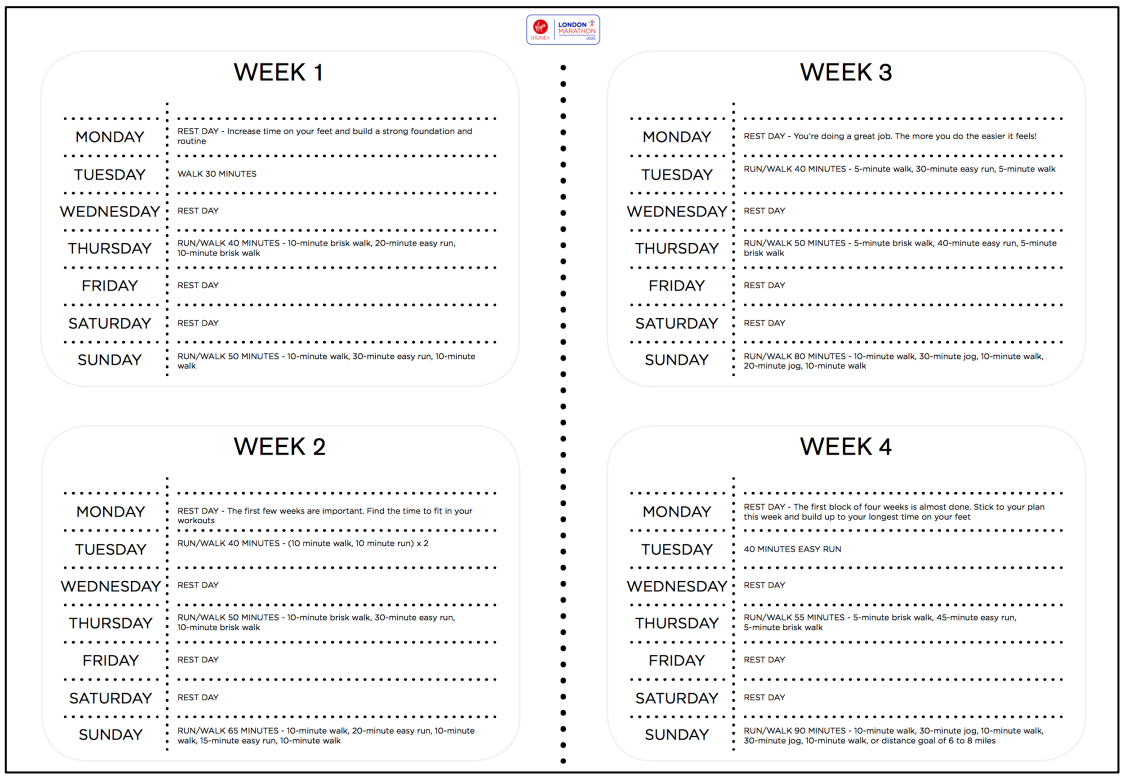
Name	*Profession*	*Present*	*Notes*
Dr Eamonn Walsh	Senior Lecturer	Yes	
Miss Zalika Xavier	Vaccine Sales Representative	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Miss Jenna Woodburn	REC Assistant

A.1.2 Further project details

A.1.2.1 Marathon training plan: London Marathon Beginner training programme (virginmoneylondonmarathon.com)



WEEK 1

MONDAY	REST DAY - Increase time on your feet and build a strong foundation and routine
TUESDAY	WALK 30 MINUTES
WEDNESDAY	REST DAY
THURSDAY	RUN/WALK 40 MINUTES - 10-minute brisk walk, 20-minute easy run, 10-minute brisk walk
FRIDAY	REST DAY
SATURDAY	REST DAY
SUNDAY	RUN/WALK 50 MINUTES - 10-minute walk, 30-minute easy run, 10-minute walk

WEEK 2

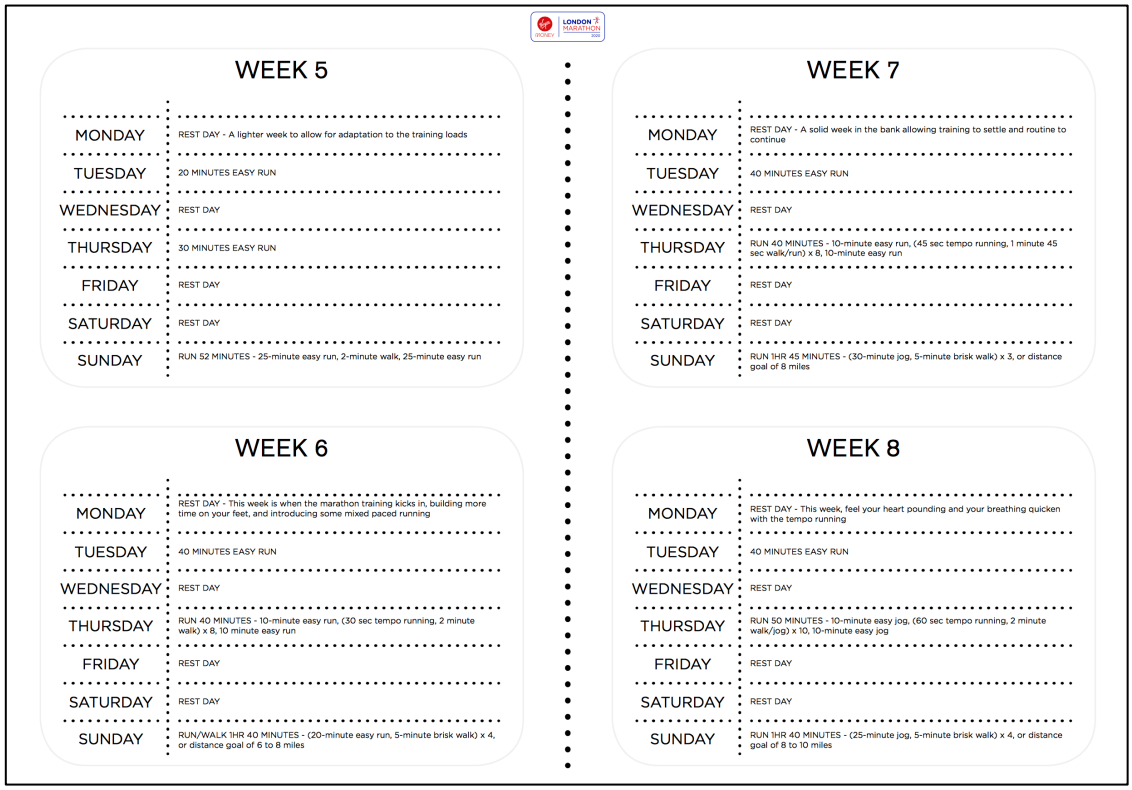
MONDAY	REST DAY - The first few weeks are important. Find the time to fit in your workouts
TUESDAY	RUN/WALK 40 MINUTES - (10 minute walk, 10 minute run) x 2
WEDNESDAY	REST DAY
THURSDAY	RUN/WALK 50 MINUTES - 10-minute brisk walk, 30-minute easy run, 10-minute brisk walk
FRIDAY	REST DAY
SATURDAY	REST DAY
SUNDAY	RUN/WALK 65 MINUTES - 10-minute walk, 20-minute easy run, 10-minute walk, 15-minute easy run, 10-minute walk

WEEK 3

MONDAY	REST DAY - You're doing a great job. The more you do the easier it feels!
TUESDAY	RUN/WALK 40 MINUTES - 5-minute walk, 30-minute easy run, 5-minute walk
WEDNESDAY	REST DAY
THURSDAY	RUN/WALK 50 MINUTES - 5-minute brisk walk, 40-minute easy run, 5-minute brisk walk
FRIDAY	REST DAY
SATURDAY	REST DAY
SUNDAY	RUN/WALK 80 MINUTES - 10-minute walk, 30-minute jog, 10-minute walk, 20-minute jog, 10-minute walk

WEEK 4

MONDAY	REST DAY - The first block of four weeks is almost done. Stick to your plan this week and build up to your longest time on your feet
TUESDAY	40 MINUTES EASY RUN
WEDNESDAY	REST DAY
THURSDAY	RUN/WALK 55 MINUTES - 5-minute brisk walk, 45-minute easy run, 5-minute brisk walk
FRIDAY	REST DAY
SATURDAY	REST DAY
SUNDAY	RUN/WALK 90 MINUTES - 10-minute walk, 30-minute jog, 10-minute walk, 30-minute jog, 10-minute walk, or distance goal of 6 to 8 miles



WEEK 5

MONDAY	REST DAY - A lighter week to allow for adaptation to the training loads
TUESDAY	20 MINUTES EASY RUN
WEDNESDAY	REST DAY
THURSDAY	30 MINUTES EASY RUN
FRIDAY	REST DAY
SATURDAY	REST DAY
SUNDAY	RUN 52 MINUTES - 25-minute easy run, 2-minute walk, 25-minute easy run

WEEK 6

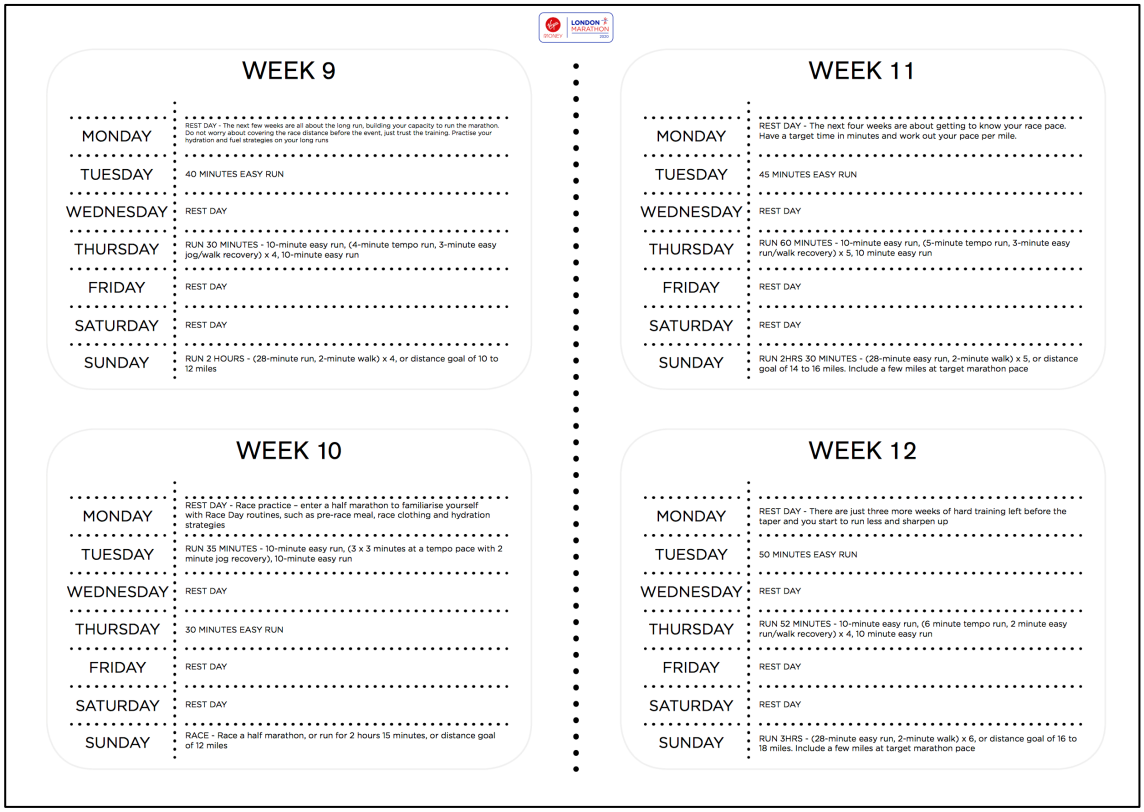
MONDAY	REST DAY - This week is when the marathon training kicks in, building more time on your feet, and introducing some mixed paced running
TUESDAY	40 MINUTES EASY RUN
WEDNESDAY	REST DAY
THURSDAY	RUN 40 MINUTES - 10-minute easy run, (30 sec tempo running, 2 minute walk) x 8, 10 minute easy run
FRIDAY	REST DAY
SATURDAY	REST DAY
SUNDAY	RUN/WALK 1HR 40 MINUTES - (20-minute easy run, 5-minute brisk walk) x 4, or distance goal of 6 to 8 miles

WEEK 7

MONDAY	REST DAY - A solid week in the bank allowing training to settle and routine to continue
TUESDAY	40 MINUTES EASY RUN
WEDNESDAY	REST DAY
THURSDAY	RUN 40 MINUTES - 10-minute easy run, (45 sec tempo running, 1 minute 45 sec walk/run) x 8, 10-minute easy run
FRIDAY	REST DAY
SATURDAY	REST DAY
SUNDAY	RUN 1HR 45 MINUTES - (30-minute jog, 5-minute brisk walk) x 3, or distance goal of 8 miles

WEEK 8

MONDAY	REST DAY - This week, feel your heart pounding and your breathing quicken with the tempo running
TUESDAY	40 MINUTES EASY RUN
WEDNESDAY	REST DAY
THURSDAY	RUN 50 MINUTES - 10-minute easy jog, (60 sec tempo running, 2 minute walk/jog) x 10, 10-minute easy jog
FRIDAY	REST DAY
SATURDAY	REST DAY
SUNDAY	RUN 1HR 40 MINUTES - (25-minute jog, 5-minute brisk walk) x 4, or distance goal of 8 to 10 miles



WEEK 9

MONDAY	REST DAY - The next few weeks are all about the long run, building your capacity to run the marathon. Do not worry about covering the race distance before the event, just trust the training. Practise your hydration and fuel strategies on your long runs
TUESDAY	40 MINUTES EASY RUN
WEDNESDAY	REST DAY
THURSDAY	RUN 30 MINUTES - 10-minute easy run, (4-minute tempo run, 3-minute easy jog/walk recovery) x 4, 10-minute easy run
FRIDAY	REST DAY
SATURDAY	REST DAY
SUNDAY	RUN 2 HOURS - (28-minute run, 2-minute walk) x 4, or distance goal of 10 to 12 miles

WEEK 10

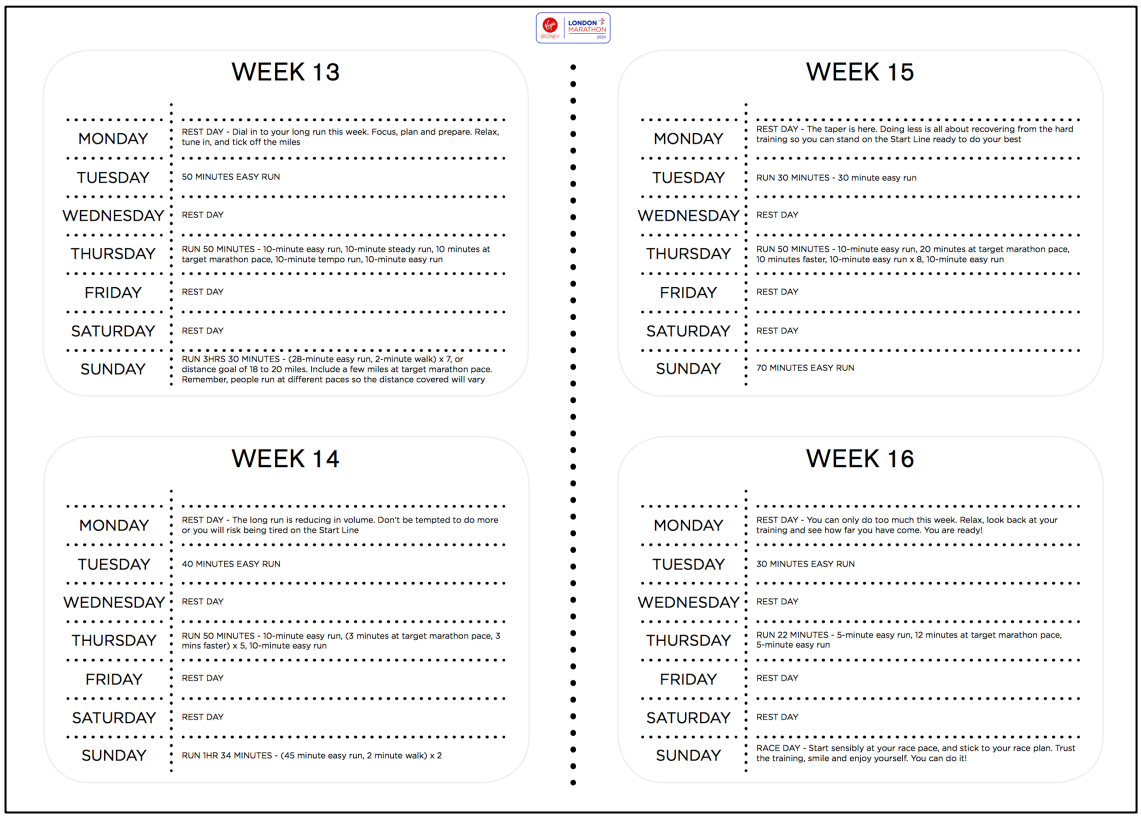
MONDAY	REST DAY - Race practice – enter a half marathon to familiarise yourself with Race Day routines, such as pre-race meal, race clothing and hydration strategies
TUESDAY	RUN 35 MINUTES - 10-minute easy run, (3 x 3 minutes at a tempo pace with 2 minute jog recovery), 10-minute easy run
WEDNESDAY	REST DAY
THURSDAY	30 MINUTES EASY RUN
FRIDAY	REST DAY
SATURDAY	REST DAY
SUNDAY	RACE - Race a half marathon, or run for 2 hours 15 minutes, or distance goal of 12 miles

WEEK 11

MONDAY	REST DAY - The next four weeks are about getting to know your race pace. Have a target time in minutes and work out your pace per mile.
TUESDAY	45 MINUTES EASY RUN
WEDNESDAY	REST DAY
THURSDAY	RUN 60 MINUTES - 10-minute easy run, (5-minute tempo run, 3-minute easy run/walk recovery) x 5, 10 minute easy run
FRIDAY	REST DAY
SATURDAY	REST DAY
SUNDAY	RUN 2HRS 30 MINUTES - (28-minute easy run, 2-minute walk) x 5, or distance goal of 14 to 16 miles. Include a few miles at target marathon pace

WEEK 12

MONDAY	REST DAY - There are just three more weeks of hard training left before the taper and you start to run less and sharpen up
TUESDAY	50 MINUTES EASY RUN
WEDNESDAY	REST DAY
THURSDAY	RUN 52 MINUTES - 10-minute easy run, (6 minute tempo run, 2 minute easy run/walk recovery) x 4, 10 minute easy run
FRIDAY	REST DAY
SATURDAY	REST DAY
SUNDAY	RUN 3HRS - (28-minute easy run, 2-minute walk) x 6, or distance goal of 16 to 18 miles. Include a few miles at target marathon pace



WEEK 13

MONDAY	REST DAY - Dial in to your long run this week. Focus, plan and prepare. Relax, tune in, and tick off the miles
TUESDAY	50 MINUTES EASY RUN
WEDNESDAY	REST DAY
THURSDAY	RUN 50 MINUTES - 10-minute easy run, 10-minute steady run, 10 minutes at target marathon pace, 10-minute tempo run, 10-minute easy run
FRIDAY	REST DAY
SATURDAY	REST DAY
SUNDAY	RUN 3HRS 30 MINUTES - (28-minute easy run, 2-minute walk) x 7, or distance goal of 18 to 20 miles. Include a few miles at target marathon pace. Remember, people run at different paces so the distance covered will vary

WEEK 14

MONDAY	REST DAY - The long run is reducing in volume. Don't be tempted to do more or you will risk being tired on the Start Line
TUESDAY	40 MINUTES EASY RUN
WEDNESDAY	REST DAY
THURSDAY	RUN 50 MINUTES - 10-minute easy run, (3 minutes at target marathon pace, 3 mins faster) x 5, 10-minute easy run
FRIDAY	REST DAY
SATURDAY	REST DAY
SUNDAY	RUN 1HR 34 MINUTES - (45 minute easy run, 2 minute walk) x 2

WEEK 15

MONDAY	REST DAY - The taper is here. Doing less is all about recovering from the hard training so you can stand on the Start Line ready to do your best
TUESDAY	RUN 30 MINUTES - 30 minute easy run
WEDNESDAY	REST DAY
THURSDAY	RUN 50 MINUTES - 10-minute easy run, 20 minutes at target marathon pace, 10 minutes faster, 10-minute easy run x 8, 10-minute easy run
FRIDAY	REST DAY
SATURDAY	REST DAY
SUNDAY	70 MINUTES EASY RUN

WEEK 16

MONDAY	REST DAY - You can only do too much this week. Relax, look back at your training and see how far you have come. You are ready!
TUESDAY	30 MINUTES EASY RUN
WEDNESDAY	REST DAY
THURSDAY	RUN 22 MINUTES - 5-minute easy run, 12 minutes at target marathon pace, 5-minute easy run
FRIDAY	REST DAY
SATURDAY	REST DAY
SUNDAY	RACE DAY - Start sensibly at your race pace, and stick to your race plan. Trust the training, smile and enjoy yourself. You can do it!

A.1.2.2 Chapter 4 additional data – Changes in grades of severity

Table A.1. Changes in lesion grade from Pre- to Post- Marathon scans in articular cartilage, BME, tendons and ligaments, in marathon finishers (n=71, 142 knees) and training non-finishers (n=11, 22 knees). Grading scales are defined based on the scoring systems described in Methods.

Pre- to Post-M lesions	Change in grade	Cartilage 0-4		Bone 0-3		Tendons 0-3		Ligaments 0-3	
		F	Non-F	F	Non-F	F	Non-F	F	Non-F
New/ Worsened	0 to 1	7	0	9	2	8	2	1	0
	0 to 2	4	0	9	1	4	0	1	0
	0 to 3	5	0	4	0	0	0	0	0
	0 to 4	1	0	0	0	0	0	0	0
	1 to 2	4	1	0	0	1	0	0	0
	2 to 3	2	1	4	0	0	0	0	0
	2 to 4	0	1	0	0	0	0	0	0
	3 to 4	2	1	0	0	0	0	0	0
	Total	**25**	**4**	**26**	**3**	**13**	**2**	**2**	**0**
	Mean Change in amplitude	1.6	1	1.7	1.3	1.3	1	1.5	0
Improved	1 to 0	0	0	9	0	0	0	2	0
	2 to 0	0	0	11	1	0	0	0	0
	2 to 1	0	0	1	1	1	0	0	0
	3 to 0	0	0	0	0	0	0	0	0
	3 to 1	0	0	2	0	0	0	0	0
	3 to 2	0	0	0	1	1	0	0	0
	4 to 0	0	0	0	0	0	0	0	0
	4 to 1	0	0	0	0	0	0	0	0
	4 to 2	1	0	0	0	0	0	0	0
	4 to 3	1	0	0	0	0	0	0	0
	Total	**2**	**0**	**23**	**3**	**2**	**0**	**2**	**0**
	Mean Change in amplitude	-1.5	0	-1.6	-1.3	-1	0	-1	0

BME, bone marrow edema; M, marathon; F, finishers; Non-F, non-finishers.

Table A.2. Changes in lesion grade from Pre- to Post- Marathon scans in articular cartilage, BME, tendons and ligaments, in marathon finishers (n=71, 142 knees). Grading scales are defined based on the scoring systems described in Methods.

Knee feature		Pre- to Post-M New/Worsened lesions									Pre- to Post-M Improved lesions										
		0->1	0->2	0->3	0->4	1->2	2->3	2->4	3->4	Total	1->0	2->0	2->1	3->0	3->1	3->2	4->0	4->1	4->2	4->3	Total
Cartilage 0-4																					
Patella	M	1	0	3	0	1	0	0	1	6	0	0	0	0	0	0	0	0	0	1	1
	L	3	3	1	0	3	1	0	1	12	0	0	0	0	0	0	0	0	0	0	0
Trochlea	M	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
	C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	L	0	1	1	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0
Femur	M	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
	L	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Tibia	M	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
	L	1	0	0	1	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0
Total		7	4	5	1	4	2	0	2	25	0	0	0	0	0	0	0	0	1	1	2
Mean change in amplitude		1.6									-1.5										
Bone 0-3																					
Patella	M	1	2	2	-	0	0	-	-	5	1	0	0	0	0	0	-	-	-	-	1
	L	1	3	1	-	0	1	-	-	6	0	0	0	0	1	0	-	-	-	-	1
Trochlea	M	1	3	0	-	0	1	-	-	5	0	0	0	0	0	0	-	-	-	-	0
	C	1	0	0	-	0	0	-	-	1	0	0	0	0	0	0	-	-	-	-	0
	L	1	0	0	-	0	1	-	-	2	0	0	0	0	0	0	-	-	-	-	0
Femur	M	0	0	1	-	0	0	-	-	1	3	5	1	0	0	0	-	-	-	-	9
	L	1	1	0	-	0	0	-	-	2	1	1	0	0	0	0	-	-	-	-	2
Tibia	M	1	0	0	-	0	1	-	-	2	4	5	0	0	1	0	-	-	-	-	10
	L	2	0	0	-	0	0	-	-	2	0	0	0	0	0	0	-	-	-	-	0
Total		9	9	4	N/A	0	4	N/A	N/A	26	9	11	1	0	2	0	N/A	N/A	N/A	N/A	23
Mean change in amplitude		1.7									-1.6										
Tendon 0-3																					
Patellar		2	1	0	-	0	0	-	-	3	0	0	1	0	0	0	-	-	-	-	1
Quadriceps		0	0	0	-	0	0	-	-	0	0	0	0	0	0	0	-	-	-	-	0
Semimembranosus		3	3	0	-	1	0	-	-	7	0	0	0	0	0	0	-	-	-	-	0
Sartorius		1	0	0	-	0	0	-	-	1	0	0	0	0	0	0	-	-	-	-	0
Gracillis		2	0	0	-	0	0	-	-	2	0	0	0	0	0	1	-	-	-	-	1
Total		8	4	0	N/A	1	0	N/A	N/A	13	0	0	1	0	0	1	N/A	N/A	N/A	N/A	2
Mean change in amplitude		1.3									-1										
Ligament 0-3																					
ACL		0	0	0	-	0	0	-	-	0	0	0	0	0	0	0	-	-	-	-	0
PCL		0	0	0	-	0	0	-	-	0	0	0	0	0	0	0	-	-	-	-	0
MCL		0	0	0	-	0	0	-	-	0	2	0	0	0	0	0	-	-	-	-	2
LCL		1	1	0	-	0	0	-	-	2	0	0	0	0	0	0	-	-	-	-	0
Total		2	2	0	N/A	0	0	N/A	N/A	2	2	0	0	0	0	0	N/A	N/A	N/A	N/A	2
Mean change in amplitude		1.5									-1										

BME, bone marrow edema; M, medial side; C, central; L, lateral side.

A.1.2.3 Chapter 5 additional data – Changes in grades of severity

Table A.3. Prevalence and types of improved pre-marathon lesions at the 2 weeks post-marathon scan, with sustained improvement at the 6 months follow-up (by grade of severity), in the cartilage and bone marrow. 'Improvement' was defined as reduction in the extent of lesion (score/grade) between MRI scans. The scoring systems were defined in Methods.

Knee features per region	Marathon finishers				Training non-finishers			
	Lesion Grade			Number of lesions with sustained improvement	Lesion Grade			Number of lesions with sustained improvement
	Pre-M	Post-M	6 months FU		Pre-M	Post-M	6 months FU	
Cartilage lesions								
Patellofemoral	4	3	3	1	-	-	-	-
Medial tibiofemoral	4	2	2	1	-	-	-	-
Lateral tibiofemoral	-	-	-	-	-	-	-	-
Total				2				0
BME								
Patellofemoral	-	-	-	-	-	-	-	-
Medial tibiofemoral	1	0	0	1	2	0	0	1
Lateral tibiofemoral	2	0	0	1	-	-	-	-
	1	0	0	1	-	-	-	-
Total				3				1

BME, bone marrow edema; M, marathon.

Table A.4. Prevalence and types of newly improved pre-marathon lesions at the 6 months follow-up (by grade of severity), in the cartilage and bone marrow. 'Improvement' was defined as reduction in the extent of lesion (grade) between MRI scans. The scoring systems were defined in Methods.

Knee features per region	Marathon finishers				Training non-finishers			
	Lesion Grade			Number of lesions with new improvement at MRI 3	Lesion Grade			Number of lesions with new improvement at MRI 3
	Pre-M	Post-M	6 months FU		Pre-M	Post-M	6 months FU	
Cartilage lesions								
Patellofemoral	4	4	3	2	3	3	1	1
	2	2	1	1	2	2	1	1
	-	-	-	-	1	1	0	1
Medial tibiofemoral	-	-	-	-	-	-	-	-
Lateral tibiofemoral	-	-	-	-	-	-	-	-
Total				3				3
BME								
Patellofemoral	3	3	2	1	-	-	-	-
	2	2	1	1	-	-	-	-
	2	2	0	1	-	-	-	-
	1	1	0	1	-	-	-	-
Medial tibiofemoral	-	-	-	-	-	-	-	-
Lateral tibiofemoral	2	2	1	1	-	-	-	-
Total				5				0

BME, bone marrow edema; M, marathon.

Table A.5. Prevalence and types of reversible lesions (by grade of severity) from pre-marathon through to post-marathon to 6 months follow-up scans, in the cartilage and bone marrow. 'Reversibility' was defined as resolution/reduction in the extent of those lesions that appeared/progressed at post-marathon from the pre-marathon, and then reversed or showed signs of reduction back to the pre-marathon grade at the 6 months follow-up. The scoring systems were defined in Methods.

Knee features per region	Marathon finishers				Training non-finishers			
	Lesion Score/Grade			Number of lesions that showed reversibility	Lesion Score/Grade			Number of lesions that showed reversibility
	Pre-M	Post-M	6 months FU		Pre-M	Post-M	6 months FU	
Cartilage lesions								
Patellofemoral	0	3	0	1	-	-	-	-
	1	2	1	2	-	-	-	-
Medial tibiofemoral	-	-	-	-	-	-	-	-
Lateral tibiofemoral	-	-	-	-	-	-	-	-
Total				3				-
BME								
Patellofemoral	0	1	0	2	0	1	0	1
	0	2	0	2	-	-	-	-
	0	3	0	2	-	-	-	-
	0	3	1	1	-	-	-	-
	2	3	1	1	-	-	-	-
Medial tibiofemoral	0	3	2	1	-	-	-	-
Lateral tibiofemoral	0	1	0	1	-	-	-	-
Total				10				1

BME, bone marrow edema; M, marathon.

Table A.6. Prevalence and types of improved pre-marathon lesions at the 2 weeks post-marathon scan, with sustained improvement at the 6 months follow-up (by grade of severity), in tendons and ligaments. 'Improvement' was defined as reduction in the extent of lesion (score/grade) between MRI scans. The scoring systems were defined in Methods.

Knee features per region	Marathon finishers				Training non-finishers			
	Lesion Score/Grade			Number of lesions with sustained improvement	Lesion Score/Grade			Number of lesions with sustained improvement
	Pre-M	Post-M	6 months FU		Pre-M	Post-M	6 months FU	
Tendon lesion								
Patellar	-	-	-	-	-	-	-	-
Quadriceps	-	-	-	-	-	-	-	-
Semimembranosus	-	-	-	-	-	-	-	-
Sartorius	-	-	-	-	-	-	-	-
Gracilis	-	-	-	-	-	-	-	-
Total				0				0
Ligament lesions								
ACL	-	-	-	-	-	-	-	-
PCL	-	-	-	-	-	-	-	-
MCL	1	0	0	2	-	-	-	-
LCL	-	-	-	-	-	-	-	-
Total				2				0

ACL, anterior cruciate ligament; PCL, posterior cruciate ligament; MCL, medial collateral ligament; LCL, lateral collateral ligament.

Table A.7. Prevalence and types of reversible lesions (by grade of severity) from pre-marathon through to post-marathon to 6 months follow-up scans, in tendons and ligaments. 'Reversibility' was defined as resolution/reduction in the extent of those lesions that appeared/progressed at post-marathon from the pre-marathon, and then reversed or showed signs of reduction back to the pre-marathon grade at the 6 months follow-up. The scoring systems were defined in Methods.

Knee features per region	Marathon finishers				Training non-finishers			
	Lesion Score/Grade			Number of lesions that showed reversibility	Lesion Score/Grade			Number of lesions that showed reversibility
	Pre-M	Post-M	6 months FU		Pre-M	Post-M	6 months FU	
Tendon lesions								
Patellar	-	-	-	-	0	1	0	1
Quadriceps	-	-	-	-	-	-	-	-
Semimembranosus	0	2	1	1	-	-	-	-
Sartorius	-	-	-	-	-	-	-	-
Gracilis	-	-	-	-	-	-	-	-
Total				1				1
Ligament lesions								
ACL	-	-	-	-	-	-	-	-
PCL	-	-	-	-	-	-	-	-
MCL	-	-	-	-	-	-	-	-
LCL	0	1	0	1	-	-	-	-
	0	2	1	1	-	-	-	-
Total				2				0

ACL, anterior cruciate ligament; PCL, posterior cruciate ligament; MCL, medial collateral ligament; LCL, lateral collateral ligament.

A.2 Studies described in Chapters 6-7 (Hip project)

A.2.1 Ethical approval

UCL RESEARCH ETHICS COMMITTEE
OFFICE FOR THE VICE PROVOST RESEARCH

29th November 2018

Professor Alister Hart
Division of Surgery and Interventional Sciences
Institute of Orthopaedics and Musculoskeletal Science
UCL

Dear Professor Hart

Notification of Ethics Approval with Provisos
Project ID/Title: 13823/001: Imaging evaluation of the effect of marathon running on the hip joint

Further to your satisfactory responses to my comments, I am pleased to confirm in my capacity as Chair of the UCL Research Ethics Committee that I have ethically approved your study until **1st December 2021.**

Ethical approval is subject to the following conditions:

Notification of Amendments to the Research
You must seek Chair's approval for proposed amendments (to include extensions to the duration of the project) to the research for which this approval has been given. Each research project is reviewed separately and if there are significant changes to the research protocol you should seek confirmation of continued ethical approval by completing an 'Amendment Approval Request Form'
http://ethics.grad.ucl.ac.uk/responsibilities.php

Adverse Event Reporting – Serious and Non-Serious
It is your responsibility to report to the Committee any unanticipated problems or adverse events involving risks to participants or others. The Ethics Committee should be notified of all serious adverse events via the Ethics Committee Administrator (ethics@ucl.ac.uk) immediately the incident occurs. Where the adverse incident is unexpected and serious, the Joint Chairs will decide whether the study should be terminated pending the opinion of an independent expert. For non-serious adverse events the Joint Chairs of the Ethics Committee should again be notified via the Ethics Committee Administrator within ten days of the incident occurring and provide a full written report that should include any amendments to the participant information sheet and study protocol. The Joint Chairs will confirm that the incident is non-serious and report to the Committee at the next meeting. The final view of the Committee will be communicated to you.

Final Report
At the end of the data collection element of your research we ask that you submit a very brief report (1-2 paragraphs will suffice) which includes in particular issues relating to the ethical implications of the research i.e. issues obtaining consent, participants withdrawing from the research, confidentiality, protection of participants from physical and mental harm etc.

Office of the Vice Provost Research, 2 Taviton Street
University College London
Tel: +44 (0)20 7679 8717
Email: ethics@ucl.ac.uk
http://ethics.grad.ucl.ac.uk/

In addition, please:

- ensure that you follow all relevant guidance as laid out in UCL's Code of Conduct for Research: http://www.ucl.ac.uk/srs/governance-and-committees/resgov/code-of-conduct-research
- note that you are required to adhere to all research data/records management and storage procedures agreed as part of your application. This will be expected even after completion of the study.

With best wishes for the research.

Yours sincerely

[redacted]

Dr Lynn Ang
Joint Chair, UCL Research Ethics Committee

Cc: Johann Henckel & Anastasia Fotiadou

A.2.2 Further project details

A.2.2.1. Marathon training plan: Richmond Marathon Beginner training programme (richmondrunfest.co.uk)

Week No.1	Building up	
Day	**Training**	**Training notes**
Mon	25 mins jog	Just jogging, very light
Tues	40 mins steady	
Wed	Rest	
Thurs	35-40 mins steady	
Fri	Rest	
Sat	15 mins very easy	
Sun	75 mins easy run	Take walking breaks if needed

Week No.2		
Day	**Training**	**Training notes**
Mon	Rest	
Tues	40 mins steady	
Wed	Rest	
Thurs	50 mins comfortable pace	
Fri	Rest	
Sat	15 mins very easy	
Sun	75 mins run	Repeat last Sunday's session with fewer walking breaks, warm-up and cool-down

Week No.3		
Day	**Training**	**Training notes**
Mon	20 mins recovery jog	
Tues	40 mins steady	
Wed	Rest	
Thurs	50 mins	
Fri	Rest	
Sat	Rest	
Sun	80-90 mins jog with walking breaks	

Week No.4		
Day	**Training**	**Training notes**
Mon	20 mins recovery run	
Tues	40 mins steady	
Wed	Rest	
Thurs	Rest	Double rest before brisk run
Fri	40 mins brisk pace	
Sat	Rest	
Sun	90-100 mins slow	Very, very easy. Take a drink with you

Week No.5	Gradually building towards half marathon	
Day	**Training**	**Training notes**
Mon	Rest	Day off after long effort
Tues	50 mins steady	
Wed	Rest	
Thurs	40 mins steady	
Fri	20 mins steady	
Sat	Rest	
Sun	100-110 mins easy	

Week No.6		
Day	**Training**	**Training notes**
Mon	Rest	
Tues	20 mins steady	
Wed	65 mins steady	
Thurs	Rest	
Fri	40 mins	
Sat	Rest	
Sun	120 mins taken very easy	Slow with drinks

Week No.7	Taper week and half marathon race	
Day	**Training**	**Training notes**
Mon	Rest	
Tues	30-35 mins steady	
Wed	30 mins steady	
Thurs	Rest	
Fri	Rest	
Sat	10 mins jog	Really slow, just to keep loose
Sun	Half marathon (13.1 miles) and walk warm-up and cool-down	Slow all the way, just a training run

Week No.8	Start of peak mileage phase	
Day	**Training**	**Training notes**
Mon	10-20 mins recovery session	Really slow
Tues	Rest	
Wed	30 mins steady	
Thurs	60 mins brisk	
Fri	Rest	
Sat	30 mins jog	
Sun	120 mins comfortable pace	

Week No.9	**Building long endurance runs**	
Day	**Training**	**Training notes**
Mon	30 mins easy	
Tues	Rest	
Wed	60 mins brisk	Try to improve on last week's 60 mins distance
Thurs	Rest	
Fri	40 mins steady	
Sat	Rest	
Sun	130-140 mins taken very easy	Long, slow, run with drinks

Week No.10		
Day	**Training**	**Training notes**
Mon	Rest	Recovery after Sunday's long session
Tues	40 mins steady	
Wed	Rest	
Thurs	75 mins comfortable pace	
Fri	20 mins jog	
Sat	Rest	Really slow, just to keep loose
Sun	140-150 mins taken very easy	Long and slow

Week No.11		
Day	**Training**	**Training notes**
Mon	10-20 mins recovery session	
Tues	40 mins steady	
Wed	Rest	
Thurs	75 mins	
Fri	Rest	
Sat	30 mins easy pace	
Sun	150-160 mins comfortable	

Week No.12		
Day	**Training**	**Training notes**
Mon	30 mins easy	
Tues	Rest	
Wed	50 mins fast	Home time-trial!
Thurs	Rest	
Fri	50 mins easy	Avoid the temptation to run at the pace of Wednesday's session
Sat	Rest	
Sun	180 mins slow	Start slowly, take drinks

Week No.13	**Peak Week**	
Day	**Training**	**Training notes**
Mon	20 mins jog recovery	
Tues	40 mins brisk pace	
Wed	Rest	
Thurs	60 mins steady	
Fri	Rest	
Sat	Rest	Prepare for last big run
Sun	200 mins slow	Last long run, be economical

Week No.14	**Start of race taper**	
Day	**Training**	**Training notes**
Mon	20 mins slow jog or rest if tired	
Tues	30 mins brisk	
Wed	Rest	
Thurs	50 mins steady	
Fri	Rest	
Sat	Rest	
Sun	120 mins steady	

Week No.15	**Further tapering**	
Day	**Training**	**Training notes**
Mon	20 mins easy	
Tues	Rest	
Wed	40 mins easy	
Thurs	Rest	
Fri	Rest	
Sat	10 mins jog	
Sun	70 mins easy in race kit and shoes	Slower than race pace

Week No.16	**Final taper and preparation week**	
Day	**Training**	**Training notes**
Mon	30 mins jog	
Tues	Rest	
Wed	20 mins jog	
Thurs	Rest	
Fri	Rest	
Sat	10 mins very, very easy jog	Keep it slow
Sun	Race day!	THE RACE!

Appendix B

Publications, conferences, awards and media coverage

B.1 Full list of publications (current and intended)

Horga LM, Hirschmann AC, Henckel J, Fotiadou A, Di Laura A, Torlasco C, D'Silva A, Sharma S, Moon JC, Hart AJ. Prevalence of abnormal findings in 230 knees of asymptomatic adults using 3.0 T MRI. *Skeletal Radiol* 2020;**49**(7):1099-1107. doi:10.1007/s00256-020-03394-z

Horga LM, Henckel J, Fotiadou A, Hirschmann AC, Di Laura A, Torlasco C, D'Silva A, Sharma S, Moon JC, Hart AJ. Can marathon running improve knee damage of middle-aged adults? A prospective cohort study. *BMJ Open Sport & Exercise Medicine* 2019;**5:**e000586. doi: 10.1136/bmjsem-2019-000586

Horga LM, Henckel J, Fotiadou A, Hirschmann AC, Di Laura A, Torlasco C, D'Silva A, Sharma S, Moon JC, Hart AJ. Is the immediate effect of marathon running on novice runners' knee joints sustained within 6 months after the run? A follow-up 3.0 T MRI study. *Skeletal Radiol* 2020;**49**(8):1221–1229. doi:10.1007/s00256-020-03391-2

Horga LM, Henckel J, Fotiadou A, Di Laura A, Hirschmann AC, Hart AJ. 3.0 T MRI findings of 104 hips of asymptomatic volunteers: couch potatoes to ultrarunners (submitted)

Horga LM, Henckel J, Fotiadou A, Di Laura A, Hirschmann AC, Hart AJ. Magnetic Resonance Imaging of the Hips of Marathon Runners (submitted)

B.2 Conferences

Horga LM, Henckel J, Fotiadou A, Hirschmann AC, Di Laura A, Torlasco C, D'Silva A, Sharma S, Moon JC, Hart AJ. Magnetic Resonance Imaging of the Knee Before and After Marathon Running: A Prospective Cohort Study of 115 Participants. Poster presentation given at the American Academy of Orthopaedic Surgeons (AAOS) Conference. Las Vegas 2019

Horga LM, Henckel J, Fotiadou A, Hirschmann AC, Torlasco C, Di Laura A, D'Silva A, Sharma S, Moon JC, Hart AJ. Magnetic Resonance Imaging In 164 Knees Before And After Marathon Running. Podium presentation given at the European Federation of

National Associations of Orthopaedics and Traumatology (EFORT) Conference. Lisbon 2019

Hart AJ**,** Henckel J, **Horga LM**, Di Laura A, Fotiadou A. The recovery of bone marrow edema and cartilage lesions in 100 knees following first-time marathon running. Poster presentation given at the International Cartilage Regeneration & Joint Preservation Society (ICRS) Conference. Vancouver 2019

Henckel J, **Horga LM**, Di Laura A, Fotiadou A, Hirschmann AC, Hothi H, Hart AJ**,** Prevalence of asymptomatic meniscal tears of the knee in middle-aged novice marathon runners. Poster presentation given at the International Society for Technology in Arthroplasty (ISTA) Conference. Toronto 2019

Horga LM, Henckel J, Fotiadou A*,* Di Laura A*,* Hirschmann AC, Hart AJ. What Is The Effect Of A Marathon On The Pelvis And Hips: An MRI Study Of 28 Runners. Podium presentation given at British Hip Society (BHS) Conference. Newport 2020

Horga LM, Henckel J, Fotiadou A*,* Hirschmann AC, Torlasco C, Di Laura A, D'Silva A, Sharma S, Moon JC, Hart AJ. Meniscal tears do not prevent novice runners from completing a marathon: a prospective study of 230 knees. E-poster presentation given at the American Academy of Orthopaedic Surgeons (AAOS) Conference 2020 (Virtual)

Horga LM, Henckel J, Fotiadou A*,* Di Laura A*,* Hirschmann AC, Hart AJ. What Is The Effect Of A Marathon On The Pelvis And Hips: An MRI Study Of 44 Runners. Podium presentation given at the European Federation of National Associations of Orthopaedics and Traumatology (EFORT) Conference 2020 (Virtual)

B.3 Awards

Robert Brown Travel Award 2020

B.4 Media Coverage

The New York Times. Marathon Running May Be Good for Your Knees. 2019 https://www.nytimes.com/2019/12/11/well/move/marathon-running-may-be-good-for-your-knees.html (accessed 4 Sep. 2020)

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