Running and Knee Joint Health: Self-Reported Symptoms, Function and Osteoarthritis in Recreational Athletes

Richard David Leech

Thesis submitted to the University of Nottingham for the degree of Doctor of Philosophy

February 2020

Declaration

This is to certify that the work submitted in this thesis is the result of original research, conducted substantially by myself. Significant support was provided by my supervisors, Dr Kim Edwards and Professor Mark Batt to whom I am grateful.

The systematic review was performed with guidance from Alison Ashmore, Senior Research Librarian.

Questionnaire validation was conducted in collaboration with Dr Anne Grunseit (University of Sydney). Additional assistance during study recruitment was provided by parkrun UK and parkrun Australia, as well as numerous other event organisers. Three postgraduate students were involved with recruitment of non-runners and triathletes.

Professor David Hunter and Ms Jillian Eyles (University of Sydney) aided procurement of testing facilities for Australian participants. Additional testing was completed at the University of Loughborough and I am grateful to all the clerical and medical staff at the National Centre for Sport and Exercise Medicine for allowing me to use their facilities.

Abbreviations

ACL	Anterior cruciate ligament
ACR	American College of Rheumatology
BMI	Body mass index
CNS	Central nervous system
EBM	Evidence based medicine
EQ-5D-5L	EuroQol five-dimensional five-level questionnaire
JSN	Joint space narrowing
KOOS	Knee Injury and Osteoarthritis Outcome Score
KL	Kellgren-Lawrence
L	Left knee
LCL	Lateral collateral ligament
MCL	Medial collateral ligament
NICE	National Institute of Clinical Excellence
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OR	Odds ratio
PA	Physical activity
PCL	Posterior cruciate ligament
PFJ	Patello-femoral joint
R	Right knee
RCT	Randomised Controlled Trial
RR	Risk ratio

SD	Standard deviation
TFJ	Tibio-femoral joint
UK	United Kingdom
WHO	World Health Organisation
WOMAC	Western Ontario & McMaster Universities Osteoarthritis Index

Abstract

Background

The prevalence of symptomatic knee osteoarthritis (OA) is growing - largely due to ageing populations and increasing prevalence of obesity. Evidence suggests that other lifestyle factors, including participation in different sports, could be associated with either an increased risk of - or conversely, protection against - knee OA. Running is one of the most popular pastimes in the world. For many years, an association between running and risk of knee OA has been postulated, although currently there is insufficient evidence to conclude whether running has a beneficial or deleterious effect on joint health.

Objectives

This thesis seeks to examine the prevalence of self-reported knee joint symptoms, function and OA in recreational runners and non-runners. The level of agreement between self-reported running (measured using a novel questionnaire) and contemporaneous running behaviour recorded from a variety of sources (e.g. electronic devices, training diaries) will be identified.

Methods

This longitudinal study was conducted in the UK and Australia. Baseline questionnaire data was collected between September 2015 and December 2016, with follow-up data collected in Autumn 2017. Self-reported outcomes (e.g. knee symptoms and clinician diagnosed OA) were identified in two

baseline questionnaires and one follow-up questionnaire. A sub-cohort of runners submitted running diaries to identify the level of agreement between self-reported running and contemporaneous running activity. A sample of athletes also completed physical testing to objectively assess lower-limb function.

Results

The prevalence of knee OA did not differ between runners and non-runners (p 0.207). There was no statistically significant difference in Knee Injury and Osteoarthritis Outcome Score (KOOS) for any of its five sub-domains between runners and non-runners. Previous knee injury was associated with prevalence of knee pain in recreational runners (RR 3.55, 3.24-3.90). The knee was the most common site of running-attributed injury, accounting for almost a quarter of all running injuries. There was a trend for self-reported running behaviour to be over-estimated compared to running measured by contemporaneous sources. With increasing age, there was a general decline in performance of functional tests in recreational runners, but this trend was not consistent.

Conclusions

Further longitudinal data is required to assess the cause and effect relationship between running and onset and/or progression of knee OA. Additional data is also needed to explore the impact of injury in recreational runners, with the aim of developing interventions to reduce their incidence. The trend for over-estimating self-reported running may have implications for the assessment of

current and future research that explores running and health outcomes, where accurately identifying the ‘dose’ of running is crucial to the integrity of results.

Acknowledgements

I must extend my greatest thanks to my supervisors Professor Mark Batt and Dr Kim Edwards for all their support and guidance whilst completing this work. I must also thank all the other students in the department for their encouragement.

I am also extremely grateful to Jo Bartram and Bronya Norton for their help and friendship.

I would also like to thank my parents and family for their love and encouragement. I must also thank Heather for always being there.

Table of Contents

1 Introduction **17**
- 1.1 Background
- 1.2 Study Aim
- 1.3 Thesis Objectives
- 1.4 Thesis Hypothesis
- 1.5 Chapter Outline

2 Literature Review **25**
- 2.1 The Knee Joint
- 2.2 Osteoarthritis
- 2.3 Definitions of Knee OA
  - 2.3.1 Symptomatic Knee OA
    - 2.3.1.1 Pain
    - 2.3.1.2 Crepitus
    - 2.3.1.3 Reduced Range of Movement
    - 2.3.1.4 Stiffness
    - 2.3.1.5 Function
- 2.4 Imaging Knee OA
- 2.5 Epidemiology of Knee OA
  - 2.5.1 Prevalence of Knee OA
  - 2.5.2 Prevalence of Radiographic Knee OA
  - 2.5.3 Prevalence of Knee Joint Arthroplasty
- 2.6 Mechanisms of Knee OA Development
- 2.7 Running
- 2.8 The Health Effects of Running
- 2.9 Evidence for an Association Between Running and Knee OA
  - 2.9.1 Methods
    - 2.9.1.1 Study Selection
  - 2.9.2 Data Extraction and Synthesis
  - 2.9.3 Narrative Synthesis
  - 2.9.4 Evidence Discussion
  - 2.9.5 Summary
- 2.10 Study Rationale

3 Methods **83**
- 3.1 Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Guidelines
- 3.2 Study Design
  - 3.2.1 The Evidence Pyramid
- 3.3 Setting
- 3.4 Participants
  - 3.4.1 Inclusion Criteria
  - 3.4.2 Recruitment
    - 3.4.2.1 Baseline Questionnaire 1
    - 3.4.2.2 Baseline Questionnaire 2

3.4.2.3 Questionnaire Validation
3.4.2.4 Functional Testing
3.4.2.5 Follow-up Questionnaire
3.5 Variables
3.5.1 Outcome Variables
3.5.1.1 Baseline Questionnaire 1
3.5.1.2 Baseline Questionnaire 2
3.5.1.3 Functional Testing
3.5.1.4 Follow-Up Questionnaire
3.5.2 Baseline Questionnaire 1 Exposure Variables
3.5.3 Baseline Questionnaire 2 Exposure Variables
3.5.4 Follow-Up Questionnaire Exposure Variables
3.5.5 Potential Cofounders
3.6 Data Analyses
3.7 Statistical Analyses
3.7.1 Questionnaire Data (Baseline Questionnaire 1, Baseline Questionnaire 2 and Follow-Up Questionnaire)
3.7.2 Questionnaire Validation
3.7.3 Functional Testing
4 Results: The validity of self-reported running behaviour 191
4.1 Introduction
4.2 Demographic Characteristics
4.3 Current Running
4.3.1 7-day Data
4.3.2 4-week Data
4.3.3 12-week Data
4.3.4 Comparison of Current 7-Day Self Report Running and Diary Data
4.3.5 Comparison of Current 4-Week Self Report Running and Diary Data
4.3.6 Comparison of Current 12-Week Self Report Running and Diary Data
4.4 Historical Running
4.4.1 7-day Data
4.4.2 4-week Data
4.4.3 12-week Data
4.4.4 Comparison of Historical Self Report Running and Historical 7-Day Diary Data
4.4.5 Comparison on Historical Self Report Running and Historical 4 Week Diary Data
4.4.6 Comparison of Historical Self Report Running and Historical 12 Week Diary Data
4.5 Results Summary
5 Results: Markers of Knee Health in Recreational Runners and Non Runners: A cross-sectional Analysis 220
5.1 Introduction
5.2 Cohort Characteristics

5.3 History of Injury
5.4 Prevalence of Knee Symptoms
5.5 Running Status and KOOS Values
5.6 Recreational Runners
5.6.1 Running Behaviour
5.6.2 BMI and Running Behaviour in Recreational Athletes
5.6.3 Prevalence of Injury in Recreational Runners
5.6.4 Knee Symptoms in Male and Female Runners
5.6.5 Running Behaviour and Symptoms
5.6.5.1 Knee Pain
5.6.5.2 Risk Factors for Knee Pain in Runners
5.6.6 Runners and OA
5.6.6.1 Risk Factors for Knee OA in Runners
5.6.7 KOOS Values in Runners
5.6.8 Pain After Running (within 48 hours)
5.6.9 Running and Health (EQ-5D-5L)
5.6.9.1 EQ-5D-5L Analogue Health Score
6 Results: Lower limb function in Recreational Runners 272
6.1 Introduction
6.2 Cohort characteristics
6.3 The OARSI Tests
6.4 Performance Tests
6.5 Running Behaviour and OARSI Test Performance
6.6 Injury History and Test Performance
7 Results: Joint Health in Recreational Runners: A 12-month report 286
7.1 Introduction
7.2 Cohort Description
7.3 Running Behaviour of Baseline Runners at Follow-Up
7.4 Joint Health
7.3.1 Incidence of Injury
7.4 Repeat KOOS Scores
7.4.1 Change in KOOS and Baseline Running Behaviour
7.4.2 Change in KOOS and Change in Running over Previous 12 months
7.4.3 Change in KOOS and Baseline Joint Health Status
8 Discussion 296
8.1 Results Synopsis
8.2 Discussion of Joint Health in Runners and Non-Runners Results
8.3 Discussion of Validation Analysis Results
8.4 Discussion of Functional Testing Results
8.5 Follow-Up Questionnaire Results Discussion
8.6 Study Strengths and Limitations
8.6.1 Study Strengths
8.6.2 Study Limitations
8.7 Future Research Directions
8.7.1 Themes for Research
8.8 Conclusion

9 References **369**

10 Appendices **410**

List of Figures

Figure 1 Overview of Study Design
Figure 2 Features of Knee OA
Figure 3 Progression of OA
Figure 4 Pain Mechanisms in OA
Figure 5 Trend in Knee Arthroplasty in the UK, 1991-2006
Figure 6 Effect of Physical Stress on Tissue Adaptation
Figure 7 The Hypothesised Role of Joint Loading in Progression of OA
Figure 8 Estimated Number of Marathon and Half-Marathon Finishers in the USA, 1976-2016
Figure 9 Data Flowchart
Figure 10 Number of parkrun Athletes and Events in the UK
Figure 11 Training diary question in baseline questionnaires
Figure 12 Sample recruitment tweet
Figure 13 Recruitment leaflet
Figure 14 Triathlon recruitment leaflet
Figure 15 Invite email for Baseline Questionnaire 2
Figure 16 Question to identify runners from non-runners
Figure 17 Question to identify participants with training diary
Figure 18 Invite for diary validation
Figure 19 Invitation for functional testing
Figure 20 Email for functional cohort test details
Figure 21 Follow-up questionnaire invitation email
Figure 22 Knee Pain Question
Figure 23 Other Knee Symptoms Questions
Figure 24 Diagnosis of OA Question
Figure 25 Joint Surgery Question
Figure 26 Significant Injury Question
Figure 27 EQ-5D-5L Health Analogue Score Question
Figure 28 NHS Website - Knee pain and other running injuries
Figure 29 KOOS calculation
Figure 30 30s-CST Instructions
Figure 31 SCT Instructions
Figure 32 40m FPWT Instructions
Figure 33 6MWT Instructions
Figure 34 TUG Instructions
Figure 35 Reaching Directions for the SEBT (Gribble & Hertel, 2003) p 93
Figure 36 SEBT Instructions
Figure 37 Performance of the SEBT (Gribble & Hertel, 2003) p 93
Figure 38 THFDT Instructions
Figure 39 UPDB Instructions
Figure 40 Question to Identify Injury During Previous 12 months
Figure 41 Question to Identify Joint Surgery During Previous 12 months
Figure 42 Question to Identify Knee OA Diagnosis During Previous 12 Months
Figure 43 Running Exposure Question

Figure 44 Historical Running Exposure
Figure 45 Hypothetical overview of the onset of tissue injury and pain in a typical overuse injury.
Figure 46 IPAQ-SF Calculation
Figure 47 Calculation for METs (running behaviour)
Figures 48-51 7-day Current Running Data Questionnaire and Diary Bland-Altman Plots
Figures 52-55 4-Week Current Running Questionnaire and Diary Data Bland Altman Plots
Figures 56-59 Twelve Week Current Running Questionnaire and Diary Data Bland Altman Plots
Figure 60-63 7-day Historical Running Data Questionnaire and Diary Bland-Altman Plots
Figures 64-67 4-Week Historical Running Questionnaire and Diary Data Bland Altman Plots
Figures 68-71 Twelve Week Historical Running Questionnaire and Diary Data Bland Altman Plots
Figure 72 BMI categorisation of runners and non-runners
Figure 73 Age of Onset Knee Pain
Figure 74 Self-reported running type
Figure 75 Injury History Prevalence in Runners
Figure 76 Running Injury Prevalence in Runners
Figure 77 Type of Knee Injuries
Figure 78 Change in Running Behaviour and Injury
Figure 79 Distribution of Knee Pain in Male and Female Runners
Figure 80 Prevalence of Knee Pain. Male and female runners
Figure 81 Prevalence of Knee crepitus. Male and female runners
Figure 82 Prevalence of Knee reduced ROM. Male and female runners
Figure 83 Knee Pain in runners, stratified by number of years running
Figure 84 Knee Pain in runners, stratified by average weekly distance (km)
Figure 85 Knee Pain in runners, stratified by average weekly run duration (mins)
Figure 86 Knee Pain in runners, stratified by change in running
Figure 87 Body Pain after running, comparison of injured and non-injured
Figure 88 Knee Pain after running, comparison of runners with and without history of knee injury
Figure 89 Knee Pain after running, comparison of runners with and without history of knee surgery
Figure 90 Knee Pain after running, comparison of runners with and without history of knee OA
Figure 91 Age-related performance of OARSI tests.
Figure 92 Age-related performance of THT and UPSLBT
Figure 93 Change in Running and R KOOS
Figure 94 Change in Running and L KOOS
Figure 95 Hypothetical running distribution over 20-year period

List of Tables

Table 1 Chapter Outline
Table 2 Identification of Cases of Knee OA
Table 3 Inclusion Criteria
Table 4 Included Studies
Table 5 Running and Diagnosis of Knee OA
Table 6 Running and Specific Markers of Knee OA Identified with Imaging
Table 7 Running and Knee Pain
Table 8 Running and Knee Disability
Table 9 Summary of Hypothesised Mechanisms Risk and Benefits of Running and OA
Table 10 Benefits and Limitations of Study Designs
Table 11 Normative OARSI test values
Table 12 Outcome Measures
Table 13 Summary of Functional Tests
Table 14 Knee Pain and Symptoms Questions in Follow-Up Questionnaire
Table 15 Running Exposure Questions
Table 16 Follow-up Questionnaire Running Behaviour Questions
Table 17 Potential Confounders
Table 18 BMI Categories
Table 19 Data cleaning rules applied to demographic data
Table 20 Data cleaning rules applied to exposure data
Table 21 Data cleaning rules applied to injury data
Table 22 Statistical Tests
Table 23 Kappa coefficients thresholds
Table 24 Validation Analysis - Participant Characteristics
Table 25 Current Running – Analysis of Self-report and Questionnaire Running
Table 26 Historical Running – Analysis of Self-report and Questionnaire Running
Table 27 Cohort Characteristics
Table 28 Descriptive Data for Lifestyle Physical Activity in Cohort
Table 29 Injury history of runners and non-runners
Table 30 Surgery history of runners and non-runners
Table 31 Symptom history of runners and non-runners
Table 32 Prevalence of OA Diagnosis
Table 33 Mean KOOS values of runners and non-runners
Table 34 Run Status and KOOS
Table 35 Age of runners and Running Distance
Table 36 Running years and BMI
Table 37 Running average weekly km and BMI
Table 38 Average weekly total run duration and BMI
Table 39 Self report running injuries
Table 40 Prevalence of Knee Symptoms in Runners, by age group
Table 41 Distribution of knee OA in runners by BMI category
Table 42 Distribution of knee symptoms in runners by BMI category

Table 43 Risk Factors for knee pain in runners (unadjusted)
Table 44 Risk Factors for knee pain in runners (adjusted)
Table 45 Distribution of OA in runners, stratified by age
Table 46 Risk Factors for knee OA in runners (unadjusted)
Table 47 Risk Factors for knee OA in runners (adjusted)
Table 48 KOOS Scores in Runners
Table 49 Correlation of age and KOOS in runners
Table 50 KOOS Scores in Runners by Injury Status
Table 51 KOOS Scores in Runners by Knee Ligament Injury Status
Table 52 KOOS Scores in Runners by Cartilage Injury Status
Table 53 KOOS Scores in Runners by Knee OA Status
Table 54 Statistical Analysis of Running Factors and KOOS
Table 55 Responses by runners to EQ-5D-5L
Table 56 Responses by runners to EQ-5D-5L, stratified by running change
Table 57 History of running injury and EQ-5D-5L (pain or discomfort)
Table 58 History of knee injury and EQ-5D-5L (pain or discomfort)
Table 59 Correlation between age and BMI with EQ-5D-5L health score
Table 60 Correlation between running with EQ-5D-5L health score
Table 61 Cohort Characteristics
Table 62 OARSI Test Results
Table 63 Runners and Normative OARSI values
Table 64 Performance Tests, males and females
Table 65 Correlation between running and OARSI tests
Table 66 Test performance and injury history
Table 67 OARSI test performance and injury history
Table 68 Change in Running over previous 12 months
Table 69 Running behaviour at follow-up
Table 70 Joint Health Outcomes in previous 12 months
Table 71 Injuries in previous 12 months
Table 72 Follow-Up KOOS Scores
Table 73 Distribution of change in KOOS
Table 74 Correlation of Baseline Running and Change in KOOS
Table 75 Change in KOOS and baseline knee surgery, knee injury and knee OA
Table 76 Test Reliability of KOOS

1 Introduction

1.1 Background

OA is a common, chronic, joint condition that can ultimately result in pain, reduced function and impaired quality of life (Glyn-Jones et al, 2015). The entire joint is compromised, with local and systemic abnormalities contributing to disease processes (Krasnokutsky et al, 2008). The knee joint is amongst the most frequently afflicted by OA (Felson et al, 1987). Clinical management largely consists of symptom control and preservation of function (Bijlsma, Berenbaum & Lafeber, 2011). Since there is no cure, there has been a shift towards disease prevention (Neogi & Zhang, 2012). This focus has become more important as the demographics of society change. Population ageing, rising physical inactivity and the obesity epidemic - key factors associated with the disease - are expected to contribute towards an increase in future OA prevalence (Turkiewicz et al, 2014; Roos & Arden, 2016).

Running is one of the most popular recreational pastimes, enjoyed regularly by millions of people around the world. Running, like any physical activity (PA), imparts significant health benefits (including cardiovascular, psychological, metabolic and musculoskeletal) and can assist in the delay, prevention and management of many diseases (Macera, Hootman & Sniezek, 2003; Neufer et al, 2015). Exercise is a cornerstone clinical intervention for all individuals with OA, beneficial regardless of symptom severity (McAlindon et al, 2014; Bennell & Hinman, 2011). On the other hand, the link between higher doses of PA,

sport and exercise and risk of knee OA is less clear (Conaghan, 2002). Different sports have long been associated with hypothetical mechanisms and observed increased risk of incident knee OA (Lequesne et al, 1997; Richmond et al, 2013). According to a recent systematic review, current evidence is insufficient to identify the true relationship between running and knee OA (Timmins et al, 2017). Identifying and understanding any causal and/or therapeutic association between running and knee OA would have great implications for academics, clinicians and athletes alike.

The purpose of this thesis is to explore running and markers of knee joint health and/or knee OA (for example pain, joint stiffness and crepitus) in a cohort of recreational athletes and non-runners. Briefly, analyses consist of comparisons between runners and non-runners, and within runners stratified by running behaviours (for example, distance and frequency).

Participants completed multiple questionnaires (two at baseline and one at follow-up) to identify self-reported running exposure and outcomes. The level of agreement between some key components of the self-reported running behaviour questionnaire were compared with alternative, contemporaneous methods of recording running (for example, technological devices). In addition, a sub-cohort of runners were invited to complete physical testing so lower-limb function could be assessed against normative values. An overview of the study is presented in Figure 1.

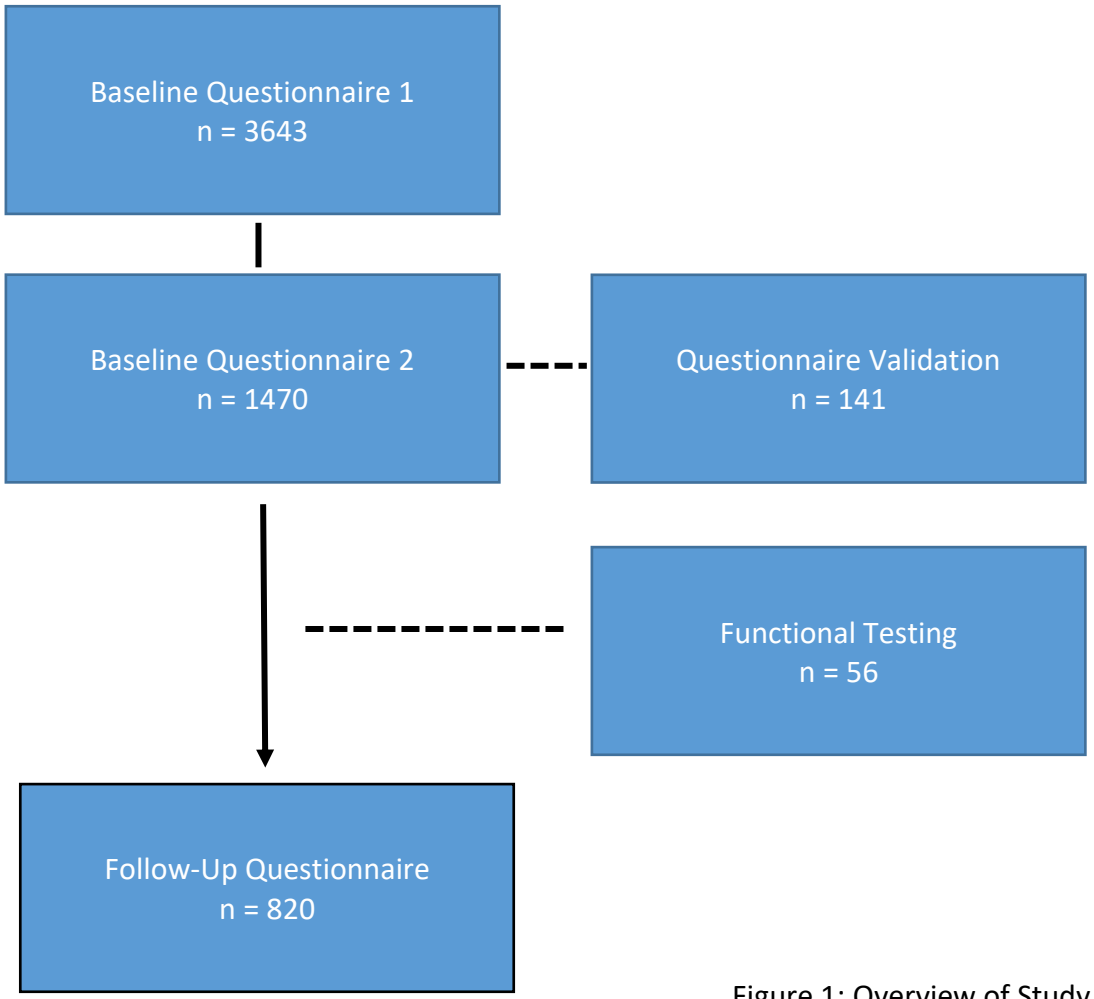


Figure 1: Overview of Study Design

Throughout this thesis, the terms in Figure 1 (i.e. Baseline Questionnaire 1, Baseline Questionnaire 2, Questionnaire Validation Analysis, Functional Testing, and Follow-Up Questionnaire) are used for relevant sections.

1.2 Study Aim

This thesis aims to identify the association between markers of knee joint health (e.g. Knee Injury and Osteoarthritis Outcome Score (KOOS)) and running status (e.g. binary running status). In addition, this thesis seeks to report the prevalence of markers of knee joint health (e.g. self-reported diagnosis of OA) within recreational athletes (for example, various measurements of running exposure, such as average weekly distance).

1.3 Thesis Objectives

This thesis has several objectives:

1. Investigate the prevalence of self-reported knee symptoms, OA and injury in recreational runners and non-runners. Identify risk ratios of factors associated with self-reported knee pain in recreational runners.
2. Identify the self-reported health status (using the EQ-5D-5L questionnaire) of recreational runners and non-runners. Report the difference in 'Pain or Discomfort' EQ-5D-5L domain between participants with a positive and negative history of knee injury.

3. Develop a questionnaire to identify self-report running behaviours (e.g. run distance, run duration) in a cohort of recreational athletes. Assess the level of agreement between components of the questionnaire and other objective measures of running and/or contemporaneously recorded running activity.
4. Describe the performance of recreational runners at tests of lower-limb function. Compare test performance of runners to normative test values. Identify whether history of knee pain or joint injury affects test performance in this cohort.
5. Investigate the 12-month incidence of self-report knee pain and injuries in recreational runners.
6. Identify the difference in KOOS domain outcomes at baseline and follow-up in recreational runners. Describe the distribution and extent of change, based on altered running behaviour compared to 12-months ago.

1.4 Thesis Hypothesis

The null hypothesis for this thesis is:

> 'There will be no statistically significant difference between runners and non-runners in KOOS values for each of the five sub-scales (pain, other symptoms, function in daily living, function in sport and recreation and knee-related quality of life).'

No statistically significant difference in KOOS scores in each of the five sub-scales would indicate that runners and non-runners have similar opinions of their knees.

The experimental hypothesis for this thesis is:

> 'Runners will report greater KOOS values for each of the five sub-scales (pain, other symptoms, function in daily living, function in sport and recreation and knee-related quality of life)' compared to non-runners and the difference is statistically significant.'

If runners report greater KOOS values and the difference is statistically significant in each of the five sub-scales, it would indicate that runners describe higher opinions of their knees compared to non-runners.

1.5 Chapter Outline

A brief overview of the content of each chapter is outlined in the table below.

For each result chapter, the research aim addressed is identified.

Chapter	Overview
2 Literature Review	Provides a background to the present study, by identifying relevant literature regarding the extent of current knowledge in this research area. Systematically evaluate current literature relating to running and knee OA, and outline areas for future research.
3 Methods	Presents the methods for how this study was conducted. Critiques the approach taken and identifies the strengths and limitations at each stage.
4-7 Results	***Chapter 4*** relates to the agreement between the self-reported running questionnaire and running identified in contemporaneous sources. ***Aim: 3*** ***Chapter 5*** relates to analysis comparing runners and non-runners, and further analysis of runners stratified by running behaviours ***Aims: 1-2*** ***Chapter 6*** identifies the performance of physical function (for example, the Osteoarthritis Research Society International tests) in a sample of recreational runners, with comparison to normative values. ***Aim: 4*** **Chapter 7** identifies the change from baseline in knee outcome (e.g. symptoms, function and confidence). This section also reviews the incidence of running injuries over the previous 12-months. ***Aims: 5-6***
8 Discussion	Each results section is discussed in turn, followed by more general observations relating to the study methodology and suggested future research to gain further knowledge in this important area.

Table 1: Chapter Outline

The data from the first results chapter (relating to the validation of self-reported running behaviour using contemporaneous records) is presented

before the other results since running is the most important exposure variable. Understanding how running has been measured, and the validity of this method, allows a more complete interpretation of subsequent evidence presented (both cross-sectional and prospective data). Data from the Baseline Questionnaires (relating to self-reported knee joint symptoms and markers of knee joint health) is supplemented by the sub-cohort analyses of functional tests undertaken. As joint health is a complex construct, a holistic approach to its assessment is necessary. The Follow-Up Questionnaire seeks to enhance the understanding of the overall study aim by exploring the 12-month incidence of injury and running status. Together with the baseline data, it is hoped that this will enhance understanding in this important area.

2 Literature Review

2.1 The Knee Joint

The knee is the largest and one of the most complex joints in the human body. What is commonly referred to as the knee is comprised of three distinct articulations across two joints; the tibiofemoral joint (TFJ) and the patellofemoral joint (PFJ) (Flandry & Hommel, 2011). The TFJ is a double condyloid articulation between the distal femur and the proximal tibia and the PFJ is the articulation between the posterior surface of the patella and the trochlear surface of the anterior femur. The knee is a synovial joint, characterised by articular cartilage covering complimentary-shaped bone endings, the presence of supportive ligaments and a synovial membrane encapsulated within a synovial capsule.

2.2 Osteoarthritis

Rather than a single entity, OA is best understood as several joint disorders with numerous aetiologies, leading to a common outcome (structural and functional failure) (Bennell et al, 2011). Definitions of OA vary according to the site of disease, behaviour and chronicity of symptoms, and method of diagnosis. The myriad of criteria and the complexity of disease presentation make identification of cases problematic in clinical practice and epidemiological research (Table 2).

Identification of Cases of Knee OA
Symptoms and Disability
Predominantly knee pain, morning stiffness and crepitus
Imaging
Classified according to structural findings on radiograph / MRI
Arthroplasty
Knee joint replacement is a surrogate of end-stage OA

Table 2: Identification of Cases of Knee OA

Heterogeneity in diagnostic criteria may contribute towards less favourable outcomes, especially early in the development of disease, when symptoms and structural changes could be slowed or reversed (Favero et al, 2015). Early and advanced cases of OA are distinct and differentiating between the two is important since risk factors for each may not be the same (Cooper et al, 2000). Evidence for mechanisms for disease progression are discussed in a later section.

OA occurs when there is a shift from the homeostatic balance towards breakdown of the structures within the join, particularly affecting cartilage and underlying bone (Baker-LePain & Lane, 2012; Tat et al, 2010). If one considers OA as a continuum, the predominant joint structure afflicted is interchangeable at each stage (Castaneda et al, 2014). Ultimately, the entire joint is compromised, owing to the intimidate anatomical and functional interrelationships between structures (Figure 2).

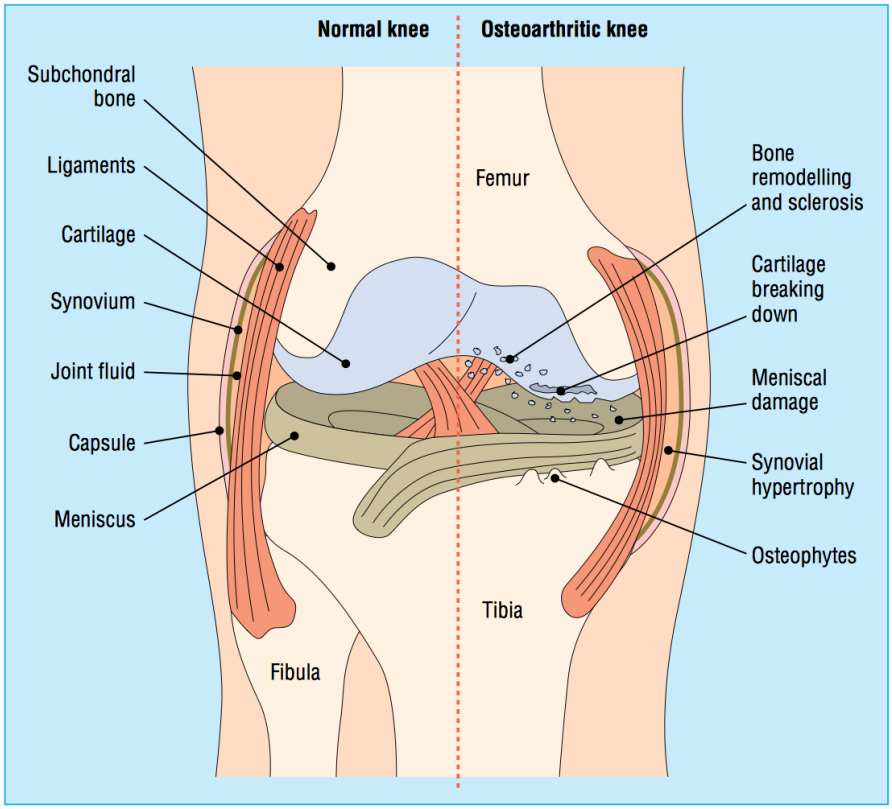


Figure 2: Features of Knee OA (Hunter & Felson, 2006) pp 640

Cartilaginous abnormalities (such as the loss of hyaline cartilage) are central to OA, but no longer considered the driver behind the disease (Berenbaum, 2013). The premise that OA occurs due to 'wear and tear' of the cartilage has largely been debunked (Lespasaio et al, 2017). This hypothesis evolved from the observation that chondrocytes, the unique cell-type within cartilage, have limited capacity to repair following insult, overload or overuse (Mathiessen & Conaghan, 2017). Instead, evidence now suggests that OA should not be considered a disease of the cartilage, but a disease of the entire joint (Brandt et al, 2006).

A review by Karsdal et al (2008) suggests there are strong structural, cellular, molecular and biochemical couplings between bone and cartilage. Mahjoub,

Berenbaum & Houard (2012) concluded alterations in one will lead to remodelling in the other. In addition, as the menisci and cartilage are exposed to similar forces, it is perhaps unsurprising that if the cartilage is affected then so too are the menisci (Englund & Lohmander, 2006). Evidence suggests that in OA, the stress-distribution and load absorbing capacity of the cartilage-bone unit are impaired. With disease progression, a vicious cycle adversely affecting the health of the cartilage and deterioration of the subchondral bone commences (Li et al, 2013).

There remains significant variation in how the disease manifests (i.e. the extent to which individual structures are affected and how symptoms present) between patients (Felson, 2010). The phenotype of OA may not always be the same, particularly early on, until symptoms become more homogenous and a common OA condition develops (Figure 3).

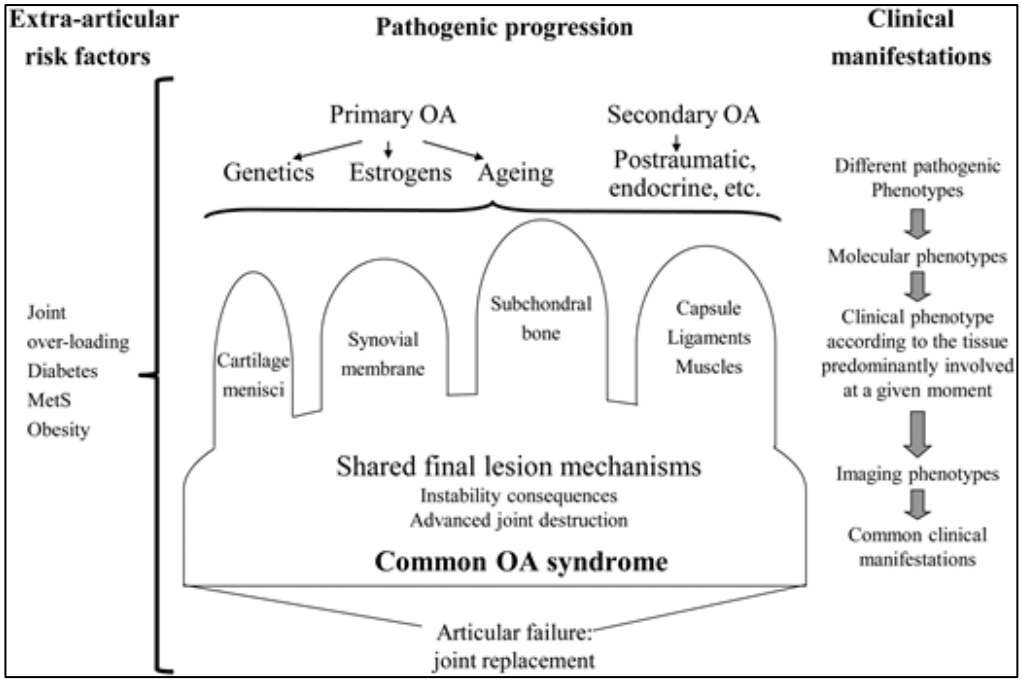


Figure 3: Progression of OA (Castaneda et al, 2014) p 2

2.3 Definitions of Knee OA

2.3.1 Symptomatic Knee OA

Pain, crepitus, reduced range of movement, stiffness, limited function and joint instability are common characteristics of OA (Hunter, McDougall & Keefe, 2008).

2.3.1.1 Pain

Pain is defined by the International Association for the Study of Pain as:

> *'An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage'*
>
> IASP (1994)

Pain is a highly complex phenomenon and the primary presenting complaint in most cases of OA. It often acts as an indicator for further investigations that confirm diagnosis (Phillips & Clauw, 2013). OA-related pain is normally located in or around the affected joint but referred pain and tenderness may also be present. It is usually described as an aching or throbbing, punctuated by episodes of sharp, stabbing sensations related to bouts of activity (Kidd, 2006).

The exact drivers for pain in knee OA are poorly understood but it is believed to result from interactions between local tissue damage, inflammation and the peripheral and central nervous systems (Salaffi, Clapetti & Carotti, 2014). There is evidence that inflammation, impingement, structural damage, progressive osteophyte formation (excess bone growth at the joint margins) and joint instability all contribute (Scanzello, Moskowitz & Gibofsky, 2008; Felson, 2005). Subchondral bone, periosteum, ligaments, muscles and joint capsule are highly innervated and are potential sources of pain, however it is uncertain how much alterations to these structures affect pain severity. Furthermore, as OA progresses, there may also be heightened sensitisation to noxious stimuli, whilst non-noxious stimuli may also inadvertently result in pain (Bolay & Moskowiz, 2002).

Patients with the same degree of structural damage experience widely different levels of pain (Hunter et al, 2009). As will be described further in section, the weak relationship between the degree of structural damage and

symptoms suggest that the biomedical model is inappropriate for understanding pain and OA (Bartley, Palit & Staud, 2017). The biopsychosocial model presents a more holistic approach that may help understand the pain perception in OA (Figure 4).

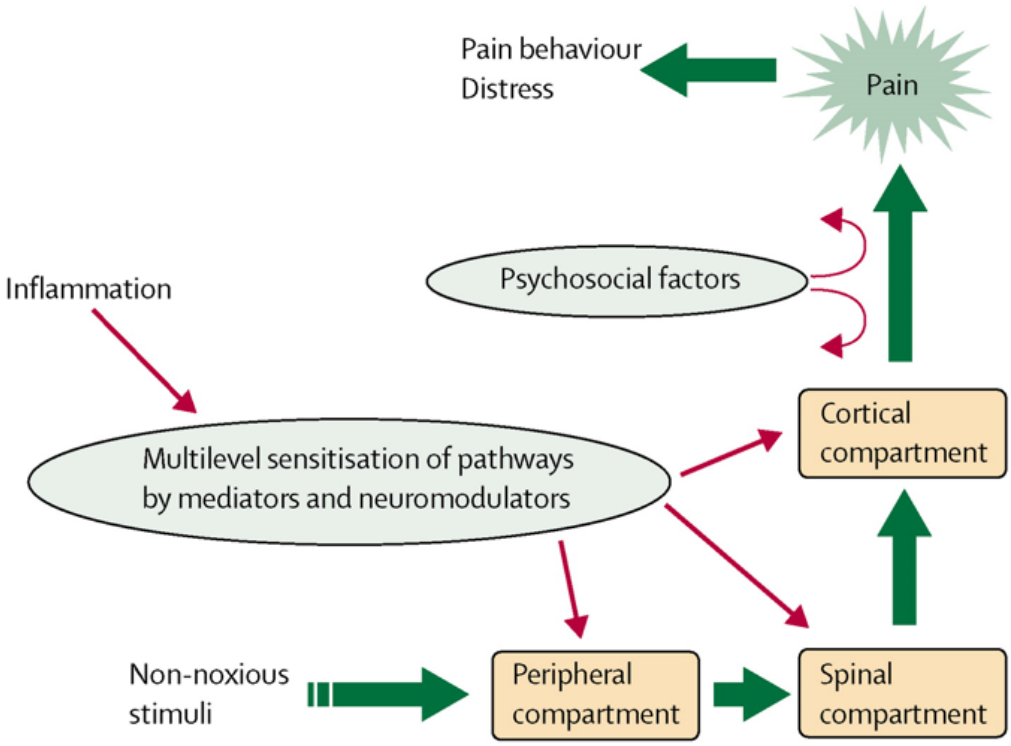


Figure 4: Pain Mechanisms in OA (Dieppe & Lohmander, 2005) p. 967

Pain perception is modified by psychosocial factors such as mood and social support, so these are important considerations when pain experiences are described (Hunter et al, 2013). The complex inter-relationship between psychological, behavioural and sociological factors may not be universal nor consistent, and the evidence appears to reveal this with regards to the actual, and potential, effects of stimuli such as physical activity (PA). For example, in a comparison of patients with and without knee pain, patients in a positive psychological mindset with knee symptoms completed more steps-per-day.

Participants without knee pain walked a similar amount, irrespective of depressive symptoms (White et al, 2013). It must be acknowledged that participants may have altered their activity due to their inclusion in the study. In addition, the presence of pain elsewhere in the body may also have affected activity levels, but this was not reported. Another study included 350 patients with symptomatic knee OA who were asked to identify their agreement with questionnaire statements, indicating fear of movement, which may negatively affect levels of PA (Gunn et al, 2018). Thirty-six percent of participants agreed with three or more of the six criteria on the questionnaire.

Pain itself can also present as one of many different sensations (Hawker et al, 2008). In this analysis of 143 patients with hip (n=52) and knee (n=91) OA, two broadly distinct types of pain emerged. The first, an intense, intermittent pain and the second, a less severe but persistent pain/ache. The authors suggest that more intense and unpredictable pain patterns may induce greater psychological distress and reduce activity levels. These studies highlight the varied - but significant - direct and indirect effects of factors outlined in the biopsychosocial model and how they may affect patients with (or at risk of) symptomatic knee OA. The cause-effect relationship between activity and pain is also subject to further investigation.

Failure to fully comprehend the pain perceived by different individuals with OA partly explains the challenges associated with implementing successful interventions, for example, analgesia, surgery and exercise (van Laar et al,

2012). As movement is considered a trigger for pain, the type and dose of exercise - a cornerstone treatment option for knee OA - must be carefully considered (Juhl et al, 2014). It appears counterintuitive, given the evidence in the previous paragraphs, that activity and exercise is strongly advocated in the management of knee OA. There is a paucity of evidence identifying which activities cause pain, although clinical experience suggests that certain activities cause pain in the osteoarthritic joint pain when they would not in the disease-free joint (Hunter, McDougall & Keefe, 2008). Therefore, it is arguably important to identify the association between specific activities and knee joint pain. Running is discussed in a later section.

2.3.1.2 Crepitus

Crepitus is audible grinding noise and/or palpable vibrations in the knee during joint movement. A study by Crema et al (2011) identified crepitus in 70.5% of all knee OA cases (255 knees), but the prevalence varied between compartments; being most common in PFJ OA (67.9%) and least common in medial (17.3%) and lateral TFJ (18.7%) OA. This study also revealed a significant association between the severity of radiographic OA and presence of crepitus ($p<0.0001$). It is postulated that this is due to joint space narrowing (JSN) and more extensive cartilage and meniscal pathology. In turn, this leads to greater friction between the joint surfaces during movement, resulting in crepitus. This study however failed to consider the potential contribution of other structures within the joint, such as tendons, and these were not reported on in the MRI

scans. Additional investigations (e.g. arthroscopy) would have been useful to identify the health of these structures and their role in the arthritic knee.

Crepitus may also be a potentially significant clinical indicator of early PFJ OA. In an analysis of females with and without a diagnosis of knee OA, a physical examination and knee MRI were completed (Schiphof et al, 2014). The presence of crepitus was associated with all features associated with PFJ OA as identified on MRI (cartilage lesions OR 4.58 (3.42-6.15); osteophytes OR 2.80 (2.20-3.57), cysts OR 2.77 (2.05-3.76) and bone marrow lesions OR 3.44 (2.62-4.52)). In contrast, crepitus was not associated with any TFJ OA features on MRI. In this paper, crepitus was defined by a clinician as an audible grinding noise and/or palpable vibrations in the knee with the hand placed on the patella. There is a degree of subjectivity around this test thus it may be pertinent to develop a standardised procedure for reporting crepitus in future research.

2.3.1.3 Reduced Range of Movement

Available joint range of movement (ROM) is dependent upon demographic (e.g. age), articular (e.g. severity of radiographic OA) and clinical factors (e.g. pain), but the causes of limitations are poorly understood (Holla et al, 2011). In an analysis of 198 patients with early OA, 60% of whom presented with knee OA, there were negative associations between reduced knee flexion (-0.23, $p<0.01$) and observed disability (e.g. task performance) and self-reported disability (questionnaire) (-0.29, $p <0.01$). This was a cross-sectional study, so

no cause-effect relationship between ROM and outcomes could be reported. It would be useful to understand how ROM and other clinical features of OA interact over time and how these affect patient outcomes and disease progression. In addition, the authors were unable to report the inter- and intra-rate reliability of the goniometry measurements. A previous systematic review has indicated that overall goniometry for knee has acceptable inter-rater reliability, although this varies between professions - however the methodological quality of research informing this conclusion was found to be relatively poor (van Trijffel et al, 2010).

The importance of understanding how symptoms affect one another (in addition to other disease outcomes, such as disability) was reported in an analysis of 198 patients with hip and/or knee OA, as defined by ACR classification criteria (Steultjens et al, 2000). Approximately 20-25% of the variance in disability was attributable to differences in ROM, although the authors acknowledge that other factors besides OA status can affect available range (e.g. strength and other symptoms may limit how far a participant moves their knee). To identify this accurately, additional research would be necessary.

2.3.1.4 Stiffness

OA-related stiffness is typically divided into morning stiffness and stiffness related to activity (Claessens et al, 1990). A study of 205 patients with symptomatic OA at multiple joints (47% of whom had radiographic knee OA) explored the association between clinical symptoms and structural findings

associated with knee OA (Kornaat et al, 2006). The findings suggest that knee stiffness on most days during the previous month is a common (present in 47% of cases), but not universal finding. In comparison, pain was present in 59% of patients. The only MRI finding to be statistically associated with knee stiffness was moderate to severe effusion (OR 4.67, 1.26-26.1; $p<0.01$). In this analysis, the presence of stiffness was identified using a relatively subjective, binary question, whereas a more detailed - or objective test - may have provided greater clinical insight. Another study of 116 participants showed baseline knee stiffness was found to be a significant factor for increased risk of developing knee osteophytes, but not JSN, after a 30-month follow up period (Mazzuca et al, 2007). Knee stiffness therefore may be a useful marker of underlying joint health before radiographic features become identifiable.

It has been suggested that increased stiffness impairs function (e.g. task self-efficacy and walking) (Dixon et al, 2010). The conclusions of one study suggest that more severe OA is associated with greater dynamic stiffness during walking (Zeni & Higginson, 2009). This may result from increased friction due to osteophyte formation and incongruency of joint surfaces. Additionally, muscle activity may limit flexion and stabilise the joint to avoid pain. Further research is necessary to establish the true contribution or effect of each factor and how these relate to clinical outcomes.

2.3.1.5 Function

Functional deficits and disability represent the cumulative impact of several components such as those mentioned in previous sections, as well as other components (e.g. strength, proprioception and confidence). How disability is defined and measured depends on the methods employed by individual researchers and clinicians. One of the most common methods of assessment is a questionnaire. Different questionnaires include various constructs across several domains and require the self-report of symptoms and/or difficulty experienced during specified activities (Collins et al, 2011). Functional capacity can also relate to performance of specific tasks, for example, simple, objective tests which replicate requirements of more complex activities. Such assessments can be repeated to identify change over time (Stratford, Kennedy & Woodhouse, 2006).

Several independent factors have been identified that relate to functional ability. An analysis of 159 patients who completed the Stanford Health Assessment Questionnaire at a general practice, identified the strongest inverse relationship exists between quadriceps strength and disability (McAlindon et al, 1993). This questionnaire has been widely validated and can be self-administered (Bruce & Fries, 2003). Presence of knee pain and increasing age were also important variables, yet there was no significant association between radiographic OA severity and function. The authors suggest that pain and muscle strength are the mechanisms through which OA influences function. The external validity of these findings may be limited by

the small geographical region from which participants were identified. The age profile (mean age 73 years) may also means the findings may not be directly translatable to younger patients with knee OA.

2.4 Imaging Knee OA

Diagnosis of OA using radiograph has long been considered the gold-standard and is common in epidemiological studies. Radiographs show active pathological processes associated with the condition including JSN, osteophyte formation and subchondral bone deformation and sclerosis (Peat, McCarney & Croft, 2001; Buckland-Wright, 2004).

JSN is used as a surrogate measure of cartilage loss, meniscal damage or a combination of both. Degeneration of the meniscus has been found to explain a significant proportion of JSN in patients with knee OA rather than articular cartilage damage (Hunter et al, 2006). In this study using both MRI and radiograph, there were differences in the medial and lateral joint compartments. Results for the lateral joint space were not included as the model was too unstable, and as only 25% of the variance in the medial compartment could be explained, much remains unknown. The authors report these findings support the assertion that structural processes in OA progression are collinear, affecting the articular cartilage and other structures, including the menisci, in parallel.

Osteophytes are an integral feature of OA pathology, commonly seen at joint margins, starting as cartilaginous outgrowth before ossification (Felson et al, 2005). Nagaosa, Lanyon & Doherty (2002) describe osteophytes as a remodelling and reparative feature of OA, but acknowledge factors determining their onset and progression are unknown. Other authors go further, suggesting marginal osteophytes stabilise the joint and protect against OA (Brandt, 1999). Osteophyte formation may be a beneficial adaptation, leading to greater joint surface area aiding load distribution in individuals who undertake significant lower-limb loading. For example, in comparison to sedentary individuals, larger joint surface areas have been identified in endurance athletes, although this is only from a small cohort (n=18 athletes) (Eckstein et al, 2002). The effects of mechanical load are discussed further later.

In most cases, osteophytes are asymptomatic. Despite the importance of osteophytes for diagnosis of radiographic OA, subchondral bone damage is postulated to be a more important source of pain than osteophyte formation or loss of cartilage (Szebenyi et al, 2006). A correlation between the presence of pain and osteophytes does not equate to a causal relationship. On the other hand, it is suggested that osteophytes may be a source of pain and limit function through nerve compression, reduced movement and tissue obstruction (van der Kraan & van den Berg, 2007).

Research repeatedly highlights a discordance between the severity of symptoms and radiographic features. In isolation, radiographs will identify individuals as having abnormalities indicative of OA, yet many will have minimal or no symptoms. In the Framingham study, 35% of men and 43% of women with definite radiographic OA reported symptoms (Felson et al, 1987). Following a review of 17 papers, Bedson & Croft (2008) concluded that knee pain is an imprecise marker of radiographic knee OA. They found the prevalence of radiographic OA ranges between 15-76% in subjects with knee pain (depending on the subject age, choice of radiological view and disease definition). Studies may not necessarily define the specific part of the knee afflicted when describing cases. This limitation is exposed by Duncan et al (2006) who reported that isolated OA of the PFJ (24%) is more common than isolated TFJ OA (4%), but OA is present in 40% of cases. Failure to acknowledge the contribution of the PFJ in knee OA means it is largely underappreciated (Hinman & Crossley, 2007; Culvenor et al, 2013). Of patients over the age of 60 reporting knee pain, only 13.6% of females and 15.4% of males have isolated radiographic TFJ OA (Davies et al, 2002). This may go some way towards explaining the lack of agreement between radiological findings and clinical symptoms. Since radiographic changes indicative of OA and symptoms may not always co-exist, use of radiograph in isolation is questionable and comprehensive, holistic assessment is optimal (NICE, 2014).

MRI can produce a more detailed and comprehensive image of the entire joint compared to x-ray, particularly early in the disease process. This may include

defects affecting the menisci, cartilage, ligaments, synovium, bone or presence of oedema (Cibere, 2006). Semi-quantitative MRI assessment tools for knee OA are being developed, and their use in early OA could prompt helpful clinical interventions at this stage (Hunter et al, 2011). Despite clear advantages for MRI over radiograph, a review by Conaghan (2006) concluded there are currently no indications for routine use of MRI in OA diagnosis or management, mainly due to the high financial costs and impracticality. As a result, radiograph remains the gold standard due to its ease and low-cost (Bijlsma, Berenbaum & Lafeber 2011).

2.5 Epidemiology of Knee OA

Along with joints of the hands (chiefly those involved with pincer grips) and the spine, load bearing joints - hips, knees and great toe - are most susceptible to OA. Lifetime risk of symptomatic knee OA is approximately 40% in males and 47% in females (Murphy et al, 2008).

2.5.1 Prevalence of Knee Pain

Prevalence of knee pain is on the rise. In a study of data from two different American cohorts (National Health and Nutrition Examination Surveys (NHANES) and Framingham Osteoarthritis (FOA) study), significant trends were observed. In the NHANES cohort, age and BMI-adjusted prevalence rose 66% between 1974-1994. In those without radiographic OA, prevalence of knee pain tripled in women and more than quadrupled in males (Nguyen et al, 2011). This was partly, but not entirely, due to increasing obesity. Interestingly, in the

FOA cohort, there was an increase in symptomatic OA but not radiographic OA. This suggests that pain should be a prominent aspect of OA research, since pain is likely to be modifiable and important in terms of pathology burden.

The definition of pain will affect the prevalence of symptoms reported. As an example, in an assessment of a US cohort, 23% of participants reported ever having knee pain and 15% reported pain in the previous year (Lethbridge-Cejku et al, 1995) The choice of question to identify the subjective experience of pain is therefore a critical methodological consideration.

2.5.2 Prevalence of Radiographic Knee OA

Felson et al (1987) reported data from an elderly population and found radiographic OA prevalence increases with age. Of all participants (males and females, n=1420), the prevalence was 27.4%, 34.1% and 43.7% for those aged <70, 70-79 and 80+ respectively. A limitation of this study is that it did not include any black or other ethnic groups, although other evidence suggests that this may influence the prevalence reported. Significant racial differences have been identified in other American cohorts, for example in an analysis of over 3,000 African American and Caucasians aged over 45, African American men were approximately 36% more likely than Caucasian men to have radiographic TFJ OA (Jordan, 2015). In contrast, prevalence of TFJ OA in females was not significantly different. Participants in this study were largely from a rural community, thus environmental or other unidentified confounding factors may

predispose certain individuals in this cohort to develop knee OA, especially in comparison to trials including more urban-based participants.

Another study in an elderly, Japanese population (n=2,282) reported OA prevalence of 47% in males and 70% in females. This study also reported prevalence of medial and lateral TFJ OA with medial OA far more common in males (20% compared to 2%) and females (34% compared to 3%) (Muraki et al, 2009). The authors noted that the methods used to identify cases of radiographic OA may not always be consistent within, and between, investigators.

The Kellgren-Lawrence (KL) (Kellgren & Lawrence, 1957) and OARSI Atlas (Altman & Gold, 2007) are common tools to identify knee OA and assess disease progression. They use ordinal scales to identify the extent to which osteophytes and JSN are present. Neither is considered gold standard (Ratzlaff et al, 2018). Depending on which criteria is used, the rates of diagnosis can vary significantly. In a review of 1,178 knee radiographs, a single reader identified 14% of knees with TFJ OA using the Kellgren-Lawrence criteria whilst TFJ OA was present in 26% of knees using the OARSI Atlas (Culvenor et al, 2015). One study identified the effect of experience and profession on radiographic assessment (Klara et al, 2016). The results suggest that inter-reader and intra-reader reliability of the two criteria varies, as does the extent of agreement when specific radiographic features are identified. The sample size was small (n=36) and did not include any longitudinal analysis to identify progression of

disease. These findings suggest that radiographic interpretation remains, at least in part, subjective and this should be considered when interpreting radiographic prevalence of OA.

2.5.3 Prevalence of Knee Joint Arthroplasty

Arthroplasty is an orthopaedic surgical intervention, indicated when unremitting symptoms persist after conservative management for OA has failed (Ferket et al, 2017). The number of knee replacements has tripled in the UK over recent years (1991-2006) (Culliford et al, 2010; Figure 5).

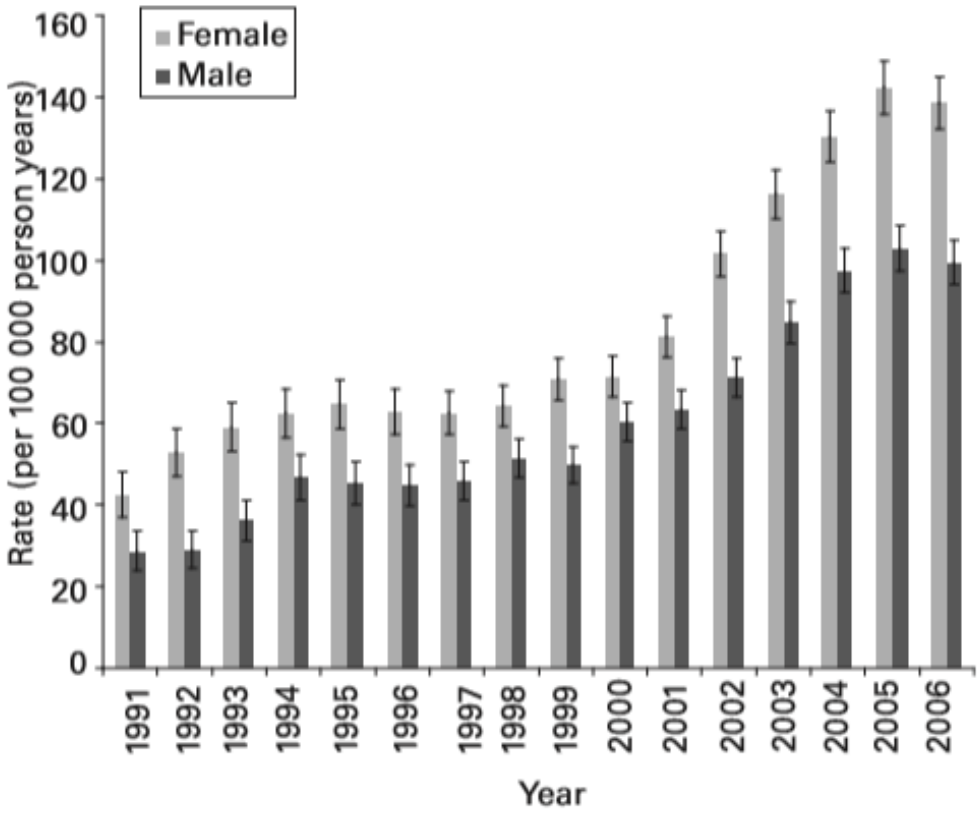


Figure 5: Trend in Knee Arthroplasty in the UK, 1991-2006 (Culliford et al, 2010) p.132

Although this trend is not limited to the UK, rates of surgery vary dramatically between countries, making comparisons between geographies limited. A survey of 18 countries identified a range of 8.8/100,000 population in Romania to 234/100,000 in the USA (Kurtz et al, 2011). This study is limited by the availability of publicly available data sources and the information they provide. For example, it did not seek to determine which factors drove this increase in surgery in individual countries nor did it identify the underlying OA prevalence. It is likely that demographic and societal factors are responsible for this changing trend - which is expected to continue - for example, rising life expectancy and increasing obesity rates (Culliford et al, 2015). Furthermore, the number of procedures in younger patients is increasing, although this will likely increase the number of revisions required (Price et al, 2018). Importantly, patient satisfaction levels following total knee arthroplasty are approximately 80% (Bourne et al, 2010). Therefore, a relatively large proportion of those that undergo the procedure have ongoing symptoms and/or functional deficits despite surgery.

2.6 Mechanisms for Knee OA Development

OA is described by many authors as a disease of systemic and local mechanical factors (Guilak, 2011; Felson, 2013; Roos & Arden, 2016). Guilak (2011), for example, argues abnormal biomechanical factors are implicated in the development of OA and play a significant role in prominent risk factors for the disease, such as obesity and joint injury. This is apparently supported by the

findings of systematic reviews that consistently identify these as significant risk factors for knee OA (Silverwood et al, 2015; Muthari et al, 2011).

Bone is a dynamic structure, a principle underpinned by Wolff's Law. This theory states that repetitive loading results in adaptive responses in bone that enable it to better withstand the mechanical forces applied (Frost, 1994). It is argued that the principles which underpin this hypothesis are applicable to early knee OA, although much of the evidence supporting this is from animal models (Teichtahl et al, 2015). The generalisation of these findings into humans is therefore questionable and should be subject of further research. The authors propose a disease paradigm where overload of structures, or a shift in load bearing within the joint (for example, post-injury), ultimately leads to an impaired healing response in bone and deleteriously affects the cartilage. The coupled nature of structural changes in OA has previously been described in section 2.2.

Different activities will impart various effects on joints and the relationship between load and biological effects are highly complex. Structures have a limited tolerance to external force application before damage occurs. On the other hand, beneficial adaptation may occur when loads increase gradually, ensuring they can withstand the imposed demands. Figure 6 identifies the response of tissue according to the stress levels (Mueller & Maluf, 2002).

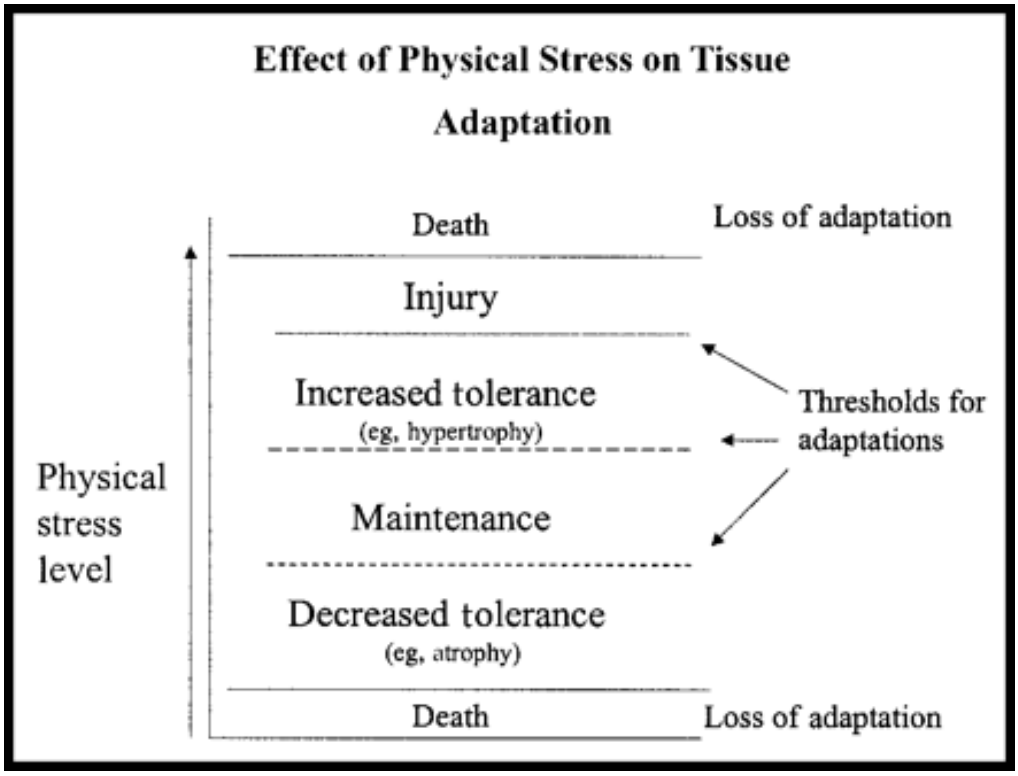


Figure 6: Effect of physical stress on tissue adaptation (Mueller & Maluf, 2002) p 388

According to the theory proposed in the diagram above, there are five possible responses to stress (decreased tolerance, maintenance, increased tolerance, injury and death). If the load is great enough, increased tolerance to that stress can be developed. This suggests that behaviours, environmental factors and other internal mechanisms that impart load will influence the structural properties of joints - and perhaps onset and progression of knee OA. Both models presented above do not directly provide guidance regarding the threshold beyond which loading could become deleterious rather than beneficial.

To add a further level of complexity, it is possible that the mechanisms involved in the pathways for OA onset and progression (including loading) are not the

same, whilst individual risk factors may have varying significance at different stages of disease. Andriacchi & Mundermann (2006) propose that the degree of functional loading dictates the speed of OA progression (Figure 7).

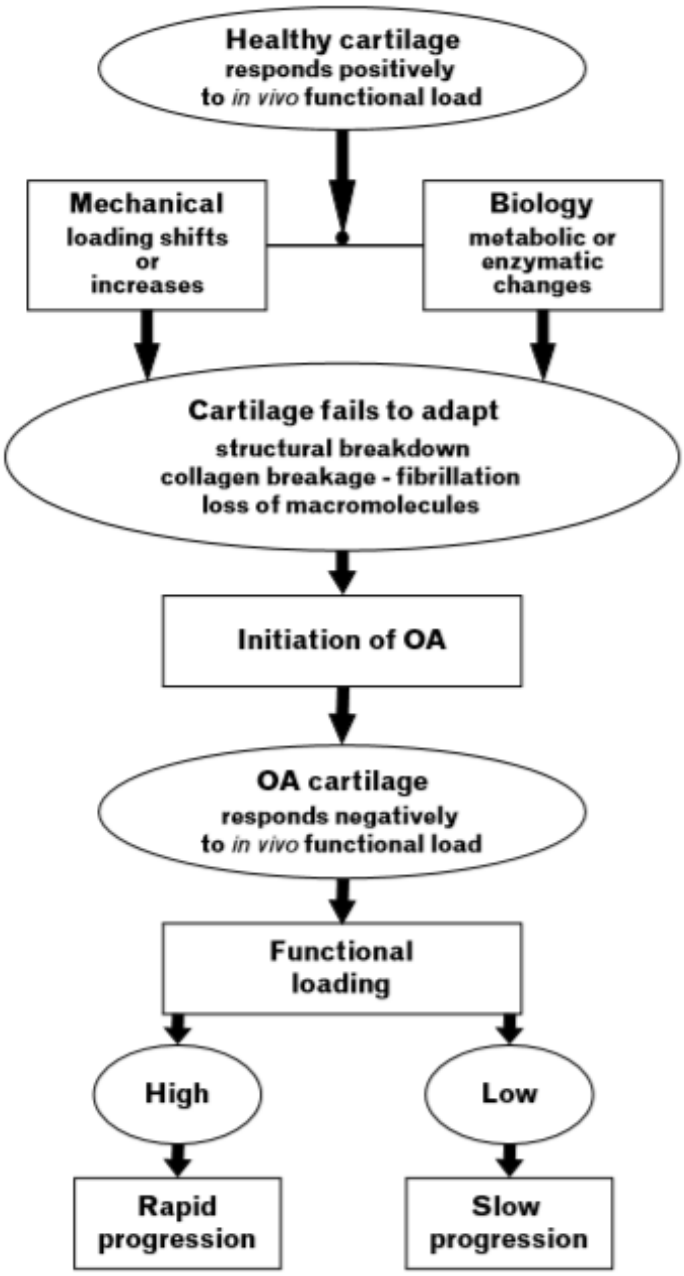


Figure 7: The hypothesised role of joint loading in progression of OA, Andriacchi & Mundermann (2006) p 517

Figure 7 shows that higher loads could be associated with a more rapid progression of OA. It should be recognised that mechanics alone may not

entirely explain the role of obesity in development of knee OA (Aspden, 2011). Other systemic factors may play a role as evidence from upper limb OA shows that risk is increased in obese individuals, despite the hand not being a weight bearing joint (Felson & Chaisson, 1997). Metabolic and inflammatory markers are coming under greater scrutiny in OA research and these are related to the ageing process and obesity - prominent risk factors for the disease (Singh & Newman, 2011; Mobasheri et al, 2015; Lohmander et al, 2009). Systemic inflammatory markers are higher in patients with OA (Attur et al, 2013). Body fat, adipokines, cytokines and hyperglycaemia can trigger systemic inflammation that can impact risk of onset and progression of the disease (Wang, Hunter & Ding, 2015). Metabolic-triggered inflammation ('meta-inflammation') could therefore be implicated in the pathogenesis of OA (Gregor & Hotamsligil, 2011). Considering this evidence, joint loading experienced throughout life may not be the sole pathway for OA onset and progression. Furthermore, evidence for a direct causation between loading accumulated through activity and knee OA is arguably weaker than the in-vivo evidence, animal studies and hypothesised models suggest. Henriksen et al (2014) conducted a systematic review of the evidence for a causal link between joint loading accumulated through walking and structural knee OA progression. The methodological quality of five eligible papers included was deemed 'low' and a high risk of bias was identified. The paper concluded there was no evidence for an association between walking knee joint loading and structural OA progression. Despite a paucity of evidence for the underlying mechanisms, reducing knee loading during gait is often the focus of clinical interventions to

manage knee OA (e.g. weight loss and insoles) (Gross & Hillstrom, 2008; Simic et al, 2011).

One may consider that given the theoretical evidence for loading increasing or protecting against risk of knee OA, activities that impart large forces on the joints (such as running) should be the focus of additional scrutiny. The loads involved during a marathon are vast - the lower limb joints of a 70kg athlete must withstand a vertical force equivalent to 2800 tons (Hohman et al, 2004). Running should therefore be explored in greater detail.

2.7 Running

Running is now one of the most popular sports worldwide (Hulteen et al, 2017). In 1976, there were approximately 25,000 marathon finishers in the USA. By 1980 this was up to 143,000, and by 1990, it had reached almost a quarter of a million (Running USA, 2018). The growth in marathon running has been sustained over the past 40 years up to 2016, and despite a recent slowing, the overall increase is 1930% (Figure 8). Vast increases have also been observed in the number of half-marathon finishers. From 1990-2016, the numbers of athletes completing these events rose 527%.

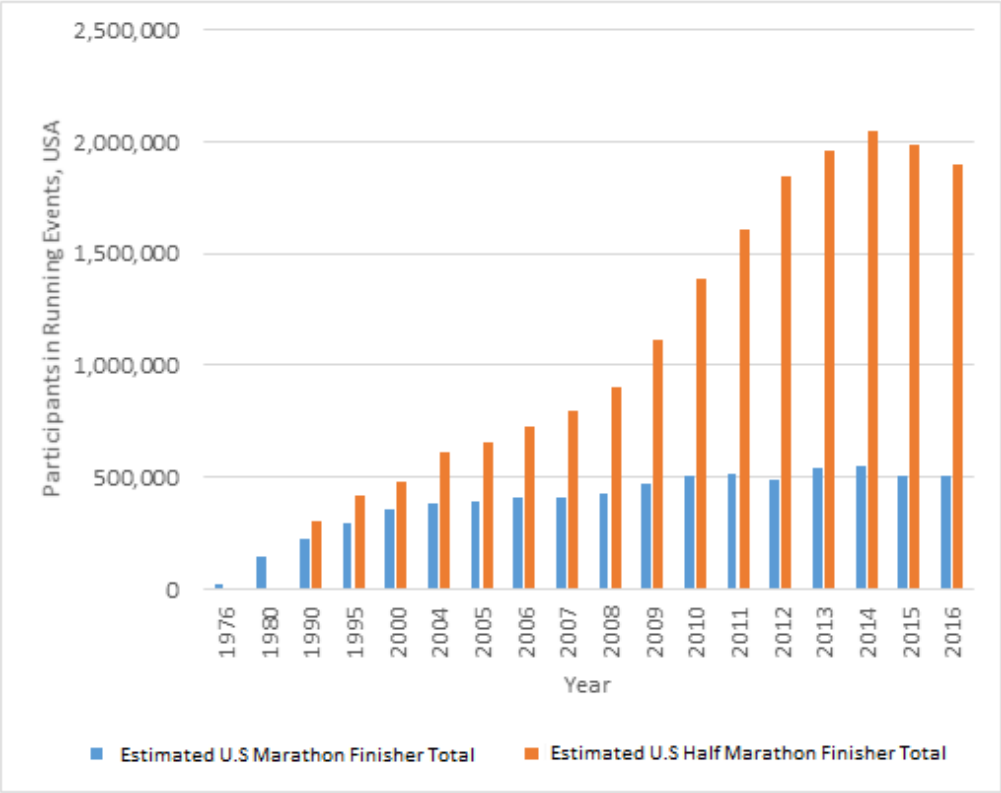


Figure 8: Estimated Number of Marathon and Half-Marathon Finishers in the USA, 1976-2016 (Running USA, 2018)

In England, there has been a steady increase in the number of runners over recent times (Sport England, 2016). Sport England data relates to athletics (defined as running - including other track and field events, road running, track running, cross-country, ultra-marathons and jogging), but nevertheless, there is a trend for more runners taking part regularly. If figures for runners participating monthly rather than weekly are reported, the number increases to over 3 million in 2015/2016. This means that running is the third most popular sport in England (behind swimming and cycling). In 2016, Sport England data reveals only 190,000 runners were affiliated to a club, therefore a substantial proportion of recreational athletes are independent of formal coaching or support networks.

2.8 The Health Effects of Running

The benefits PA are indisputable. It is considered a critical component of a healthy lifestyle (Reiner et al, 2013; Warburton, Nicol & Bredin, 2006). Exercise - a sub-component of PA - is a potent stimulator of molecular and cellular cascades, leading to anatomical remodelling of numerous bodily systems that enhance physical and psychological wellbeing in healthy and diseased individuals (Wilson, Ellison & Cable, 2015). Furthermore, inactivity and low levels of PA are the 10th greatest attributable cause of disease burden globally (Lim et al, 2012). For many individuals, especially those in sedentary occupations, the most effective means of increasing overall PA could be through participation in sports or exercise, with exercise emerging as a key intervention used to prevent and treat disease (MacAuley, Bauman & Fremont, 2016). Encouraging inactive individuals to increase and sustain activity levels is one of the greatest challenges facing healthcare in the 21st century (Trost, Blair & Khan, 2014). Greater awareness of the benefits for maintaining a healthy lifestyle could be a key driver behind the increased popularity of running (Verhagen, 2012).

Different sports impart different effects on various bodily systems when completed to various levels (Oja et al, 2016). Evidence from observational studies suggests that running can reduce the incidence of chronic conditions such as hypercholesterolemia, diabetes, coronary heart disease, stroke and hypertension, ultimately contributing to reduced risk of all-cause and cardiovascular disease mortality (Lee et al 2014; Chomistek et al, 2012). The

results of a systematic review including 49 articles suggest that the health benefits of running are widespread, largely due to cardiovascular and metabolic adaptation, which appear greatest when history of running is longest (Junior et al, 2015). The authors acknowledge the evidence informing these conclusions is limited due to the risk of bias emanating from difficulty in participant and researcher blinding.

A health benefit of running is observed, even at lower doses (5-10 mins per day) and slower speeds (<6 miles per hour) (Lee et al, 2014). This study included a sample (total n=60,003) with a mean follow-up period of 14.6 years. In this cohort, runners had 30% and 45% lower risks for all-cause and cardiovascular mortality respectively. Runners who remain active an average of 5.9 years later had the greatest mortality benefit (risk reductions of 39% and 50% for all-cause and cardiovascular mortality respectively). A second paper reported findings from runners (n=1,098) stratified by running dose (calculated from a combination of frequency and pace) (Schnohr et al, 2015). The results suggest a U-shaped or reverse J-shaped curve for dose of jogging and all-cause mortality, highlighting too much or too little increases mortality risk. The conclusions from this paper have led to some debate (Andersen, 2015). For example, the number of runners included in the highest quartile of running quantity, frequency and pace in the fully adjusted analysis were relatively small; 47 (1 death), 80 (5 deaths) and 192 (6 deaths) respectively. The confidence intervals for these groups were very broad and overlapped, so the differences are statistically insignificant. Further research is warranted in larger

samples of runners to confirm these findings - especially including more athletes completing higher running volumes. On the other hand, these studies do provide useful methodological insight (i.e. comparison of runners and non-runners, identification of runners and which running behaviours are considered important).

The contemporary emphasis on exercise as medicine is reliant upon critical assessment of all available evidence to support clinical decision-making. Thus, the risks of participation must also be acknowledged (e.g. injury) (Soligard et al, 2016). At the highest levels of PA, there may be some associated mortality risk (Merghani, Malhotra & Sharma, 2016) but data from elsewhere shows this increase in risk does not rise above inactivity (Eijsvogels & Thompson, 2015). Benefits of PA are greatest when an individual increases activity above complete sedation with larger benefits at higher activity levels (Kyu et al, 2016). This implies there could be an optimal amount of PA - the point at which risks are lowest and benefits greatest - but the thresholds are not known and most likely unique to each individual and activity. The extent of benefit and risks of running must be determined prior to promoting participation.

2.9 Evidence for an Association Between Running and Knee OA

Despite the popularity of running, surprisingly few studies have looked at recreational running explicitly in relation to the risk of knee joint OA. The following section includes a systematic review of the evidence.

2.9.1 Methods

Three electronic databases were searched (MEDLINE via OvidSP, EMBASE via OvidSP, SPORTDiscus via EMSCOhost) in June 2019, using similar search strategies to those employed in previous reviews (Timmins et al, 2017; Alentorn-Geli et al, 2017). Search strategies are included in Appendix 1. Searches were limited to literature in the English language and to those published before December 2019. Grey literature and abstracts were excluded.

2.9.1.1 Study Selection

To identify relevant literature, each reference was assessed against a pre-determined inclusion and exclusion criteria (Table 3) in two phases; the first, an assessment of title and abstract, the second, a full-text article review.

Factors	Inclusion Criteria
Reference type	Must be a journal article; cohort (retrospective or longitudinal), retrospective cohorts, case-control studies, nested case-control studies, randomised control trials
Population	Study includes human adult subjects (>16 years of age)
Exposure	Study reports running, or another sport with a predominant element of running where it is indicative of performance (for example, fell-running, triathlon, orienteering). Includes running at all levels of participation, regardless of definition of jogging and/or running in any location (e.g. treadmill). Running must be measured prospectively or retrospectively to the outcome. Running participation must be quantified, and greater than 12 months prior to the measurement of knee pain/OA. Runners are identifiable and grouped together in any relevant analyses.
Comparator	A comparison group (e.g. non-runners or physically inactive individuals), runners stratified by different levels of exposure or intensity, duration, level of participation, location or different running types)
Outcome	Prevalence or incidence of knee OA - Self-report diagnosis - Physician-reported or cases identified with health records - Radiographically diagnosed (e.g. using the KL) - Symptomatic Radiographic markers of knee OA - Radiographic rating scale used to assess knee (e.g. using the KL) - Presence or number of knee joint osteophytes - Knee joint space narrowing Knee joint replacement / arthroplasty - Self-reported/medical record cases of knee arthroplasty or on waiting list for the procedure - Self-reported recommendation of knee arthroplasty Knee Pain - Self-reported chronic knee pain (any definition of 'chronic', as measured in original study) - Knee pain as indicated by questionnaire rating tool (e.g. WOMAC) Knee-associated disability - Scale or score outcome, from tools used to assess disability/function (e.g. KOOS) General disability indices, not specific to the knee (e.g. HAQ)

Table 3: Inclusion Criteria

This search was conducted to capture the broadest definitions of running (e.g. including jogging) across various distances (e.g. marathon) and sports that involve running predominantly as part of performance (e.g. triathlon and orienteering). As discussed in previous section 2.3, OA can be defined using various methods and this search incorporates several outcomes accordingly.

2.9.1.2 Data Extraction and Synthesis

The Newcastle-Ottawa scale (NOS) was used to assess the risk of bias in included studies. This tool contains three dimensions - selection, comparability and outcome (for cohort studies) or exposure (case-control studies) (Stang, 2010). The NOS has been widely used in cohort and case control studies and thus identified as the most appropriate tool for this purpose, given the expected literature that would be identified. Previous knee injury was considered the most important covariate. This is because of previous evidence consistently highlights previous injury as a risk factor for OA (Roos et al, 2005).

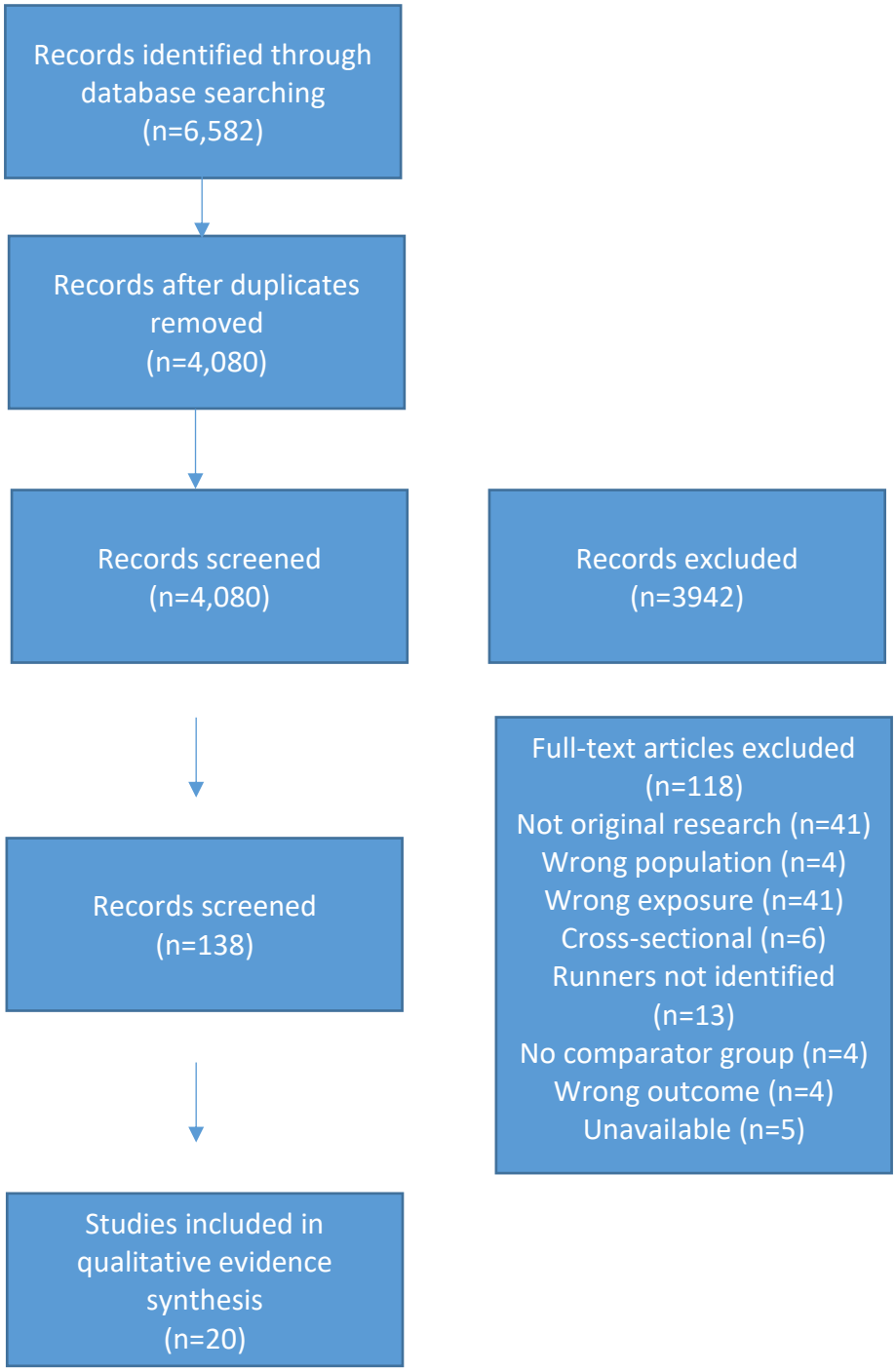


Figure 9: Data Flowchart

The results of papers included in this review which identified an association between running and knee OA and associated outcomes are included in Table 4 below. Several papers describe the same study, so these are grouped.

Reference	Study Type	Type of Running	Running Level	Length of Follow-up (years)	Number of Participants	Exposure Definition and Demographics	Non-Exposed Sample and Demographics	Running Definition
Chakravarty et al (2008)	Prospective cohort	Running	Not reported	18	98	Club runners M 56% MA 57.5 n 45	Stanford Lipid Research Study. Age, occupation and education matched M 56% MA 57.7 n 53	Club membership or self-report current runner
Lane et al (1986)								
Lane et al (1990)								
Lane et al (1993)								
Lane et al (1998)								
Panush et al (1986)	Ambispective cohort	Running	Not reported	5 retrospective; 8 prospective	35	Unclear recruitment method M 100% MA 56 n 17	Unclear recruitment method M 100% MA 61 n 46	Run ≥32km/wk for ≥5 years
Panush et al (1995)								
Konradsen, Hansen & Sondergaard (1990)	Retrospective cohort	Orienteering	Competitive and elite	Approximately 35-40	60	County team members (1950-1955) M 100% MA 71.3 n 46	Sedentary hospital patients; age, height, weight and occupation matched M 100% n 30	County team members (1950-1955)

Table 4: Included Studies

Reference	Study Type	Type of Running	Running Level	Length of Follow-up (years)	Number of Participants	Exposure Definition and Demographics	Non-Exposed Sample and Demographics	Running Definition
Kettunen et al (1994)	Ambispective cohort	Long distance running	Competitive and elite	Approximately 28-72 (retrospective) 3 prospective	117 / 1911	International event competitors 1920-1965 M 100% MA 59.7 n 28 / 199	Public archives; age and geography matched M 100% n 1712 International event competitors 1920-1965 (football, weightlifting and shooting) M 100% MA 56.5-61 n 89	International event competitors 1920-1965
Kettunen et al (1999)								
Kujala et al (1994)								
Kujala et al (1995)								
Kujala et al (1999)								
Raty et al (1997)								
Spector et al (1996)	Retrospective cohort	Middle and long distance running	Competitive or elite	Approximately 20-46	1044 / 282	National / international event athletes (1950-1979) M 0% MA 52.3% n 67	Chingford cohort or twin study	National / international competition representative (1950-1979)
Kujala et al (1999)	Prospective cohort	Orienteering	Competitive or elite	11	529	Orienteer ranking records (1984). M 100% MA 48.6 n 300	Public archives (excluding smokers, obese, heart disease and OA) M 100% MA 60.3 n 229	National orienteering rankings from 1984

Table 4: Included Studies cont.

Reference	Study Type	Type of Running	Running Level	Length of Follow-up (years)	Number of Participants	Exposure Definition and Demographics	Non-Exposed Sample and Demographics	Running Definition
Thelin et al (2006)	Case-control	Orienteering	Not reported	n/a	1473	Diagnosis of TFJ OA (Ahlback Scale Grade ≥3, or knee surgery or moderate cartilage reduction or JSN less than 3mm. M 43.2%, MA 62.6 n 778	Population register; age, gender and municipality matched M 42.2% MA 62.6 n 695	Self-reported regular orienteering; ≥1 year since aged 16
Felson et al (2007)	Prospective cohort	Jogging or running	Not reported	8.75	1279	Framingham Offspring cohort subjects, report jogging or running M 44% MA 53.2 n 1279	Framingham Offspring cohort subjects, no report of jogging or running M 44%, MA 53.2 n 1279 (same sample)	Self-reported history of jogging or running
Mosher et al (2010)	Retrospective cohort	Long distance running	Not reported	≥5yr	37	Club marathon runners M 59%, MA 25.7 and 52.6 (two groups) n 22	Community controls (not run in last 5 years) M 40, MA 28.4 and 54 (two groups) n 15	Self-reported marathon runners; Mean ≥10 miles/week over last 5 years
Lo et al (2017)	Retrospective cohort	Jogging or running	Not reported	≥1 year	2637	Osteoarthritis Initiative subject; self reported runners before age 50. Top 3 activities in one or more age period in life M 44.2%, MA 64.3 n 443-445	Osteoarthritis Initiative subject; never reported running as one of top 3 activities in life. M 44.2% MA 64.3 n 1859	Self-reported history of running as one of top 3 activities during a decade of life before age 50

Table 4: Included Studies; Abbreviations: M = male, MA = mean age. Some *n* refer to different analyses

2.9.3 Narrative Synthesis

Most of the 20 papers were cohort studies and contained a retrospective element. All the studies were based in the USA or Europe. There was a range of sample sizes (range 35 - 2637). Some studies only included male participants, whilst one only included females. There was also a variance in the level of athlete, as some studies only included elite performers, whilst in others it was not defined. Mean age of outcome was generally in the fifth and sixth decade of life. Most studies were reliant on self-reported running, whilst others used records from team representation or rankings as a proxy for higher performance level. In cohort studies, the duration of follow-up ranged from >1 year to over 40 years.

Running and Diagnosis of Knee OA

Panush et al (1986), Konradsen et al (1990), Kujala et al (1999) and Felson et al (2007) found no statistically significant difference between controls and runners for knee OA. Prevalence of knee OA was higher in elite runners compared with community controls, but no statistical comparison was performed (Kujala et al, 1994) (Table 5). Lo et al (2007) identified non-significant confidence intervals for OR values between prior runners and never runners (Table 5). The number of subjects used in the comparisons varied, and cohorts that included smaller numbers of participants are likely to be unrepresentative of the populations from which they are derived (for example. Panush et al, 1986). Two larger cohorts presented non-significant differences

between runners and controls, whilst another cohort of elite male orienteers found significant OR for knee OA (Konradsen et al, 1990; Kujala et al, 1999).

Reference	Comparison (n)	Outcome	Results	NOS Risk of Bias			Knee Injury Accounted For
				Selection	Comparability	Outcome	
Panush et al (1986)	Male runners (12); unspecified controls (10)	Ahlback grade ≥1	0/12 runners, 2/10 controls. NS (statistical methods not recorded)	*		**	No
Kujala et al (1994)	Male elite runners (163); community controls (1403)	ICD code (hospital records)	2.5% (0.7-6.3%) of runners; 1.3% (0.8-2% controls). No statistical analyses	***	*	*	No
Kujala (1994)	Male elite runners (28); elite sportsmen (89)	KL Grade ≥ 2	4/28 runners No statistical analyses vs other sports.	***	*	**	Not recorded
Konradsen et al (1990)	Male elite orienteers (27); hospital patients (27)	Ahlback radiograph	Grade 1: 31/54 runners; 27/54 controls. Grade 2: 0/54 runners knees; 0/54 control knees. Grade 3: 4/54 runners; 0/54 control. MWU Test: Not statistically significant	**	**	**	Not recorded
Kujala et al (1999)	Male elite orienteers (264); community controls (179)	Self-report OA	Runners vs Controls OR 1.79 (1.10-3.54)	***	**	**	No
Felson et al (2007)	Runners (68); non-runners	KL Grade ≥ 2 and symptoms (pain, aching stiffness on most days)	Runners vs controls OR 1.00 (0.27-3.68)	****	**	***	Yes
Lo et al (2017)	Previous runners (443-445); never runners (1859)	ROA: KL Grade ≥ 2; SOA: KL Grade ≥ 2 and symptoms	ROA: Prior runners vs non-runners OR 0.98 (0.78-1.25) SOA: Prior runners vs non-runners OR 0.88 (0.67-1.14)	***	**	**	Yes

Table 5: Running and Diagnosis of Knee OA

Running and Specific Markers of Knee OA Identified with Imaging

A variety of different structures were explored, with osteophytes the most common (Table 6). Only Lane et al (1986) identified a statistically significant difference between runners and controls, where the mean sclerosis score in female athletes was greater than controls at baseline. Other authors separated their analyses into individual knee compartments, but these did not reveal statistically significant results (Panush et al, 1986). Whilst most papers used radiograph, Mosher (2010) reported cartilage thickness before and after a 30-minute run. The only significant finding reported was pre-running femoral cartilage thickness amongst older runners only. There was no difference in cartilage response to running between the runners and controls.

Reference	Marker	Comparison (n)	Outcome	Results	NOS Risk of Bias			Knee Injury Accounted For
					Selection	Comparability	Outcome	
Lane et al (1986)	Osteophytes	Club runner (28); unspecified controls (10)	Sum of spurs (0-3)	Runners: mean score 1.24; control 1.13. Score for change: Runners: 0.8; control 0.67. Not statistically significant (t test)	**	*	***	No
Panush et al (1986)	Osteophytes	Male runners (12); unspecified controls (10)	Number of osteophytes	Runners: mean 0.4 (range 1.4); controls mean 1.3 (range 4.1). Not statistically significant	*		**	No
Konradsen et al (1990)	Osteophytes	Male elite orienteers (27); hospital patients (27)	Number of osteophytes	Runners: median 1 (0-3); controls 1 (range 0-5) Not statistically significant	**	**	**	Not recorded
Kujala et al (1994)	Osteophytes	Male elite runners (28); other elite sportsmen (89)	Osteophytes graded ≥2 on 0-3 scale	Runners 4/28, shooters 1/29, football 9/31, weightlifters 10/29 Not statistically significant	***	*	**	Not recorded
Spector et al (1996)	Osteophytes	Female elite runners (67); controls (977) Female elite runners (67); elite tennis players (14)	Osteophytes graded ≥2 on 0-3 scale	Runners 13/67 TFJ osteophytes and 30/67 have PFJ osteophytes; Controls 145/977 TFJ osteophytes and 6-/215 have PFJ osteophytes No statistical comparison	**	**	**	No
Lane et al (1986)	Sclerosis	Club runners (41); community controls (41)	Sum of baseline sclerosis rating, scale (0-3)	Females: Runners mean 6.7; controls 5.1 ($p<0.05$ t test) Males: Runners mean 5.5; controls 5.5 (not statistically significant)	*	*	*	No
Panush et al (1986)	Cartilage	Club runners (12); unspecified controls (12)	Thickness of cartilage in both knees (mm)	Runners: medial mean 5.18 (+/- 0.71) lateral mean 6.58 (+/-1.06) Controls: medial mean 4.94 (+/- 1.12) lateral mean 5.85 (+/- 1.08) Not statistically significant	*		**	No

Table 6: Running and Specific Markers of Knee OA Identified with Imaging

Reference	Marker	Comparison (n)	Outcome	Results	NOS Risk of Bias			Knee Injury Accounted For
					Selection	Comparability	Outcome	
Konradsen et al (1990)	Cartilage	Male elite orienteers (27); hospital patients (27)	Thickness of cartilage in both knees (mm)	Runners: medial median 4, lateral median 5 Controls: medial median 4 lateral median 5 Not statistically significant	**	**	**	Not recorded
Lane et al (1986)	Joint space	Club runners (28); community controls (27)	Joint space narrowing score	Runners mean 1.12 (0.22); Controls mean 1.32 (0.24)	**	*	***	No
Lane et al (1986)	Total knee score	Club runners (28); community controls (27) Club runners (45); community controls (53)	Sum of osteophytes, JSN, sclerosis, cysts or erosions (0-66 scale)	Total knee score not associated with pace per mile (0.27, 0.15) p = 0.88 Running not associated with total knee score (0.72 - 1.64-3.08). Not statistically significant	**	*	***	First analysis: No Second Analysis: Yes
Mosher et al (2010)	Cartilage thickness	Club marathon runners; community controls	Thickness of femoral and tibial cartilage (mm), before and after running for 30 mins	Greater cartilage thickness in runners. Not statistically significant, expect in participants aged over 45, femoral cartilage pre-running only (p value not reported). No difference between runners and controls for acute response in knee to running (p value not reported)	***	*	**	Yes (participants excluded)

Table 6: Running and Specific Markers of Knee OA Identified with Imaging cont.

Running and Arthroplasty for Knee OA

No papers were identified regarding risk of joint arthroplasty (a surrogate of severe knee OA) and running.

Running and Knee Pain

Four papers were identified although in two there was no statistical comparisons. In the papers by Kujala et al (1999) and Lo et al (2017), there were non-significant OR's between elite male orienteers and prior runners respectively (Table 7).

Reference	Comparison (n)	Outcome	Results	NOS Risk of Bias			Knee Injury Accounted For
				Selection	Comparability	Outcome	
Panush et al (1986)	Male runners (12); controls (10)	Unspecified	Runners 0/12, Controls 0/19. No statistical comparison	*		**	No
Kujala et al (1994)	Male elite runners (28); other elite sportsmen (89)	Knee pain reported monthly or more for previous 12 months	Runners 6/28, 5/29 shooters, 14/31 football players, 8/29 weightlifters reported pain. No statistical comparison.	***	*	**	No
Kujala et al (1999)	Male elite orienteers (264); community controls (179)	Weekly or more knee pain for previous 12 months	Runners OR 1.75 (0.96-3.18) compared to controls. Not statistically significant	***	**	**	No
Lo et al (2017)	Previous runners (445); never runners (1859)	Pain, aching or stiffness in or around knee on most days for at least one month	Prior runners 36.6%: OR 0.82 (0.65-1.04); Controls 41.1%: Referent value Not statistically significant	***	**	**	Yes

Table 7: Running and Knee Pain

Running and Knee Disability

Two papers reported disability in runners and non-runners, but Kujala et al (1999) was the single paper with a statistical comparison between the two groups. This revealed a non-significant difference between male elite orienteers and controls (Table 8).

Reference	Comparison (n)	Outcome	Results	NOS Risk of Bias			Knee Injury Accounted For
				Selection	Comparability	Outcome	
Kujala et al (1994)	Male elite runners (71); community controls (460)	Score >3 assessed on 7-point scale, assessing 7 different activities	Disability reported in 5/71 runners and 59/460 controls. No statistical comparison	***	*	**	No
Kujala et al (1999)	Male elite orienteers (264); community controls (179)	1) Score >1 on 5-point scale, assessing 5 activities 2) Knee pain when using stairs	1) Runners OR 0.69 (0.39-1.21) vs controls. Not statistically significant 2) Runners OR 0.78 (0.43-1.41) vs controls. Not statistically significant	***	**	**	No

Table 8: Running and Knee Disability

2.9.4 Evidence Discussion

The evidence presented here uses a broad range of running exposure definitions and a variety of outcome measures indicative of, or related to, knee OA. The current evidence is insufficient to identify an association between running and knee OA.

Two of the larger, and higher quality studies revealed no significant differences for diagnosis of knee OA and running status (Felson et al, 2007; Lo et al, 2017). Only two papers reported a formal statistical comparison between runners and non-runners for knee pain and neither presented statistically significant results. Most studies in this systematic review were generally of low quality, with the NOS identifying risk of bias. Much of the current data is from case control studies, therefore the cause-effect cannot be interpreted and subject to recall inaccuracies of critical exposures and outcomes where self-reported (e.g. running behaviours). Identifying objectively measured running behaviours, for example using technology, would provide greater accuracy. Many of the studies also failed to account for previous injury, which has consistently been shown to be a significant risk factor for knee OA (Roos et al, 2005).

There was a lack of consensus for how runners and running behaviours were identified and reported. In most studies, this was self-reported, but this may be inaccurately reported (Ainsworth et al, 2015). This review of the evidence was intentionally broad to include as many types of running as possible. Evidence for specific running-based activities (i.e. orienteering and track running) is sparse, but different types of running may not relate to knee OA in a consistent way, although this is conjecture at this point. For example, the environmental effects of different surfaces and terrain may alter the impact of injury and knee OA.

Furthermore, the level of the athlete is also important to recognise. Professional or elite runners are not the same as recreational athletes and unspecified confounding factors within both groups may influence risk of OA. These may relate directly to running (e.g. tolerance to training) or other lifestyle factors (e.g. diet). A systematic review by Driban et al (2017) reports that there is a significant risk associated with elite, male long-distance running and knee OA (Crude OR 3.25; 1.40-7.53). This review only included two papers which identified just eight cases of OA in 191 runners. Furthermore, it appears that both papers included in this review are from the same cohort, thus participants may have been included twice in the analysis. As previously discussed, the limitations of using different OA diagnosis methods are clear (section 2.3.1).

Most literature identifies the impact of injury as more detrimental than any risk attributed to participation in sport itself (Vignon et al, 2006). It is therefore possible that, in the absence of injury, running has a different effect than when previous injury is present. Few of the current papers considered injury (Felson; Lo et al, 2017). Lo et al (2017) reported the prevalence of prior knee injury (53% in runners and 47% in non-runners) and controlled for this in their adjusted odds ratio. Neither paper reports specific details for what knee injuries were sustained (i.e. diagnosis or treatment). This analysis assumes that all knee injuries, regardless of type, age of incident, or severity, all have an equivalent impact in this population, but this may not be true.

PA and exercise are key treatment modalities for patients with knee OA (Fransen & McConnell, 2008). Conversely, PA has come under scrutiny regarding its potential role in knee OA onset. Conflicting evidence has been presented which shows PA has a detrimental effect (Spector et al, 1996) and beneficial effect (Racunica et al, 2007). Few papers in the current review identified specific responses to knee joint structures to running. A systematic review by Urquhart et al (2011) suggests that general PA does not have a uniform effect within the joint. For example, in their best-evidence synthesis, the authors concluded there is strong evidence for a positive relationship between osteophytes and PA; strong evidence of no relationship between JSN and PA; strong evidence for a positive relationship between cartilage volume and PA and strong evidence for an inverse relationship between cartilage defects and PA. These findings suggest that future studies should not solely focus on individual radiographic markers of OA (e.g. osteophytes) as they may be misinterpreted as a sign of arthritic disease, when in fact they are a normal response. Data presented in the current review shows that osteophytes were the most common radiographic marker under investigation. These results should be reviewed with caution (as should results using KL radiographic grading, since it is reliant on osteophyte identification), as instead of a marker of OA, osteophytes may be a functional adaptation to exercise and protect against disease (section 2.4).

Other systematic reviews have been conducted relating to types of PA, sports and exercise and reported similar observations and conclusions in relation to

running. Tran et al (2016) published a systematic review assessing the relationship between each of the 32 most popular participation sports in England and OA. Long distance running was the second most common studied sport (12 cohorts) accounting for 26.1% of studies included. Only two (16.6%) academic papers reported increased risk of OA associated with long distance running, whereas the remaining ten did not. They reported different risk ratios for elite (RR 0.99) and non-elite (RR 0.79), concluding future research should be conducted in recreational cohorts as results from one group may not be generalisable to the other.

Alentorn-Geli et al (2017) reported the prevalence of hip and/or knee OA in recreational runners (3.5%) was lower than competitive runners (13.5%) and controls (10.2%). This paper also identified different OR for recreational (OR 0.83) compared to competitive athletes (OR 1.16). The research that forms the conclusions from these systematic reviews is limited in several ways but most of the studies confirmed no significant findings suggestive of a link between running and knee OA. The overall sample size from these studies is relatively small, arguably underpowered to provide a meaningful result, from which to make clinical recommendations for the millions of runners around the world, given the substantial individual differences within this population.

Miller (2017) presented two hypotheses why the loads involved in running do not contribute to increased risk of OA compared with walking. The first, is that whilst the peak load per stride is significantly greater in running than walking

(approximately 8x BW for running and 3x BW for walking), the cumulative load is actually very similar and not statistically different when the same distance is covered. Running involves shorter duration of foot-to-floor contact time compared to walking (Miller et al, 2014). As a result, the high peak load is short in duration when running, whereas in walking, the peak load is lower but lasts longer. The second hypothesis suggests running conditions cartilage which becomes tolerant of the forces involved. Therefore, if the forces applied are appropriate and there is enough rest between running bouts, cartilage can cope with the forces involved. These theories have yet to be substantiated with observations from exposure to real-world running, that would supplement the evidence presented here.

This data synthesis has identified various sources which include a range of methods and definitions to report the exposure (running) and outcome (related to knee OA) of interest. Although the search criteria were relatively broad, the number of pertinent studies identified was relatively small. When analysed separately according to their outcome (e.g. pain), the quantity of evidence reduced further. There were gaps in evidence relating to surgical outcomes and running. Further prospective data in this area would be of great clinical value, as this relates to severe knee OA.

The NOS was used to evaluate bias in research. There is no widely accepted gold-standard tool for assessing data quality. Strengths of the NOS include how quick it is to perform, although some authors have criticised it as difficult to use

(Hartling et al, 2013). Oremus et al (2012) identified the inter-rater reliability of inexperienced assessors using the NOS. The test-retest reliability of the assessment was generally suboptimal (ICC 0.62; 0.25-0.83 for cohorts and ICC 0.83; 0.48-0.95 for case-controls), when systematic differences between raters were controlled for. It is suggested that there may have been some discrepancy in subjective elements that are reported upon as part of the assessment. This systematic review was performed by a single assessor, which may have introduced a greater degree of subjectivity when systematically identifying and evaluating the evidence. Furthermore, the experience of the author was limited in conducting systematic review, and this may have affected how the review was performed (Bonfield, Fearnside & Cramp, 2017). To support this research process, the search terms were developed with support from experienced library staff.

This systematic review was limited to English language papers. Other reviews have identified foreign language articles which may have been relevant to this search (Timmins et al, 2017). It is possible that this may introduce a degree of bias into this evidence evaluation. This should not be overlooked when the results are considered. Furthermore, the initial screening method (i.e. title and abstract) may not have revealed all papers where runners were identified separately in the analyses. This may mean that other papers have been inadvertently missed.

Evidence for the effect of running on progression of knee OA was not fully explored in the search strategy. A recent study identified running status in those with established knee OA (n=138 runners) (Lo et al, 2018). It confirmed the findings of an earlier paper assessing progression of knee OA in runners where running was not associated with increased worsening of knee pain or structural progression of OA (Lane et al (1998). Greater understanding of the effects of running on established knee OA would be beneficial, as the risk factors for onset and progression of the disease related to running may not be the same.

2.9.5 Summary

OA is the most common joint disorder and the greatest contributor to disability in the elderly, with the knee commonly affected. Prevention of OA has become an increasingly important focus because there is no cure. With the population becoming older, and obesity levels rising, the current (and future) prevalence of OA should not be underestimated.

It is important to understand the effects of participation in running on the knee joint given its popularity. Currently, there is insufficient evidence to identify whether running elevates the risk of knee OA. Running places forces equivalent to multiple times body weight through the lower limb joints. The physiological responses to joint loading are considered one of the key potential drivers for the condition, but paradoxically, could provide a stimulus that promotes joint health and protects against OA. Additional direct and indirect mechanisms

associated with running, such as injury and altered BMI, could also affect risk of knee OA.

The mechanisms and risk factors outlined in previous sections could lead to hypotheses that running has either a positive or negative effect on joint health and the overall risk of OA being increased or reduced as a result of participation (Table 9).

Factor	Risk of OA Increased by Running	Risk of OA Decreased by Running
Body weight	Running involves high forces. Running when at a high body weight puts a high force through the joint	Running can contribute to obtaining and maintaining a lower body weight thus reducing forces through the joint and affecting systematic factors
Injury	Running may cause, or contribute to, knee injury. Running after injury may not be tolerated and accelerate OA progression	Compared to other sports, running is a low-risk activity. Running could positively influence muscle strength and contribute towards appropriate loading of healing structures
Joint Loading / Mechanics	Inappropriate loading disrupts the internal homeostasis; inducing sub-acute (pre-OA) symptoms/structural changes that develop into OA with continued loading or results in injury	Running stimulates joint health adaptations that have a positive effect on structures within the knee

Table 9: Summary of Hypothesised Mechanisms Risk and Benefits of Running and OA

Ultimately, the complexity of the condition means that it is multifactorial and interactions between individual factors could combine to explain risk of OA

onset. It is therefore important to identify each of the factors listed above separately in the analyses presented in this thesis.

2.10 Study Rationale

Evidence-based medicine (EBM), has become a foundation of healthcare.

EBM is defined as:

> *'…the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research'*
>
> Sackett, 1996, p. 71

Evidence is vital for ensuring that the most efficacious interventions are used to 'maximise the quality and quantity of life for individual patients' (Sackett et al, 1996, p. 72). This has led to the development of guidelines for methodological and publication standards for research upon which evidence is based. The development of clinical guidelines for specific diseases and conditions, for example those created and maintained by NICE, is dependent on continued production, appraisal and interpretation of research. The strength of recommendations can then be judged (Hill, Bulluck & Alderson, 2011). The identification of clinical areas which require further research is often based on analysis of what is already known (for example through systematic

reviews), but to do so requires an understanding of the strengths and limitations of each study.

Research is the most effective method of confronting OA and decreasing its impact. Despite considerable progress over recent decades much remains unknown regarding the pathology, causes, prevention and management of OA - especially relating to knee OA and running. Given that running is so popular and exploration of the risk factors and mechanisms by which OA progresses remains incomplete, further evidence is needed. Large cohorts of recreational athletes are needed to identify the long-term effects of running on knee joint health and strengthen the interpretation of previous research. Further data is required to enhance clinical decision making to advise recreational runners regarding the risks and benefits of participation in the presence and absence of OA (Roberts, 2018). This is important to assist promotion of an active lifestyle in potential and current runners. This study aims to enhance understanding of recreational running and how it relates to knee joint function, symptoms and OA. Specifically, the present literature review and systematic appraisal of the evidence has identified the need for several areas of research to be explored in greater detail:

1. Defining Exposure

   The evidence described included varied definitions of running exposure. Running is often self-reported, thus validation of methods used to identify detailed running behaviours would strengthen this methodology.

2. Defining Cases

   A variety of knee OA outcomes are required in order to capture the full continuum of disease. This should involve presence/absence of knee pain, other symptoms, function, radiological/imaging assessment, healthcare professional diagnosis and joint replacement. Excluding any of the criteria above may bias the results, since the threshold for defining cases may be skewed. Markers associated with knee OA, such as function and symptoms can also be reported using self-report questionnaires. This may provide insight in runners without a diagnosis of knee OA (e.g. KOOS) that would otherwise be missed if the threshold for disease is set too high (i.e. radiographic evidence of OA).

3. Recreational Populations

   The evidence from the systematic review was based on cohorts of relatively small cohorts of recreational runners, whilst other papers focussed on elite populations. Generalising the results from different running populations may not be optimal. Larger populations of runners of all ages are required to support the results of these cohorts. In addition, it may be beneficial to introduce athletes from more than one country to enhance the external validity.

3.0 Methods

3.1 Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Guidelines

The methodology below is outlined in accordance with the recommendations of the STROBE guidelines (Elm et al, 2007). These aim to strengthen the transparency in methodological reporting to strengthen confidence in results (Vandenbroucke et al, 2007). Each criterion of the guidelines is listed separately using a distinct section heading.

Approval was obtained from the Faculty of Medicine and Health Sciences Research Ethics Committee (University of Nottingham) (G14072015) and the University of Sydney (2015/839). Additionally, the parkrun research board provided approval for recruitment at their events.

3.2 Study Design

This was a prospective observational study which took place between September 2015 and September 2017.

3.2.1 The Evidence Pyramid

Proponents of EBM often refer to systems that rank grades of research used to inform clinical practice. This is based upon the purported quality of evidence produced from each study design. The pyramid generally presents the 'gold standard' of research design as randomised-controlled trials (RCTs) at the apex,

with the lowest ranking of evidence (expert opinion) at the base (Murad et al, 2016). The presentation of hierarchical levels represents the supposition that experimental methods at one level are superior to those below and inferior to those above. Given that observational studies are regarded as inferior to other research methods, justification for the use of an observational study design and why an alternative was not used is warranted. Double-blinded RCTs are generally accepted as the gold standard since there can be no bias (deliberate or subconscious) nor prejudicial analysis of the outcome (Kaptchuk, 2001), but their undertaking can be challenging. Some authors argue that RCTs are not always the gold-standard in every research scenario since they can be inappropriate, unnecessary, impossible to conduct or inadequate in answering the question at hand. Limitations of RCTs can emanate from the nature of the method (limited principles) or how it is conducted (limited procedures) (Sanson-Fisher et al, 2007). There are many difficulties of conducting an RCT exploring running and risk of knee OA. Some examples are described below:

- A placebo for one experimental group in place of running is impossible to create. Participants would therefore be aware of which group they were in, removing an essential element of the blinding procedure.
- The ethics of prescribing running, over the duration (many years) required to observe onset and progression of OA, especially if symptoms develop, is difficult to implement and justify.
- The sample size required would be discouragingly large based on the assumption that the running cohort would have low adherence to a defined running programme. This would elevate attrition rates and introduce the

possibility that those that continue to run differ somehow from those that stop (e.g. motivation).

- The resources for researchers and burden on participants to monitor performance of either intervention would be vast (i.e. contemporaneously reporting running, ensuring adherence to stipulated levels of running).

Given the above examples, it could be argued that it is too simplistic to consider RCTs as the gold standard of research to address the present research aims. On the other hand, observational epidemiology has contributed immensely towards our understanding of the cause and treatment of disease and ultimately changed policy or development of effective treatments.

The benefits and limitations of the observational studies are outlined below (Table 10):

Benefits of Cohort Study Design	Limitations of Cohort Study Design
Can provide an estimate of prevalence. Non-diseased individuals can be reviewed for the development of an outcome. Progression can be assessed in those with established disease (i.e. worsening symptoms) Multiple outcomes and exposures can be analysed simultaneously	Large populations require logistical, administrative and financial support Attrition of the sample at follow-up, especially in chronic disease when prolonged periods of assessment are necessary Maintenance of standardised methodology can be difficult, for example as techniques evolve and technology improves
Benefits of Cross-Sectional Study Design	**Limitations of Cross-Sectional Study Design**
Relatively easy to perform Lower participant burden	Inability to identify causal relationships as both exposure and disease are reported at the same point in time

Table 10: Benefits and Limitations of Study Designs

Cohort studies can involve retrospective, ambispective or prospective data collection. In the present study, the cross-sectional analysis is designed to describe the population of runners, including the presence of risk factors and outcomes of interest at the time when recruitment occurs. As it is conducted at a single time point, it is not able to infer causality (Levin, 2006). The prospective study will look at 12-month incidence and progression of markers of knee joint health e.g. pain.

3.3 Setting

The study was population-based with participants recruited from the UK and Australia. By recruiting recreational athletes from two countries where running is popular, it was hoped this would introduce international variance and strengthen the external validity of conclusions drawn. Previous studies have only included runners from one country and focussed on the USA or Europe (Timmins et al, 2017).

The functional testing was conducted at Queens Medical Centre, Nottingham, the National Centre for Sports and Exercise Medicine, Loughborough, and Royal North Shore Hospital, Sydney. This convenience sampling was enforced due to limited access and availability to facilities that would enable testing to occur. This made it a fast and easy way to identify appropriate participants, although it may have introduced bias due to under- or over-representation of characteristics within the larger population (e.g. age, ethnicity).

The validation of the questionnaire data was limited to UK-respondents. This was for ease of data-transfer and bilateral communication as it was anticipated that some participants would submit paper-based running records by post.

3.4 Participants

The current study used a cohort of recreational runners and non-runners. Running status was self-reported (explained in further detail in Section 3.5.2). To achieve the aims of the study, it was necessary that a variety of runners (for

example, wide range of frequency of participation) is involved. Using a broad definition of ‘runner’ ensured that a comprehensive spectrum of runners were included in the cohort.

The runners were primarily recruited from parkrun, an organisation that provides free 5km running events, and/or other recreational running clubs and events. parkrun have been one of the most successful event organisers since it began in 2004 with substantial increases in both the number of runners and event locations across the UK (parkrun, 2018) (Figure 10). Initially limited to the UK, it now promotes free 5km events in over 20 countries. Their ethos of inclusivity means that it is a likely destination for those that complete programmes such as the ‘Couch to 5k’, but it is completed by athletes of all running performance levels and ages.

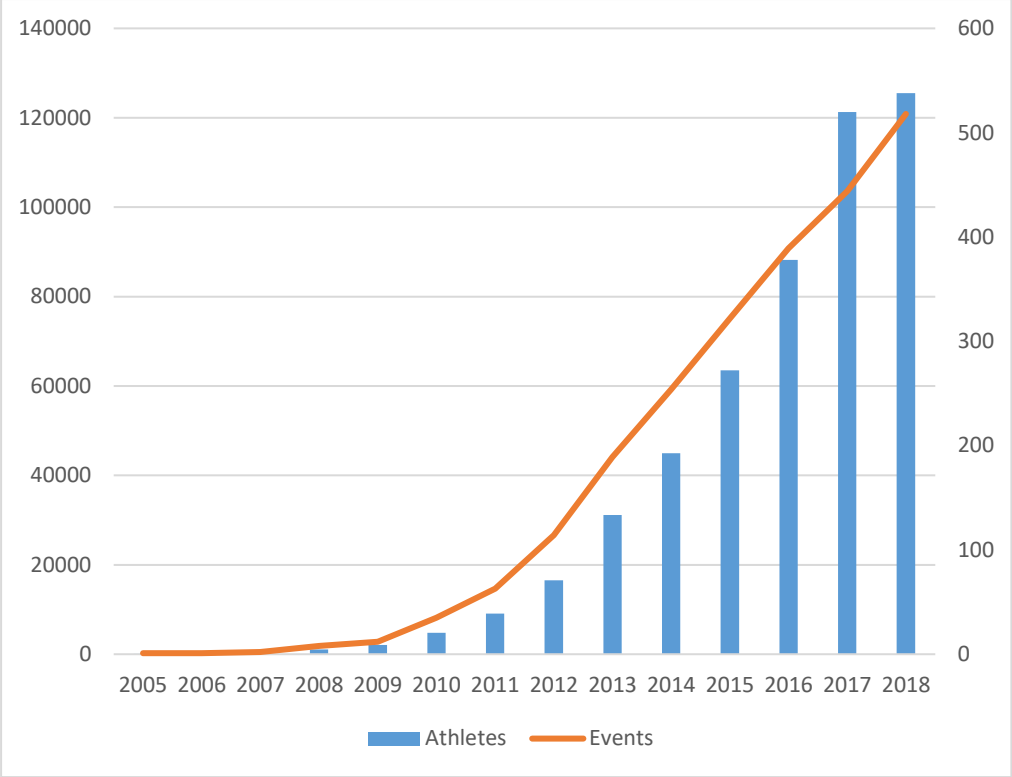


Figure 10: Number of parkrun Athletes and Events in the UK (parkrun, 2018)

Since all parkrun events are the same distance (5km), other running events and running clubs were contacted to ensure that runners that complete other events (from 5km to marathon and ultra-marathons) could take part. Running, triathlon and orienteering events and clubs were also approached for potential participants. Running is a key component of other endurance sports and it directly influences performance outcomes. Running, jogging, triathlon and orienteering were used as exposure criteria for running in a systematic review exploring the running and knee OA (section 2.9). Runners were not expected (or requested) to change any lifestyle factors (such as running) during participation. It was anticipated that changes in running that occurred would be captured in the questionnaire.

Non-runners were recruited to enable comparison of outcomes (e.g. knee pain) between runners and non-runners. Non-runners in clubs (e.g. musical societies in the local geographical area close to Nottingham) were also encouraged to take part. In addition, non-runners present at parkrun and other running clubs and races (i.e. volunteers and marshals that did not complete the event) that were also approached.

3.4.1 Inclusion Criteria

All runners and non-runners aged over 18 and able to provide consent (i.e. ability to communicate in English language) were eligible to take part in the questionnaires which comprised the self-report section of the study. Completion of the questionnaire was deemed consent. Participation was limited to people living in the UK and Australia. Any participants from other territories were excluded from the analysis and future study components.

Participants that completed Baseline Questionnaire 1 and indicated that they were willing to take part in further components of the study were eligible to take part in subsequent research components (e.g. Baseline Questionnaire 2, Functional Testing and Validation). The follow-up questionnaire was limited to UK-based respondents.

For the functional testing, participants that completed the baseline questionnaire, consented to further participation in the study and lived within an approximate radius of 20 miles of the assessment locations were invited to

take part in the present study. This was calculated based on the postcode provided by participants. Participants were asked to declare any comorbidity or recent injury which they felt would affect their ability to safely perform the tests in a pain-free manner.

The questionnaire validation analysis was limited to UK-based recreational runners. Participation was also limited to those runners that indicated they used a training diary, tool or aid to monitor their running training or performance in the questionnaire. The following binary question was used to identify such athletes (Figure 11):

Do you currently use any training diaries, tools, aids or other paper or electronic devices to monitor or record your training or performance? (e.g. GPS, smart phone app, training diary, heart rate monitoring, Nike+, fitbit, Garmin, pedometer, etc.)

Figure 11: Training diary question in baseline questionnaires

Limiting this analysis to subjects with a training diary made the collection of data convenient for participants, as the data required by the researcher was already in existence. It also correlated to the running reported in the questionnaire. Due to the sequencing of data collection (i.e. the questionnaire was completed before the training diary was requested), this also meant that runners could not alter their self-report running to match their diary data. On the other hand, this method of identifying eligible participants meant that the diary data was received by the researcher in many formats and required

significant manual manipulation. These all required significant researcher time to identify pertinent information and organise it for analyses.

3.4.2 Recruitment

Recruitment for Baseline Questionnaire 1 took place between September 2015 and December 2016. Strategies for recruitment varied between components of the study and which population was being approached. These are described for each study component below:

3.4.2.1 Baseline Questionnaire 1

<u>parkrun Recruitment</u>

The parkrun research board agreed to provide significant support to recruit athletes at their events. This involved:

- Including a 400-word article in the parkrun (UK and Australian) newsletter (with links to the questionnaires (Appendix 2), participant information sheet (Appendix 3)) and the researcher contact details (phone number and email address).
- Sharing the link to the survey or lay summary throughout the recruitment period via national and individual events social media (example social media content, Figure 26).
- Attendance at parkrun events by the researcher to discuss the project and distribute information leaflets (Figure 27). parkrun provided consent for attendance at nationwide events throughout 2016. This included sharing

social media on the event twitter and facebook sites. The researcher made every effort to attend a geographically diverse selection of events. For example, Edinburgh, Southampton, Norwich and Swansea were the furthest extremity events attended. Attendance figures at parkrun's were assessed to ensure that the distance travelled would facilitate optimal recruitment.

Distrust of researchers, discordance between lay beliefs and medical practice and demands of the trial (e.g. duration) are common barriers to participation in research (Booker, 2011). It was hoped that attendance at parkrun events would allow runners to learn more about the research by speaking to the researcher and allay any fears. Runners may have held a preconceived belief regarding the effects of running on their joints. This could have either increased or decreased their enthusiasm to take part depending on their view. By explaining the research more thoroughly, it was hoped that athletes would take part regardless of their view on whether running caused knee OA. Although this would be a time-consuming process, it was felt that attendance at events every week was appropriate use of resources to supplement other recruitment methods.

Office for National Statistics (2018) suggest that 90% of the British population have internet access. This data also shows the sharp growth in popularity of social media - almost two-thirds of adults have used these sites within the previous three months, up from under half in 2011. The use of social media

declines with age, for example only 27% of over 65-year olds use social media compared to 93% of 16-24-year olds. These observations are supported by the results of a systematic review which reported social media as the best recruitment method in 40% of medical-related studies and helpful in targeting younger populations (Topolovec-Vranic & Natarajan, 2016). The use of internet-based recruitment would also reduce the bias towards fit and active athletes that were at the events. Other runners have not been able to attend on that date (for example, other commitments, injury), but they may still see the social media advertisement. Furthermore, a strength of social media is that it can be user friendly and allow sharing of simple messages in a visual way (George, Rovniak & Kraschnewski, 2013). The social media was designed with this approach in mind (Figure 12). These were accompanied by links to further detail of the research project.

A participant information sheet (Appendix 3) was accessed through the front cover of the online questionnaire, or a paper version was supplied to those that wished to have a copy.



Figure 12: Sample recruitment tweet



Figure 13: Recruitment leaflet

Recruitment at Running, Triathlon and Orienteering Events and Clubs

A similar approach to that described above was used for recruitment at other running-related events and clubs:

- The literature (e.g. contact emails) was individually tailored to certain events and clubs as necessary (i.e. triathlete-specific information leaflet (Figure 13)).
- Emails sent to the secretary or other principal contact of running groups, clubs and events to ask for assistance in distributing information to any athletes that may be interested. Lists of running clubs were identified through the British Athletics website.
- Attendance at events by the researcher to present and discuss the project and distribute information leaflets.
- Placement of research information leaflets in the finisher's bags at events (e.g. 10km races, half marathons, marathons across the UK).



Figure 14: Triathlon recruitment leaflet

3.4.2.2 Baseline Questionnaire 2

All participants that fulfilled the inclusion criteria for the Baseline Questionnaire 1, indicated that they were willing to complete further aspects of the research and provided valid contact details (e.g. email address or postal address) were notified of this questionnaire (Figure 15).

To [name]/ID number,

We are contacting you as part of the Health of Adults Observational Study (HALO) Questionnaire. We greatly appreciate your involvement in the first questionnaire and would value your further input.

Please find attached a link to the second questionnaire that we would like you to complete. Some of the questions may not be relevant to you and these can be skipped. We anticipate that this questionnaire will take approximately 30 minutes to finish. Paper versions are also available, please contact us and we will send one out to you.

The questionnaire can be found here: [url]

This link also contains a 'participant information sheet' which provides further information about the questionnaire. If you have any questions, please do not hesitate to contact us (email: theHALOstudy@nottingham.ac.uk; phone: 0115 8231411).When completing the questionnaire, you will be asked to provide your unique participant identification number. Your number is: [ID number].

Please note that participation is entirely voluntary and you can complete as much or as little as you wish.

If we do not hear from you over the next few weeks, we will send a reminder about this questionnaire. If you do not wish to receive any further correspondence from the research team, then please let us know and we will update our records.

Thank you again for being a part of our research. We hope you remain a part of the team for many years to come.

Figure 15: Invite email for Baseline Questionnaire 2

3.4.2.3 Questionnaire Validation

To be eligible to complete this part of the research, participants had to satisfy several criteria:

1. Based in the UK (derived from postcode, reported in Baseline Questionnaire 1).
2. Self-defined as a current runner at time of completing Baseline Questionnaire 2, by responding 'Yes' to the question (Figure 16):

Do you run? By running we mean in its own right e.g. not running as part of other sports such as in football or tennis… (i.e. have run at least once in the last 12 months)

Figure 16: Question to identify runners from non-runners

3. Had completed Baseline Questionnaire 1 and Baseline Questionnaire 2. Participants had to have completed Baseline Questionnaire 2 because the question below (criteria number 4) was in there.
4. Responded positively when asked if they used a training diary (Figure 17).

Do you currently use any training diaries, tools, aids or other paper or electronic devices to monitor or record your training or performance? (e.g. GPS, smart phone app, training diary, heart rate monitoring, Nike+, fitbit, Garmin, pedometer, etc.)

Figure 17: Question to identify participants with training diary

5. Consented to take part in further aspects of the study

Participants were sent the following email for recruitment (Figure 18):

We are contacting you in relation to our ongoing research as part of the Health of Adults Observational (HALO) Study.

You have completed the first questionnaire and indicated that you would be happy to be contacted again regarding our research. We are extremely grateful that you have decided to take part in our work.

Please find below details of a further aspect of our research we wish to complete. Whilst we have already asked people to answer some questions about their physical activity (e.g. what they do and how often), we wish to collect more detailed physical activity information on a small group of people. You are being invited to take part in this. Full information about what is involved is in the attached Participant Information Sheet and/or you can phone or email one of the team for more information.

If you are interested in this aspect of our work, please respond to this email and we will provide details on how to proceed. Please note that there is no expectation that you will agree to take part. If we do not hear from you within 28 days, we will attempt to contact you once more. If you do not wish to receive any further correspondence from the research team regarding this aspect of our research, then please do not hesitate to contact us.

Thank you again for being a part of our research.

Best wishes

Figure 18: Invite for diary validation

3.4.2.4 Functional Testing

A sub-set of runners that completed Baseline Questionnaire 1 who consented to further participation in the study and lived within an approximate radius of 20 miles of Queens Medical Centre, Nottingham, the University of Loughborough or North Shore Hospital, Sydney, based on residential postcode, were invited to participate.

To be contacted, potential participants also had to have included an email address in their baseline questionnaire response. The following email was sent (Figure 19):

Dear _____

I am contacting you in relation to our on-going research as part of the Health of Adults Observational (HALO) Study. You have previously completed a questionnaire and indicated that you would be happy to be contacted again regarding our research. We are extremely grateful that you have decided to take part in our work. Please find below details of a further aspect of our research we wish to complete.

We seek to undertake physical assessments within a sample of respondents to our questionnaire. The purpose is to identify the function of individuals and review them over time. In addition to the data from your questionnaire, this will provide greater understanding of how your lifestyle affects your joints.

Briefly, these simple tests comprise of:
Mobility tests (walking, stairs)
Strength / power tests (hopping)
Balance (standing on one leg)
Knee joint movement (range and quality)
Limb (thigh and knee) circumference and position

People of all abilities, ages and levels of fitness can complete them. The tests will be conducted by a qualified physiotherapist and should take approximately one hour, inclusive of explanation and discussion.

The assessments are planned to take place at the University of Nottingham (QMC) and Loughborough University (*changed to Royal North Shore Hospital, Sydney for use in Australia*). Depending on your availability on certain dates, we will endeavour to arrange a location and time that suits you (*where applicable*).

We hope that you are able to assist us with this aspect of our research. Further details of the assessment and what is involved are included within the attached participant information sheet.

If you are interested in this aspect of our research, please respond to this email ensuring that you include the following information:

- Your preferred location for testing (*where applicable*)
- Your general availability (days of the week, times of day e.g. morning/afternoon) throughout July and August
- Your preferred method of communication (e.g. email / telephone). Please include contact details if different to the information we already hold

We will then contact you to discuss this research further and arrange your assessment.

If you have any questions, please do not hesitate to contact us.

Thank you again for being a part of our research.

Figure 19: Invitation for functional testing

If a positive response to this email was received, the authors then checked with the participant to confirm that they had not suffered a recent lower limb injury (i.e. one that had occurred since completion of the questionnaire) (Figure 20), or they did not have any other medical condition that would adversely affect test performance or result in them being unsafe during the tests. Information was then sent to ensure participants could attend safely (Figure 20).

Testing
The procedure is a series of very simple assessments which should take no more than an hour to complete. You will be asked to sign a consent form and I shall print a copy of the participant information sheet (previously provided in the invitation email) for you too.
I would just like to draw your attention to the following reasons that may prevent you from taking part:
• No injury that you feel prevents you from being able to undertake the tests in a pain free manner
• No recent surgery (for any reason) that would otherwise prevent full participation in normal physical and functional requirements
• No co-morbidities that alter balance such as any condition that causes dizziness or light-headedness

If you feel any of these are relevant, please let me know immediately, as the testing cannot be done safely under these circumstances.

It would be great if you could bring some comfortable shoes/trainers and clothing with you for the testing. Shorts would be particularly helpful as it makes accessing the knees a lot easier, but loose-fitting trousers that can be rolled up are fine if you would prefer.

Directions
The testing will take place in the National Centre for Sport and Exercise Medicine, Loughborough University.

You can access the site via the main entrance on Epinal Way and you should tell the Gatehouse that you are here for a research study and need to get to car park 9. If car park 9 is full then you can park in any other car park **except** patient parking at the back of the building. Also, please bear in mind that the students are starting to come back to campus and it does get quite busy for parking so allow time for this when planning your route.

I have attached a map of the University sites. The National Centre for Sport and Exercise Medicine is shown on the East Park (yellow map)
On entering the building, if you let reception know that you have arrived, then I will come and meet you. I will wear an orange Arthritis Research UK t-shirt so you know that its me.

Contact
I can be contacted via mobile 0********** and I will keep this with me in case of any issues. In addition to this email account (which I cannot check at home in the evenings or over weekends) I can be contacted anytime via msxrl5@nottingham.ac.uk (this is my personal university account and I will check it regularly) therefore if you have any problems you can contact me via that method too.

I look forward to meeting you soon.
Richard

Figure 20: Email for functional cohort test details

The participant information for functional testing is included as Appendix 4. A consent form for participation was completed prior to testing (Appendix 5). The design of the functional testing analysis was to compare the test performance of recreational runners to the OARSI normative values expressed within the test literature (Dobson et al, 2013) (Table 11). These tests are described in further detail later (Section 3.5.1.3).

Test	Age Range / Criteria	Average count for women	Average count for men
30-second Chair Stand Test (number of repetitions)	60-64	12 to 17	14 to 19
	65-69	11 to 16	12 to 18
	70-74	10 to 15	12 to 17
	75-79	10 to 15	11 to 17
	80-84	9 to 14	10 to 15
	85-89	8 to 13	8 to 14
	90-94	4 to 11	7 to 12
40m (4 x 10m) Fast Paced Walk Test (seconds)	40s	16.26	
	50s	19.32	
	60s	20.73	
	70s	19.24	
Stair Climb Test (seconds)	Healthy	10.22	8.72
	Moderate OA	19.48	11.78
	End-stage OA	23.59	17.43
Timed Up and Go Test (seconds)	60-69	8.1	
	70-79	9.2	
	80-99	11.3	
Six Minute Walk Test (distance, m)	60-69	538	572
	70-79	471	527
	80-89	392	417

Table 11: Normative OARSI test values (adapted from Dobson et al, 2013)

Normative values provide average population performance benchmarks for common outcomes in relation to knee joint health. A limitation of the OARSI normative values is that they do not extend to all age-groups. Since they are designed for patients with hip and knee OA, it is perhaps unsurprising that

there is a bias in the data towards an older population. On the other hand, it may be expected that these values would be reported for those in their 40s since this is the decade of life suggested in guidelines for diagnosing OA (NICE, 2014). Further, the age-ranges are inconsistent and not all tests have gender-specific values. In addition, the 30-second chair stand test values are ranges (with relatively large variation) which limits the ability to accurately compare.

A second limitation of using normative data as a comparator is that some individuals in these groups may have been runners. It is therefore not possible due to the study design to attribute any difference between these cohorts to running. To identify a cause and effect relationship, longitudinal data would be required (i.e. repeated testing and contemporaneous PA assessment). For practical reasons, there was only a very small number of potential non-runners in the cohort that could complete testing. Ideally, matched (age and gender) non-running controls would also have been recruited.

Performance of the tests in this cohort of runners was analysed based on gender, age, running behaviour, and injury history status. As evident in the normative values, age and gender affect performance of the OARSI tests (e.g. declines with age). Screening tools, such as hop tests, are used to identify functional deficits in those with prior injury (Xergia et al, 2013). These tests may identify a difference in limb performance because of injury history.

3.4.2.5 Follow-up Questionnaire

The follow-up questionnaire was limited to UK-based participants that had completed a minimum of Baseline Questionnaire 1. It was not a requirement that Baseline Questionnaire 2 had been completed. Location of participants was derived by postcode (or where not provided, an Australian email address (ending in *.com.au*) was used to differentiate). Australian respondents were excluded from this analysis due to the logistics of the research and practical issues relating to ethics.

The email to invite potential participants is in Figure 21:

Dear Sir/Madam,

We are contacting you as part of the Health of Adults Observational (HALO) Study. We are extremely grateful that you have volunteered to take part in the study.

Please find below a link to the Year 2 HALO Questionnaire we would like to ask you to complete. Everyone, regardless of how much or how little you have participated in our research so far, is invited to take part. We are interested to see if there has been any change in your running and to your health, particularly relating to your joints, bones and muscles. Everyone can take part - it doesn't matter if you currently run or if you haven't had any problems with your joints - we would like to hear from you.

Depending on your answers, it will take approximately 15-20 minutes to finish. If you would prefer a paper version, please contact us by responding to this email and we will post one to you, including a pre-paid envelope for you to return it to us.

The link to access the questionnaire is: https://nottingham.onlinesurveys.ac.uk/haloyeartwo

This email also contains a 'participant information sheet' providing further information about the questionnaire. If you have any questions, please do not hesitate to contact us (email: theHALOstudy@nottingham.ac.uk; phone: 0115 8231411).

When completing the questionnaire, you will be asked to provide your unique participant identification number. Your number is: [ID number].

Please note that there is no expectation that you will complete the questionnaire. If you do not want to complete it, you do not have to provide a reason why.

If you do not wish to receive any further correspondence from the research team, then please just let us know and we will update our records.

Thank you again for being a part of our research. We hope you remain a part of the team for many years to come.

Figure 21: Follow-up questionnaire invitation email

The participant information sheet is attached as an appendix (Appendix 6)

3.5 Variables

In the following section, the variables for each component of the research has been broken down into their constituent components (i.e. Baseline Questionnaire 1, Baseline Questionnaire 2, Validation of Questionnaire, Functional Testing, and Follow-Up Questionnaire).

3.5.1 Outcome Variables

3.5.1.1 Baseline Questionnaire 1

Knee Pain

Knee pain is a common focus of interest in research regarding PA and musculoskeletal health. It is a key clinical finding and can be self-reported (i.e. no clinical tests such as radiography are required, thus financial costs and burden (on participants and researchers) are kept low in large cohorts). Pain has been reported using different questions and the wording can relate to different periods of time, i.e. symptoms at any time in life, during the previous 12 months or last month (O'Reilly, Muir, Doherty, 1996; Bedson & Croft 2008). Prevalence is affected according to the choice of definition, with the lowest prevalence identified in questions that require current symptoms to be reported in short timeframes. A review by Bedson & Croft (2008) identified that the proportion of populations with knee pain and radiographic OA varies from 15-76%, depending on how knee pain is defined.

In the present study, the following question was used to identify cases of knee pain (Figure 22):

Have you ever had a **significant pain** in and around **your knees** for **most days for at least one month**?

Figure 22: Knee Pain Question

Persistent knee pain, lasting for most days for at least one month is a common definition for identifying cases. This wording has been modified depending on the specific methods and research question. For example, Driban et al (2016) were only interested in the right knee. In another paper, pain in one knee (singular) was used to define cases of pain (Lethbridge-Cejku et al, 1995). In these instances, neither question would adequately identify all cases of knee pain in the current cohort. In a cohort of patients aged over 55 with symptomatic knee OA, approximately half of men and three quarters of women have bilateral disease. In the present study, identifying pain only in one knee may have led to confusion about which knee they should respond about if they had bilateral symptoms. If the question was only directed at one knee (e.g. the right knee), the authors may miss out on valuable data since running places significant physical demand on both legs.

<u>Other Knee Symptoms</u>

Crepitus, restricted movement and morning stiffness are symptoms separate from knee pain and used in diagnostic criteria for OA (Altman et al, 1986). In the present study, these were self-reported rather than assessed by clinician.

The binary questions used to identify self-report crepitus, morning stiffness and limited joint range of movement were (Figure 23).

Have you had any **morning stiffness** that lasted for **less than 30 minutes** in and around your knees for most days for at least one month? Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.

Have you ever felt any **grinding, heard clicking or any other type of grinding noise** when you straighten or bend your knees for most days for at least one month?

Have you ever had **limited joint movement** (preventing you from fully straightening or bending) in and around your knees for most days for at least one month? This is in comparison to the other leg.

Figure 23: Other Knee Symptoms Questions

No single clinical test (either performed by the healthcare practitioner or from medical history) can accurately predict radiographic OA, but many show a clear association. The reasons for a reduction in ROM in knee OA are not well understood, but it is a common characteristic (Holla et al, 2011). Crepitus has a strong association with PFJ cartilage lesions on MRI (OR 5.49 (95% CI 3.79-7.94) and osteophytes in the PFJ (OR 2.61 (2.00-3.40) (Schiphof et al, 2014). Knee stiffness is common finding in patients with OA compared to controls (Dixon et al, 2010). A clinical assessment of all participants in the present study would have been impractical and logistically impossible to conduct. Self-reported symptoms were therefore included. The time frame (‘*have you ever…’*) for these questions was consistent with the pain question.

Diagnosis of Knee OA

There is no single definition of OA (Section 2.3), therefore multiple definitions were used in the research:

- Self-reported diagnosis of OA has been used previously in research, for example using the question 'Has a physician ever told you that you have osteoarthritis?' (Hootman, 2003).
- Joint replacement required due to OA (Sohn & Michaeli, 1985)

Self-Reported OA

Diagnosis of OA was reported as being made by either a physician (e.g. a general practitioner) and/or any other healthcare provider (e.g. a physiotherapist) (Figure 24). Details of joint surgery were provided according to the type (e.g. joint replacement), body area, age and indication for surgery.

Have you ever been **diagnosed with osteoarthritis** (sometimes also referred to as joint degenerative disease or wear and tear) in any of your joints **by a physician**? (for example, your GP)
Have you ever been **diagnosed with osteoarthritis** (sometimes also referred to as joint degenerative disease or wear and tear) in any of your joints **by any other healthcare provider**? (for example, a physiotherapist)

Figure 24: Diagnosis of OA Question

This definition of OA is reliant on the participants accurately recalling clinical interactions and information provided by their healthcare professionals. Potentially, some healthcare professionals did not correctly diagnose OA. There is evidence that the diagnosis of OA in primary care is poor, and there is discordance between the language used by GPs and patients. This could

negatively affect the reliability of the data in this study (Peat et al, 2005). An alternative method to confirm cases of OA would have been to access medical records, including assessment of radiograph. This would have been beneficial since the authors could confirm the existence of disease and more review the severity of cases. This method would raise issues regarding the information governance and ethics surrounding data collection and storage by the researchers (Strobl, Cave & Walley, 2000). Although not insurmountable, the process (extra ethics approvals, data collection, data storage) would have added significant additional burden on the researchers and participants (and thus impacted on the response rate).

Joint Replacement due to OA

A history of knee joint replacement was identified using the following question (Figure 25):

Have you previously had **joint surgery**?

Figure 25: Joint Surgery Question

If this was answered positively, then further details (type of surgery, body area, age at time of surgery and reason for surgery). Cases of replacement were recorded when adequate details were reported in this table. For example, the type of surgery had to be 'joint replacement', 'arthroplasty' etc. and 'OA', 'wear and tear' etc. had to be the reason for surgery.

Self-report history of joint surgery placed a responsibility on participants to accurately recall details of their surgery. Agreement between self-report medical history and medical records varies between populations and conditions (Eze-Nliam et al, 2012). It is recommended that in studies reporting disease prevalence, the use of electronic health records may be superior to self-report. A limitation of this approach is that errors in medical records (miscoding, mis-reporting or non-reporting) will be reflected in the analyses. Such errors could affect the associations identified between exposures and outcomes, especially amongst smaller cohorts (Smith et al, 2008)

Knee Injury

The results of a study involving 909 participants identified that meeting or exceeding PA guidelines was associated with increased risk of musculoskeletal injury (Morrow et al, 2012). Since running is a popular activity, it may be expected that injuries attributed to running will be common in this cohort, especially to the lower limb. If knee joint injuries are common, this may have an impact on risk of developing OA (Roos et al, 2005. In the current study, injury was self-reported using the following question (Figure 26).

Have you **ever sustained a significant injury** that caused pain for at least most days during a one month period and for which you **consulted a medical professional** or a healthcare provider such as a GP?

Figure 26: Significant Injury Question

Significant injuries were defined as those that required consultation with a health professional and caused pain for most days during a one-month period.

Injury details were provided in a structured table. Participants were asked to report which (if any) activity they were completing when the injury occurred. Where more than one sport or multiple activities were given as a cause of injury, these were categorised separately. An injury attributed to duathlon, triathlon (multi-discipline sports that includes running) or athletics where running was not explicitly specified as the cause were also classified separately. Obstacle and adventure races were not included as running injuries. Jogging and orienteering injuries were included within running attributed-injuries.

A prospective study of over 1,600 runners assessed the use of six different injury definitions on the incidence of injury over a six-week period. Incidence proportions varied from 7.5% to 58% depending upon the definition used (Kluitenberg et al, 2016). This study highlighted the importance of using a standardised injury registration method. The Orchard Sports Injury Classification System (OSICS) is widely used and freely available for use in injury epidemiology research (Orchard, 2010). The latest version of OSICS (10.1) was used in the present study to classify injuries based on the self-report diagnosis provided. The OSICS system has four hierarchical levels; anatomical location, injured tissue and two further levels describe in increasing detail the pathology and provide diagnosis. Finch et al (2014) report that the first two levels of the classification system (anatomical location and injured tissue) are enough for use in sports injury epidemiology. In an assessment of 1,082 injury records, an epidemiologist and sports physician agreed 95% of the time on the first level

and 86% of the time on the second. In the present study a physiotherapist (RL) independently coded all injuries.

Some minor modifications were made to the OSICS system in the present study. First, where an injury was reported as OA, this was removed from the injury analysis. OA was not considered to be an injury in this instance, since injury was used as a risk factor for knee OA in some analyses. Second, all medical conditions were also removed. This was to ensure that musculoskeletal injuries alone were recorded.

The format of the injury question in the present study may lead to some ambiguity in responses. For example, an injury may be attributed to running, but symptoms or structural damage may have been initiated during another activity. It is also possible that the injury occurred because of an accumulated activity from different sources (including running). It may therefore be difficult to attribute just one activity to the injury. Further, the definition of running in this question may not be consistently interpreted. For example, an individual may be injured when running during another sport (e.g. football, basketball). In this instance, the respondent has correctly identified running to be the cause of injury, but it has been incorrectly attributed. This may skew the results, particularly in relation to more severe joint injuries, such as meniscus and ligament injuries, that may be expected to happen less in road running due to the mechanisms involved.

General Health

The EuroQol five-dimensional (EQ-5D) questionnaire is an instrument used widely to explore self-report health in a variety of patient groups (Rabin & Charro, 2001). Five dimensions are measured (Herdman et al, 2011):

1. Mobility: walking capacity
2. Self-care: ability to wash or dress oneself
3. Usual activities: performance of work, study, housework, family or leisure activities
4. Pain / discomfort: symptom severity
5. Anxiety / depression: symptom severity

For each of these dimensions, there are five possible options in the updated version (EQ-5D-5L) as two additional responses have been added to the original design (EQ-5D-3L) (Herdman et al, 2011). The EQ-5D-5L has been found to be more discriminative than the previous version (Wang et al, 2016). The addition of two extra possible responses improves the sensitivity and/or responsiveness to health status (van Hout et al, 2012). In addition, participants are asked to subjectively evaluate their overall health on a scale from 0 (worst health) to 100 (perfect health). This questionnaire is one of the most used in research to assess general health status. It is simple to use and has been shown to be valid and reliable (Devlin & Krabbe, 2013).

There is one additional final question as part of the EQ-5D-5L. A scale is presented from 0 (the worst health imaginable) to 100 (best health

imaginable). Due to the online format of the questionnaire, this could not be presented in the original format (i.e. a visual analogue scale on which participants were asked to mark their response in the appropriate location). Instead, the wording from the questionnaire was retained but were asked to record a number as follows (Figure 27):

> We would like to know how is your health today. This scale is marked from **0 - 100**. 100 means the **best health** you can imagine. 0 means the **worst health** you can imagine. Write the **most appropriate number** to indicate how is your health **today**.

Figure 27: EQ-5D-5L Health Analogue Score Question

For this study, it was felt that overall health was an important construct to include therefore it was retained, despite the lack of a visual analogue interface. Further, it is noted that the EQ-5D-5L can be conducted over the phone, so alternative delivery methods are possible in the absence of physically completing this question. Using this outcome is important for the study since it broadens the overall assessment of runners and non-runners within this cohort to make it more holistic. As defined in the Literature Review, there are significant health benefits to running (section 2.8). In isolation, the musculoskeletal outcomes in this study may only provide one perspective. Thus, the addition of a report of health-related quality of life provides an important differential.

The outcome measures for the aims of the study dependent upon the questionnaire are summarised below (Table 12).

Outcome	Concept	Question	Response	Thesis Aim
Knee symptoms	Pain	Have you ever had a significant pain in and around your knees for most days for at least one month?	Binary	1
	Morning stiffness	Have you had any morning stiffness that lasted for less than 30 minutes in and around your knees for most days for at least one month? Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.	Binary	1
	Crepitus	Have you ever felt any grinding, heard clicking or any other type of grinding noise when you straighten or bend your knees for most days for at least one month?	Binary	1
	Limited joint movement	Have you ever had limited joint movement (preventing you from fully straightening or bending) in and around your knees for most days for at least one month? This is in comparison to the other leg.	Binary	1

Table 12: Outcome Measures

Outcome	Concept	Question	Response	Thesis Aim
Subjective knee health status	Significant injury	Have you ever sustained a significant injury that caused for at least most days during a one-month period and for which you consulted a medical professional or a healthcare provider such as a GP?	Binary	1
		Injury details	Body part, age at injury, type of injury, sport at time of injury, time to return to sport	
	Joint surgery	Have you previously had joint surgery?	Binary	1
		Surgery details	Type of surgery, body area, age at time of surgery, reason for surgery	
	OA	Have you ever been diagnosed with osteoarthritis (sometimes also referred to as joint degenerative disease or wear and tear) in any of your joints by a physician / healthcare provider? (for example, your GP / physiotherapist	Binary	1
		OA details	Joint affected, age at diagnosis, date of last symptoms, diagnose, tests/investigations performed	
Health-related Quality of Life	Current health status	EQ-5D-5L	Categorical, health score	2

Table 12: Outcome Measures, cont.

3.5.1.2 Baseline Questionnaire 2

The second baseline questionnaire provided additional details of knee joint outcomes.

Post-running Knee Pain

Pain after running has not been extensively explored in the literature, yet its prominence on the NHS website (NHS, 2018; Figure 28) suggests that it is a common complaint amongst recreational athletes in the UK.



Figure 28: NHS Website - Knee pain and other running injuries

Instead of assessing the presence of acute knee symptoms, structural changes in the knee joint post-running (assessed with radiograph or MRI) have been the principle outcome of interest (Mosher et al, 2010). However, the broader implications of symptoms after running are potentially large, particularly amongst novice or runners seeking health benefits (e.g. weight loss). If knee symptoms after running are common, it may contribute towards runners ceasing activity.

For this question, pain was defined according to 'pain, aching, discomfort' during the previous 12 months. Pain location was selected from a pre-determined list of body parts and pain severity indicated by a numerical scale (0 = no pain, 100 = worst imaginable pain).

Knee Injury and Osteoarthritis Knee Injury and Osteoarthritis Outcome Score (KOOS)

The KOOS is very widely used in research regarding OA and joint health. It is designed to report opinions of individuals on their knees and associated problems. Roos et al (1998) identified that this self-administered questionnaire was valid, reliable and responsive to change. It can be used over short and longer periods to assess change post-injury and/or in OA (Roos et al, 2003). Each item is ranked on a Likert scale from 0 (no problems) to 4 (extreme problems). The overall score for each sub-scale is calculated using a scale from 0 (extreme problems) to 100 (no problems). The formula for the calculation is in Figure 29:

100-[(actual raw score x 100)/possible raw score range]

Figure 29: KOOS calculation (www.koos.nu) (KOOS, 2012)

As per the KOOS guidelines, at least 50% of the responses are required for a domain to be considered valid. In addition, to prevent erroneous completion, the online version of the questionnaire prevented more than one response being given for each question.

The KOOS uses five key sub-scales in relation to joint health over the previous seven days:

- Pain (9 items)
- Symptoms (7 items)
- Activities of daily living (17 items)
- Sport and recreation function (5 items)
- Knee-related quality of life (4 questions)

The KOOS is not designed to be aggregated across the sub-scales. Each sub-scale remains separate during analysis and is interpreted independently (Roos et al, 1998). For use in the current research, the KOOS was modified so participants completed it separately for each knee. The reason for this change was that the KOOS is generally used post- injury or in knee OA, with the implicit demand for data relating to one knee only (i.e. the one affected). It was anticipated that runners may have bilateral symptoms, history of injury or OA. Thus, data from both knees was included. An alternative would have been to report only one knee (e.g. the right knee) in every participant as a reference. The burden on the participant to complete the survey for both knees was not considered to be that great. As such, left and right knee responses were requested.

Peer & Lane (2013) report that there is a lack of evidence relating to its clinical utility (e.g. feasibility, appropriateness and interpretability). Further, their review suggests variable reliability and construct-validity in some scales. Other

alternative knee scales have been identified and assessed. Those identified for potential use in this research included the (Western Ontario & McMaster Universities Osteoarthritis Index (WOMAC) (McConnell, Kolopack & Davis, 2001) but it was considered too focused on OA, whereas the KOOS provides a broader assessment of multiple components in those with injury too. The author is unaware of long-term trials that have used measures like the KOOS or WOMAC to assess joint health in specific populations (such as runners), regardless of knee injury history or knee OA status.

3.5.1.3 Functional Testing

Function is a key marker of joint health, especially in OA or post-injury (Krasnokutsky et al, 2008). Body functions are defined by the International Classification of Functioning, Disability and Health (WHO, 2002) as:

> '…physiological functions of body systems (including psychological functions).
>
> WHO, 2002 p.10

In the case of this study, the body system of interest is primarily the musculoskeletal system. A restriction or limitation in joint health that can further limit activity levels and overall quality of life. Physical function is highly complex combination of many physiological constructs (strength, proprioception, balance, range of movement, visual and vestibular and higher cortical function) (Bennell et al, 2003). As a result, there is no gold standard for

assessing function in hip or knee OA. In patients with knee OA, there are two options for assessing function; self-report or objective assessment (Maly, Costigan & Olney, 2006). Objective tests involve the participants conducting an activity that can be measured (i.e. duration, distance). It is now widely accepted that a combination of self-report and objective measures are most useful, rather than one being superior to the other.

Participants completed eight tests which are divided into two groups for descriptive purposes (Table 13). Each test is explained and critiqued below in turn.

The Osteoarthritis Research Society International (OARSI) Performance Tests	**Functional Tests**
30-second sit to stand (30s-CST)	Star excursion balance test (SEBT)
Stair climb (SCT)	Triple hop for distance test (TSLH)
40m walk fast paced walk (40m FPWT)	Unipedal dynamic balance test (UPDB)
Six-minute walk (6MWT)	
Timed up and go (TUGT)	

Table 13: Summary of Functional Tests

The OARSI Functional Tests

The OARSI functional tests were developed by consensus from 138 clinicians and researchers. The tests were performed in accordance with instructions provided in official documentation (Dobson et al, 2013). A review by Dobson et al (2012) identified 21 different measures of objectively assessing function and suggested three themes of activity that could be assessed with tests; walking, sit to stand and stair negotiation. These are broadly the themes contained in the OARSI tests.

30s-CST

Lower limb strength is an important component of function (section 2.3.1.5). One method of assessing strength is the 30s-CST. It has previously been reported that timed protocols which require participants to complete a certain number of repetitions, for example 10 full sit-to-stands, may be too difficult for certain individuals to complete (Csuka & McCarty, 1985). This means that participants are unable to obtain a time and thus no score can be recorded. This was shown in a cohort of elderly participants following a similar protocol where, although only five repetitions were required, 22% of the population were unable to record the minimum number of repetitions. An alternative method may therefore be superior for widespread use in a large cohort.

The 30s-CST involves the total number of repetitions of a full stand from a seated position are completed. The advantage of this approach is that an objective score (number of repetitions completed within a limited time) can be

recorded. The test-retest reliability and validity of this protocol has been assessed in a cohort of elderly participants (Jones, Rikli & Beam, 1999). The test-retest reliability was good (ICC 0.89; 0.79-0.93) and there was moderate correlation between 30-CST performance 1 repetition-max strength assessed on a leg press (ICC 0.71-0.78). There was a significant decline in test performance with age, although the study did not report any further information regarding level of PA performed by the participants. Eligible participants in this study were pain-free, but no history of injury was provided. It would be interesting to see how these factors affect test performance.

A systematic review of different sit-to-stand test methodologies reveals that there are no standardised protocols nor are they often sufficiently described in some study methodologies (Silva et al, 2014). A second systematic review revealed several determinants of the sit-to-stand movement: including the chair (e.g. height from floor to seat, presence/absence of armrests, chair-type and presence/position of the backrest) and participant strategy (e.g. speed, body position and arm movement) (Janssen, Bussmann & Stam, 2002). For example, a higher seat reduces the range of movement required at the hips and knees in order to complete the movement (by approximately 60% and 50% respectively). Therefore, the environment (chair positioning, the testing chair) and verbal instructions (how the participant was told to complete the test) were consistent across all subjects. A criticism of the 30s-SCT test is that the procedure is not a perfect assessment of the real-life activity of rising and

lowering into a chair (Tolk et al, 2019). However, appropriate interpretation of the test is necessary and consideration of how the results are used is important.

The 30s-CST protocol defined by OARSI was used. This requires participants to stand up from a seated position in a chair and to repeat this action as fast as possible. In the standing position, the hips and knees had to be fully extended. In the seated position, the bottom had to fully touch the seat. The number of repetitions completed in a 30-second period is recorded. The chair was located with its backrest against the wall to prevent it from moving during the test. The tester was located to the side of the chair to ensure that the technique could be easily assessed (i.e. to discard incomplete or incorrectly performed repetitions), and repetitions counted.

The following verbal instructions were used to explain the procedure to the participant (Figure 30)

"For this test, do the best you can by going as fast as you can but don't push yourself to a point of overexertion or beyond what you think is safe for you.

1. *Place your hands on the opposite shoulder so that your arms are crossed at the wrists and held close across your chest. Keep your arms in this position for the test.*
2. *Keep your feet flat on the floor and at shoulder width apart.*
3. *On the signal to begin, stand up to a full stand position and then sit back down again so as your bottom fully touches the seat.*
4. *Keep going for 30 seconds and until I say stop.*
5. *Get ready and START".*

Figure 30: 30s-CST Instructions

Once this had been read out, the participants were given opportunity to ask any questions and clarify any instructions. Participants could also complete one

or two practice efforts (not timed) to confirm their understanding and to ensure that the test was completed correctly.

On commencing the test, a stopwatch was started by the assessor. The number of repetitions was recorded. A full repetition was counted when they returned to a seated position. If a partially completed repetition (i.e. a full stand had been completed or they were returning to the seat from a standing position) was in progress when the 30-second period was over, then this was counted as a full repetition.

SCT

The SCT is an assessment of how long it takes (in seconds) to ascend and descend a flight of stairs. This functional activity is a test of balance, strength and power. Power has been identified as more significant than muscular strength when mobility skill is assessed in an elderly population (Bean et al, 2003). The authors acknowledge within these findings that discriminating between significant differences in strength and power are more likely to be recognised when functional performance is lower.

Benefits of using the stair climb test are the ease of completion, the limited facilities and equipment needed and the duration. The test-retest reliability of a stair climb test in female patients with bilateral knee OA (n=21) was assessed over 11-steps (Humby, Hughes & Jawad, 2018). Across two separate visits, within-subject variability was 4% whilst between-subject variability was 96%.

The weighted kappa correlation score was 0.79, demonstrating good correlation. However, the protocol in this study provides minimal information relating to the how the test was performed (i.e. instructions to patients). Nightingale, Pourkazemi & Hiller (2014) report in their systematic review of stair climb tests that a wide range of different protocols that have been published. For example, some protocols only required ascent whilst others varied the number of stairs completed (range 4-180 steps). Additionally, how participants were asked to climb the stairs (e.g. at normal pace or as fast as possible) or whether the use of handrail was instructed were also inconsistent. These would all have a significant effect on test performance.

To minimise the effect of these factors in the current study, the same verbal instructions were used, and identical steps were used in each location. Despite the same number of steps being used in each test location, it is possible that there is a discrepancy in step-height. This is unavoidable but should be acknowledged.

The OARSI verbal instructions were given to participants (Figure 31).

"For this test, do the best you can by going as fast as you can but don't push yourself to a point of overexertion or beyond what you think is safe for you.

1. *Start with both feet on the bottom landing.*
2. *On start, go to the top of the stairs as fast but as safe as you can, turn around and return back down and stop with both feet back on the ground landing.*
3. *Use the rail only if needed.*
4. *Get ready and START".*

Figure 31: SCT Instructions

After instructions had been given, participants had the opportunity for a practice effort. This was followed by one effort which was timed. Timing began on the signal to begin. Timing ended when both feet were on the ground level. This was recorded to the nearest 100th of a second. The use of the handrail was allowed, if required. During the test, the assessor was located on the bottom landing to observe when the trial ended. It was ensured before the test occurred that the stairs were clear of objects or people that may impede progress during the test.

40m FPWT

This test is a timed assessment of walking over a short distance. It incorporates straight line speed walking and the ability to change direction. The inter-rater and intra-rater reliability of the 40m FPWT were optimal (ICC > 0.9) and the measurement error (the systematic and random error of measurement not attributable to true change) was less than 10% (Dobson et al, 2017). The review by Dobson et al (2017) included the procedures prescribed by the OARSI protocol (and used in the current study). The intra-rater reliability results however were only reported for one clinician - albeit with significant practical and research experience - perhaps reducing the external validity of these findings. In addition, the authors acknowledge that the degree of reliability may vary between participants with hip and knee OA, but no results were reported due to an inadequate sample size.

Alternative walk tests, over different distances (e.g. 20m), have been used in knee OA patients (Motyl et al, 2013). Various distances (8ft - 80m) and implementation technique (e.g. self-paced or fast-paced) of objective walking tests were assessed in a systematic review (Dobson et al, 2012). The ICC of these tests were consistent (where reported); the lowest was ICC 0.83 was for a 13m self-paced walk, although the number of participants in these studies was relatively small (range 10-47). Greater walking distances would have been impractical within the available research settings and it was unclear when testing commenced exactly where it would take place.

The 40m FPWT test takes place over a 10m walkway, which is completed four times (40m distance in total). The walkway was marked out using coloured tape on the floor. Instead of using a cone, tape was used to indicate the turn point. The reason for this was that the floor was not always carpeted and therefore if the cone was trod on during the test, it was a potential slip hazard. As a minimum, approximately 2m at the end of the 10m walkway was available for turning.

The participant was instructed using the verbal instructions (Figure 32).

"For this test, do the best you can by going as fast as you can, without running, but don't push yourself to a point of overexertion or beyond what you think is safe for you.

1. *Start with both feet on the start line.*
2. *On start, walk as quickly but as safely as possible, without running.*
3. *Walk up to the end cone, turn around and walk back to the starting cone behind you, turn again and back to the end cone, then turn once more and return back to the start cone again so that you walk the 10m walkway 4 times in total.*
4. *Get ready and START".*

Figure 32: 40m FPWT Instructions

The tester was located throughout the test in a position that enabled observation of participants to ensure that the course was completed correctly (i.e. completing the entire distance). Timing began when the participant crossed the start line. Timing was paused as participants turned around the mark at the end of each length and re-commenced when they re-cross this mark to return to the other end. The trial was complete (and timing ended) when four lengths have been completed and the participant crosses the start line for the final time. The duration of the test is recorded to the nearest 100th of a second. The results are expressed as speed (metres per second). The calculation used was:

$$\frac{\text{Distance (40m)}}{\text{Time (seconds)}}$$

6MWT

The 6MWT is a simple endurance test with results expressed as total distance walked during a six-minute period. It is recommended as an assessment of cardiopulmonary exercise capacity (American Thoracic Society, 2002). Due to the inclusion directional changes, it is also a test of dynamic balance. The construct validity of the test - the extent to which the test measures ambulatory function - has been shown the be excellent in a cohort of patients with total knee arthroplasty, since it was strongly correlated to 30-min walk test performance ($r=0.97$; $p<0.001$) (Ko et al, 2013).

The 6MWT test has been used in populations ranging from healthy elderly individuals, obese individuals with radiographic knee OA, and those with advanced knee OA (Troosters, Gosselink & Decramer, 1999; Focht et al, 2005; Kennedy et al, 2005). The aforementioned papers present separate methodological differences for conducting the same test (including varied walking track length of between 25 and 30m in two tests and laps of a gym). This would affect the number of turns completed, how many accelerations and decelerations are performed and may ultimately affect walking distance. It could be hypothesised that walking with an arthritic knee may affect the ability to turn at the end of each straight section due to pain or fear avoidance. This is pertinent since test performance has been shown to be negatively correlated with pain and disease severity in patients with knee OA (Ateef, Kulandaivelan & Tahseen, 2016).

In a sample of 39 patients pre- and post- exercise-based intervention (mean 5.8 physiotherapy attendances) for knee OA (diagnosed according to the ACR criteria), the 6MWT was more responsive to change in physical capacity than other functional tests, likely because the distance involved is greater (French, Fitzpatrick & FitzGerald, 2011). It is therefore helpful to use this test in collaboration with others to assess function holistically. The 6MWT has been shown to have excellent test-retest reliability (ICC 0.991; 0.986-0.994) in a population of knee OA patients (Ateef, Kulandaivelen & Tahseen, 2016).

A 25m walkway was marked out using tape on the floor. The same length of course was used in all test locations. The verbal instructions for the test given to participants are found below (Figure 33):

"For this test, do the best you can by going as fast as you can, but don't push yourself to a point of overexertion or beyond what you think is safe for you.

1. *Start with both feet on the start line.*
2. *On start, walk as quickly but as safely as possible around the course / up and down the hallway.*
3. *Continue the course / walkway to cover as much ground as possible over 6 minutes.*
4. *Walk continuously if possible, but do not be concerned if you need to slow down or stop to rest. The goal is to feel at the end of the test that no more ground could have been covered in the 6 minutes.*
5. *You can sit down to rest if you require".*
6. *Get ready and START".*

Figure 33: 6MWT Instructions

Following this explanation, the understanding of the test procedure was confirmed with the participants. Timing commenced when the participant crossed the start line. Timing ended after six minutes. Encouragement was given at minute intervals (e.g. "keep going you are doing really well"). Evidence shows that verbal encouragement has a statistically significant effect on endurance walking performance (Guyatt et al, 1984). With approximately 30 seconds remained, the tester began to follow the participant as they continued walking. In order to record the distance as accurately as possible, participants a verbal countdown commenced when five seconds remained. When the test ended, participants were instructed to stop, and a piece of tape was placed on the floor where the back heel was in contact with the floor. The total distance was calculated as the sum of the number of lengths completed plus any additional distance walked.

TUG

The TUG test is a simple timed assessment of ambulation, incorporating transition from sitting to standing before returning to sitting. Participants are required to rise from a chair, walk for 3m at their normal pace, turn around, walk back to the chair then return to a seated position the chair (Podsiadlo & Richardson, 1991). It is a test of dynamic balance and mobility (Herman, Giladi & Hausdorff, 2011).

The TUG test has been widely used to assess function in patients with neurological and lower limb musculoskeletal conditions (van Lummel et al, 2016). It has been advocated for clinical use to predict individuals at risk of falling, but its value has been questioned by others (Barry et al, 2014). The intra- and inter-rater reliability in patients with KL grade I-III knee OA aged 45-70 were ICC 0.97 and 0.96 respectively. The external validity of these findings to patients without knee OA is limited since no controls were used, although excellent intra- and inter-rater reliability (ICC >0.93) has been reported elsewhere in large populations of elderly patients (Lin et al, 2004). A review by Bohannon (2006) shows variance in the test performance methodology (e.g. chair type and verbal instructions). Whilst in some instances, participants were advised to walk quickly, others were at instructed to walk at a comfortable or normal speed. These would affect how the test was performed. In the current study, the following verbal instructions were used (Figure 34) to ensure a consistent performance:

"For this test, do the best you can and walk at your regular pace.

1. *Start by sitting in the chair with you back resting on the back rest and your hands on the arm rest.*
2. *On start, stand up, walk to the mark, turn around, return and sit back into the chair with your back resting on the back of the chair.*
3. *Walk at your regular pace.*
4. *Get ready and START".*

Figure 34: TUG Instructions

Following explanation, a practice (untimed) effort was permitted. The chair for the test was located so that it was against a wall and could not slide. The turn point at 3m was marked using tape. It was shown to the participant before the test, to highlight its location. The distance of 3m was measured on the floor from the front legs of the chair. During the test, the assessor was located to the side of the test area, to ensure that the participant completed the course correctly but to avoid impeding participant progress. Timing began when the test was initiated and stopped when the participant was in a fully seated position in the chair (i.e. their back was on the back rest of the chair). Time was recorded to the nearest 10th of a second.

<u>Performance Tests</u>

Three further tests were completed to ensure a more comprehensive assessment of the participants (SEBT, THFDT and TSLH). Whereas the evidence supporting the OARSI tests has a bias towards those with OA, it was felt that additional tests were necessary since it was assumed most participants would not have OA and further (more complex) activities would aid further discrimination of functional performance capacity. The three tests assess physical (neuromuscular and postural control, force-generation capacity, range

of movement, proprioception and dynamic joint stability) and psychological (confidence) components relevant to joint health (Whittaker et al, 2015). They are relatively simple and quick to perform, requiring minimal equipment and space. Each test is described separately below.

For two of the tests (SEBT and TSLH) the results are presented as a percentage of leg length. Leg length was measured with the participant in supine from the anterior superior iliac spine to the medial malleolus using a tape measure (Gogia & Braatz, 1986). In their analysis of this technique in 30 subjects, Gogia & Braatz (1986) identified inter-rater reliability between two therapists and validity against radiograph. The ICC (0.99) and Pearson correlation coefficient (r 0.98) suggest that this is an accurate test. The authors caution however that there may be measurement differences arising from therapist experience, obesity or contracture. A clinical review also suggests that limb girth and angular deformities may also hinder accurate measurement (Sabharwal & Kumar, 2008). Due to restricted resources, it was considered that the tape measure technique would be appropriate, however these limitations are acknowledged. To support accurate testing, the participant completed one pelvic bridge to neutralise the position of the pelvis. Both legs were measured and recorded to the nearest millimetre. Leg length was assessed prior to all other testing.

SEBT

The SEBT is an assessment of dynamic postural control which incorporates proprioception, range of movement and strength (Gribble & Hertel, 2003). It is performed by a participant standing unshod in the centre of a grid maintaining their hands on their hips throughout. A grid, consisting of eight lines at 45 degrees to each other, is marked out on the floor (Figure 35).

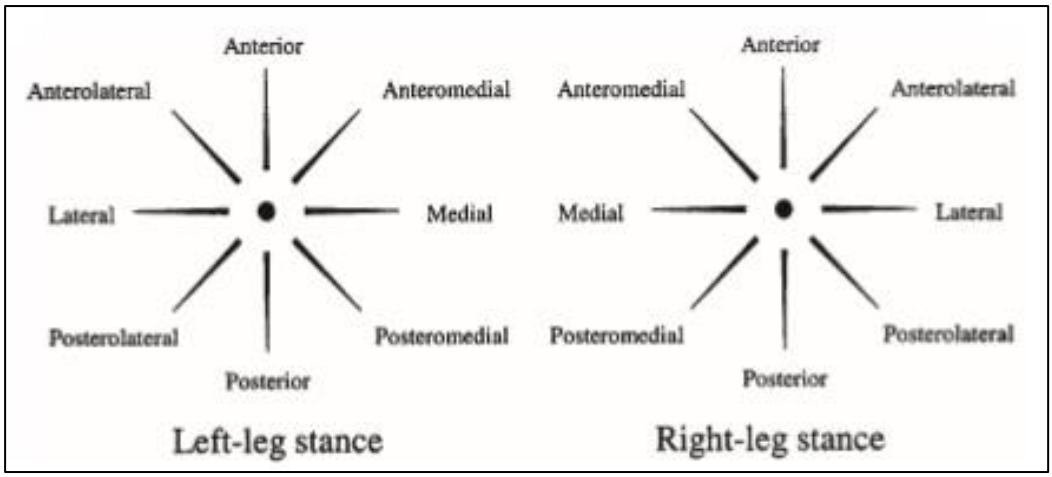


Figure 35: Reaching Directions for the SEBT (Gribble & Hertel, 2003) p 93

The aim of the test is to reach as far as possible with the non-stance leg as far as possible along each of the eight lines on the floor. Testing in multiple directions provides a unique movement challenge. The reaching leg then returns to the centre before proceeding to extend along the next line. A greater distance indicates better dynamic-postural control and the test has been widely used to compare limbs (i.e. injured and uninjured) or pre- and post-interventions to objectively assess differences or change (Gribble, Hertel & Pilsky, 2012).

The participant was instructed to reach as far as possible along each of the lines with one leg, whilst maintaining a single leg stance in the centre of the grid. The following verbal instructions were used:

1. Whilst maintaining your hands on your hips, reach as far as possible along each of the eight lines. Make a light touch on the line, and return the reaching leg back to the centre, while maintaining a single-leg stance with the other leg in the centre of the grid
2. Make a light touch on the ground with the most distal part of the foot of your reaching leg and then return it to the centre
3. When reaching in the lateral and postero-lateral directions, you must reach behind your stance leg to complete the task
4. You can bend the knee of your standing leg but you are not allowed to move the foot rom its starting position. If you lose balance, remove a hand from your hip or put too much weight through the reaching leg, this trial will be discarded and repeated

Figure 36: SEBT Instructions

A demonstration of the test was given by the assessor to reinforce the verbal instructions. Participants started with four trials to practice followed by three recorded efforts (with 15 seconds rest in-between). This is supported by Robinson & Gribble (2008) who suggest that four practice trials are optimal since there is little change in maximal performance after this. By following this protocol, participant burden is reduced by limiting the exertion caused by further repetition.

The participant always started with the anterior direction and then progressed through each line in a clockwise direction (left leg stance) or anticlockwise direction (right leg stance) (Figure 37).

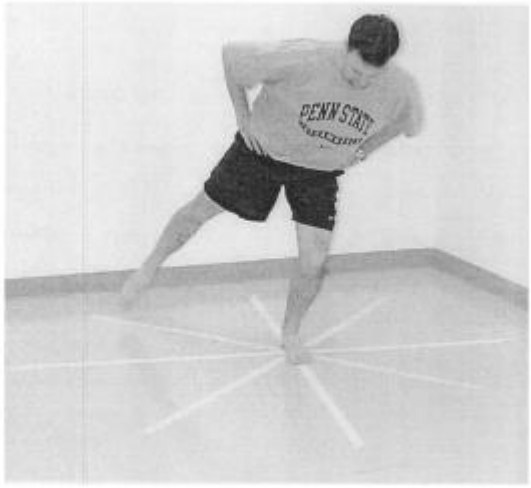


Figure 37: Performance of the SEBT (Gribble & Hertel, 2003) p 93

A trial was discarded and repeated if balance was lost, the stance foot moved (e.g. elevated heel, slide from starting position) from its position in the centre of the grid, or it failed to return to the centre after each reach. During each effort, the assessor marked the tape where the most distal part of the foot made contact. The distance was measured from the centre of the grid to the location of each mark on every line. The longest distance from the three trials in each direction was used in the sum (total distance) for analysis.

A literature review by Gribble, Hertel & Plisky (2012) reports the determinants of test performance include hip and knee movement in the sagittal plane, whilst ankle dorsiflexion accounted for 28% of variance in performance when anterior reach distance was assessed. This test therefore cannot be considered a test of knee joint health status in isolation and must be considered one of the entire kinetic chain.

The SEBT has been found to demonstrate excellent test-retest reliability (ICC 0.93) in patients with knee OA (Kanko et al, 2019). In this study, a sub-cohort of 37 participants completed the test in a biomechanics lab to review concurrent validity. The correlation between observer and 3D motion capture measurements were high ($r>0.96$) in all directions. Furthermore, this study also included a second test after a 12-week home exercise programme. The authors suggest their finding that subjective patient outcome measures (e.g. pain severity) and improvement in SEBT performance is indicative of the tests measuring different constructs and suggest both are necessary.

There are different protocols for the SEBT and the 'Y balance test' is one common modified version (Clagg et al, 2015). Instead of eight lines, this test consists of three lines (anterior, posteromedial and posterolateral) (Hertel et al, 2006). Ultimately, the decision was made to follow the methods defined by Whittaker et al (2015) for consistency.

THFDT

The THFDT is a strong predictor of lower limb strength, power and neuromuscular coordination (Hamilton et al, 2008). Single leg hop tests have been widely used in research investigating lower limb rehabilitation after injuries such as ACL rupture and PFJ pain (Logerstedt et al, 2013; Reid et al, 2007; Bley et al, 2014).

Participants stand on the test leg, with their big toe behind a line of tape on the floor. From this start position, three consecutive hops are completed on the same leg. The aim is to hop the furthest possible distance. The verbal instructions provided to the participant are shown in Figure 38.

1. Following one practice effort, you will complete two trials of three consecutive hops on one leg with the goal of jumping as far as possible
2. Your landing must be solid, without excessive unbalanced movements or twisting of the foot

Figure 38: THFDT Instructions

Each series of three hops had to be completed without losing balance (e.g. if additional small hops were required to maintain balance, or the non-test leg was placed on the floor, the trial was discarded and repeated). On the final landing, the participant did not move their foot once it made contact with the floor. A small piece of tape was placed directly behind the heel and this was used to measure the hopping distance from the start line. Different coloured tape was used for each leg so that it was clear from which trial an effort had been produced. A single practice effort was permitted for each leg prior to the two recorded trials, consistent with the methods of Whittaker et al (2015). The furthest distance on each leg (recorded to the nearest millimetre) was used in analysis.

There are many variations of hop tests (for example, single leg hop for distance, single leg timed hop, cross-over hop, square hop test, 6m hop for time) (Haitz et al, 2014). Regardless of type, hop tests are reported as useful indicator of lower limb strength. Wilk et al (1994) reported a strong correlation between

isokinetic strength of quadriceps and hamstrings assessed using a dynamometer and single-leg hop test performance in a cohort of patients following ACL reconstruction. In addition, poor hop test performance has been shown to be predictive of post-traumatic radiographic knee OA development (mean age 29 years) (Wellsandt, Axe & Snyder-Mackler, 2018). Although these are interesting findings, some limitations of the paper should be acknowledged. The presence of radiographic knee OA prior to ACL injury was not determined. As has been discussed in a section 2.4, radiographic changes may exist without symptoms. Furthermore, the follow-up period was only five years, but development of knee OA may occur after this time. Interpretation of test performance is limited to more-rapid onset of knee OA. In addition, the findings do not reveal the risk of developing knee OA within a non-injured population, thus further research is necessary to determine the ability of hop tests to predict this. The authors suggest that reduced test performance is reflective of impaired movement patterns that affect loading of the injured limb. Other authors argue that the ability of the hopping tests to differentiate between specific deficiencies in the components that comprise hopping function or how well the tests identify the contribution of individual biomechanical and neuromuscular factors remains undefined (Noyes et al, 1991; Fitzgerald et al, 2001).

UPDB

The UPDB uses a foam pad (Airex Balance Pad®, L-group, St. Louis, MO, USA) to assess how long single leg stance could be maintained on an uneven surface.

Balance deficiencies are common amongst neurological, vestibular, traumatic, and rheumatic patients (Springer et al, 2007). A systematic review identified the use of single leg stance in the assessment of patients with knee OA and healthy controls (Hatfield et al, 2016). In contrast to the current study, the eyes remained open in these trials. In the first of these papers, a cohort aged over 50 (n=25 with radiographic knee OA (K-L $\geq$ 2), n=25 controls), participants were asked to stand for as long as possible on the affected limb, maintaining the free limb at 90, up to a maximum of 90 seconds. The mean test performance was statistically significantly greater in the controls than knee OA group (p=0.01). In addition, the test-retest reliability was conducted in a sample of 20 participants with knee OA (ICC = 0.91 (0.78-0.97)). These results are limited however to this population, since those with more severe OA were under-represented in this sample (only two patents had severe (KL grade 4) OA). Patients with more advanced knee OA may exhibit worse balance, thus stratification of participants by severity of radiographic knee OA in a larger cohort where symptoms are reported would be beneficial. The second paper reported the effects of intra-articular hyaluronic acid in symptomatic patients with knee OA (grade I or II TFJ OA according to Ahlback grading system). After a six-month follow-up, there was a statistically significant improvement ($p<0.0001$) compared to baseline in single-leg stance performance. It is proposed that balance impairments in patients with knee OA may result from painful loading of the affected joint altering the centre of mass within the base of support. A longer period of follow-up with repeated x-rays to show any

association between change in radiographic knee OA severity and test performance would enhance understanding of these findings.

In the present study, a familiarisation period to adjust to the surface was permitted (Emery et al, 2005). The participants were instructed to place their hands on their hips and close their eyes before elevating the non-test leg from the pad. A benefit of doing the test with closed eyes is that participants with a balance impairment may be more reliant on their vision to maintain stance (Springer et al, 2007). This test was completed unshod.

The following verbal instructions given prior to testing are outlined below (Figure 39):

1. Stand in centre of foam pad with your hands on your hips
2. Close your eyes
3. Elevate non-test foot from the pad to balance on the test leg as long as possible

Figure 39: UPDB Instructions

Three timed trials were completed on each leg. The stopwatch was started when the non-test leg was removed from the pad. A trial ended when one of the following occurred; removal of a hand from the hip, opening of the eyes, placing the elevated foot on the floor or on the foam pad or moving the stance leg from its starting position (Whittaker et al, 2015; Emery et al, 2005). The duration of each trial was recorded to the closest millisecond.

Alternative single leg balance tests have been performed, for example without use of an uneven surface and with eyes open (Brachman et al, 2017). The test-retest reliability of single leg stance has been identified on both static and dynamic surfaces. In a comparison of eyes-closed static balance, eyes-open dynamic balance (using an Airex Balance Pad) and eyes-closed dynamic balance, the ICC was lowest in the group with eyes-closed and (ICC 0.46 (0.31-0.59) (Emery et al, 2005). The results of this study are consistent with previous evidence that a lack of vision reduces balance performance (Stribley et al, 1974).

3.5.1.4 Follow-Up Questionnaire

The following outcomes were reviewed at follow-up:

Injury

To identify injuries sustained in the previous 12-months, participants were asked for a binary response to the following question (Figure 40):

During the past 12 months, have you sustained a significant injury that caused pain for at least most days during a one month period and for which you consulted a medical professional or a healthcare provider such as a GP?

Figure 40: Question to Identify Injury During Previous 12 months

When a positive response was given, participants were asked to report the body part (e.g. right shoulder), age at time of injury, type of injury (e.g. fracture), sport / event involved in (e.g. rugby) and time to return to sport (e.g. 5 months).

Knee Joint Replacement due to OA

To identify joint arthroplasty in the past 12-months, participants were asked for a binary response to the following question (Figure 41):

During the past 12 months, have you had joint surgery?

Figure 41: Question to Identify Joint Surgery During Previous 12 months

When a positive response was given, participants were asked to report the type of surgery (e.g. joint replacement), body areas (e.g. right knee), age at time of surgery and reason for surgery. For this question, the same rules were applied at baseline and follow-up.

Knee OA

To identify cases of OA over the previous 12-months, participants were asked to report a diagnosis of OA by a healthcare practitioner, using one of the two questions below (Figure 42):

During the last 12 months, have you been **diagnosed with osteoarthritis** (sometimes also referred to as joint degenerative disease or wear and tear) in any of your joints **by a physician**? (for example, your GP)
During the last 12 months, have you been **diagnosed with osteoarthritis** (sometimes also referred to as joint degenerative disease or wear and tear) in any of your joints **by any other healthcare provider**? (for example, a physiotherapist)

Figure 42: Question to Identify Knee OA Diagnosis During Previous 12 Months

When a positive response was given, participants were asked to report the joint affected (e.g. right knee), age at time of diagnosis, month and year of

symptoms, diagnose (e.g. GP) and tests (e.g. x-ray). For this question, the same rules were applied at baseline and follow-up.

Knee Symptoms

Participants were asked to report on knee joint symptoms during the previous 12-months (see Table 14).

Symptom	Question
Pain	During the past 12 months, have you had a **significant pain** in and around **your knees** for **most days for at least one month**?
Morning stiffness	During the past 12 months, have you had any **morning stiffness** that lasted for **less than 30 minutes** in and around your knees for most days for at least one month? Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.
Crepitus	During the past 12 months, have you felt any **grinding, heard clicking or any other type of grinding noise** when you straighten or bend your knees for most days for at least one month?
Reduced joint movement	During the past 12 months, have you had **limited joint movement** (preventing you from fully straightening or bending) in and around your knees for most days for at least one month? This is in comparison to the other leg.

Table 14: Knee Pain and Symptoms Questions in Follow-Up Questionnaire

Additionally, participants were asked to report pain during or after running (within 48 hours). Pain was defined as 'pain, aching, discomfort' and excluding pain due to feverish illness such as flu'. Do not include pain due to feverish illness such as flu'. This question included details of location (e.g. right knee).

KOOS

Participants were asked to complete a KOOS separately for each knee joint at follow-up. The KOOS identifies five key constructs in relation to joint health:

- Pain (9 items)
- Symptoms (7 items)
- Activities of daily living (17 items)
- Sport and recreation function (5 items)
- Knee-related quality of life (4 questions)

General Health

As per the baseline questionnaire, participants completed the EQ-5D-5L. The same rules were applied at baseline and follow-up. The EQ-5D-5L is reported according to the health status on the day of completion, rather than a specific time period.

3.5.2 Baseline Questionnaire 1 Exposure Variables

Running

The key exposure variable in this research is running. Self-report questions sought to identify individuals that ran and identify running behaviours in those that do. Critical components that constitute overall load, as proposed by Glasgow, Philips & Bleakley (2015) include frequency, duration and intensity of activity. In section 2.6, the hypothesised link between load and knee OA has been discussed. The following questions were designed to quantify these

running behaviours so an association between them and specified outcomes, notably knee OA and associated symptoms, could be reported (Table 15). Running behaviour is a term used in the present study to describe different variables that can be used to describe running, for example distance and frequency. Recreational athletes in this cohort were stratified by running behaviour variables in the analyses.

Concept	Question	Response
Current running status	Do you currently run? (previous 12 months)	Binary
Duration	How long have you been running for?	Continuous variable (years)
Average weekly running	During the previous 12 months (or less if applicable) what has been your average weekly running distance?	Continuous variable (unit of distance)
	On average, how many running sessions are you completing per week	Continuous variable (number of runs)
	On average, how long do these sessions last	Continuous variable (unit of time)
Average monthly running	What is the average run that you have completed during the past month?	Continuous variables (unit of time; unit of distance)
	What is the average run that you have completed during the past 12 months?	Continuous variables (unit of time; unit of distance)
Change in running	Are you running more or less than you were 12 months ago?	Categorical (i.e. a lot less, a bit less, about the same, a bit more, a lot more)

Table 15: Running Exposure Questions

Current Running Status

Running status (i.e. runner or non-runner) was a binary 'Yes'/'No'. To identify as a runner, participants had to have run at least once during the previous 12 months. Those that responded 'Yes' were asked to provide more details of their running behaviour e.g. average running behaviour, such as number of runs per week and distance.

Previous research has used a variety of methods to identify running status and the extent of participation. There is no consistent approach and the method is likely to be affected by the study design. Lo et al (2017) in a cross-sectional analysis of running and knee OA, defined runners by first identifying participation in sporting activities for at least 20 minutes duration on a given day at least 10 times during one of four age periods (12-18, 19-34, 35-49 and 50+). If running was amongst the top three activities reported during these age periods, participants were defined as a runner at that time point. Alternatively, a prospective cohort defined runners according to membership of running associations with a minimum age (i.e. Fifty-Plus Runners Association) (Chakravarty et al, 2008), although this age limitation makes the inclusion of younger runners in the cohort impossible. Another prospective study identified runners from a community-based cohort if they ran as part of a PA program. If they responded positively, they were asked for frequency of running (Felson et al, 2007), although no specific details were provided. In the current study, another option would have been to include a question like that used by Bruce, Fries & Lubeck (2005) who asked, "*Have you ever run for exercise for a period*

of greater than one month?" This would identify participants that have ever run, rather than those that have run recently. The recall accuracy of a more recent time-period was considered to be more accurate (i.e. *last 12 months* rather than *ever*), although the validity of this assumption was not explored.

It is plausible that each definition of 'runner' (originating from the specific question used to identify 'runner') could influence the conclusions drawn. In the example of the literature above, definitions reliant on running being one of the top three sports may mean that very active individuals report several sports, meaning running was not included despite a substantial amount of running being completed. Running status defined by running club membership could ignore many runners that do not run as part of a club, especially if it were based on a restrictive age criterion (e.g. aged 50+).

In the present study, running was required within the previous 12 months. This definition was kept intentionally broad to obtain further details from participants regarding their running behaviour in subsequent questions. Limiting running status to a pre-determined threshold (i.e. running a certain distance or for a minimum duration) would mean that active runners would be excluded, and it would skew the cohort towards a homogenous group of athletes with less variability in running ability and/or performance. This is considered important when the outcomes of interest, e.g. pain (short or long term), could be influenced by running behaviours. On the other hand, analyses based on this broad definition of running status means that all runners - regardless of performance or ability - are equivalent in an analysis comparing

runners and non-runners. Further analysis within the running cohort was necessary to identify any differences between runners and the association with outcomes of interest (e.g. prevalence of knee pain)

A further consequence of this definition of running status is that individuals that ran at any time in life until 12 months ago may be in the non-running group. It cannot be discounted that an outcome of interest in this research (e.g. knee pain or knee OA) was responsible for them ceasing participation. Previous running in current non-runners was not confirmed in this study. A binary response to this question would be insufficient. To gain adequate running behaviour data throughout life, it would entail a significant number of additional questions to be added to allow elaboration of details (and other lifestyle factors) for meaningful analysis. This may introduce recall error since exposure (i.e. running distance or duration) would be needed over a long period of time (i.e. entire life period, potentially divided into each decade to allow change in running to be defined). If this were completed, like the methods employed by Lo et al (2017), it would be possible to report change in running over time rather than assume that running behaviour had been constant. Again, a limitation of this approach is that it would add significant burden to the participant and could affect response rate to the questionnaires.

According to the binary definition of running in this cohort, there may be runners that have run during the previous 12 months but have not done so more recently. This may be due to a variety of reasons, for example, injury or

lack of motivation. In this instance, the runners would still be appropriately categorised as a runner, but they may not report running in subsequent questions, for example 'current average running' may be zero. This is a factor to consider when interpreting the data.

Running Load

Estimates of running load were derived from several questions. As discussed in the literature review, load can be calculated from several components of running exposure (e.g. duration, intensity and frequency). The literature review did not identify any agreed calculations for reporting running load nor gold-standard methods to quantify the various ways it can be calculated (section 2.9). The present study therefore presents a novel methodology which is justified below.

Duration

Duration of running provides an indication of several factors, both physical and psychological, that could affect joint health and risk of OA. A review by Saxon et al (1999) compared the long-term effect (expressed in years training) of various sports (including running) and OA. Data suggests varying effects of duration depending on the type of activity conducted. Greater duration of running suggests how long the mechanical stresses involved in running will have been exerted on the joints for. Prolonged exposure also affects running experience and may affect running performance (technique) and body awareness (i.e. avoiding occurrence of sub-acute injury).

Duration of running was calculated by converting responses to years (defined in full years and fractions of years), for example, 2 years 6 months was converted to 2.5 years.

A limitation of this question is that it enabled participants to provide a response that combined running exposure throughout life interposed by significant periods of non-running. This may lead to false equivalence when exposure is the same, but it is unknown whether running for a defined number of years continually or with interruption have the same effect. Participants may have also interpreted the question differently, leading to differential responses. For example, a runner may have started their activity relatively slowly, with few runs completed and long breaks in between, but still included this period in their running history duration. A potential way to limit the effects of this would have been to include a statement that stipulating a minimum distance or regularity of running (e.g. minimum number of runs or minimum running distance completed per month to identify regular participation). This may have introduced error and imprecision if recall was required over a long period. It is also likely that increased duration is more common amongst relatively older athletes, since age is a limiting factor.

Average Weekly Running

In isolation, the number of runs per week is a limited measure of running load, since it does not consider the distance or duration. However, as a gross

estimate, it can indicate running frequency. Number of runs per week was used to identify usual running patterns. Where a range of runs per week was given, (i.e. 3-4), the mean was calculated.

Average monthly and annual running were used to approximate normal running behaviours. Using average running rather than actual running has two key benefits. First, it does not require the athlete to have an actual measurement of running to report, for example from training diary. It is likely that most participants would estimate these values anyway. Completing a questionnaire that requested actual running distance and/or duration for a specified period would place significant burden on the participant. Second, runners may not have run during a specified period (i.e. the last week or month) or completed running that was not representative of their normal running behaviours. This could be more pronounced due to the recruitment process. If, for example, a runner was recruited at half marathon or marathon, they may have been training specifically for that event and may have tailored their running according. Accordingly, average running over the previous 12 months was also included separately to assess running over a longer time frame. For consistency, running duration was converted to minutes if presented in hours and running distance was converted to kilometres if in miles.

Change in Running

The inclusion of a question regarding change in running compared to 12-months ago was considered useful to provide an indication of overall running behaviour. A systematic review identified reasons why levels of participation in sport and PA vary. For adults, some of the main motivators included sense of achievement, skill development, medical benefit, social support and enjoyment (Allender, Cowburn & Foster, 2006). As per other running behaviours, running duration was converted to minutes if presented in hours and running distance was converted to kilometres if in miles (multiplied mileage by 1.61).

Physical Activity

The International Physical Activity Questionnaire - Short Form (IPAQ-SF) was used to identify PA over the previous 7 days. The IPAQ-SF identifies vigorous, moderate, walking and sitting activities and the frequency and duration of each (Craig et al, 2003). A benefit of using the IPAQ-SF is that it is relatively short. It has fewer questions which was useful in this research because the author was mindful of maintaining a relatively short questionnaire to avoid negatively impacting completion rate. The long-form of the IPAQ has 31 items in comparison to the nine on the short-form (Craig et al, 2003).

The IPAQ-SF has been criticised for significantly over-estimating PA measured by objective measures. A systematic review by Lee et al (2011) reported that most studies showed negligible to small correlations with objective measures.

Depending on the tool used for comparison, over-estimation was wide, but in five studies it varied by 36-173%. The benefit of using self-report PA is that it is less invasive for the participants, for example they do not need to wear a device nor submit data. Self-report methods are useful for identifying PA but they are subject to error (under or overestimation of true activity) and bias (recall and response, for example, inaccuracy, social desirability) (Prince et al, 2008). This general criticism of self-report data is relevant in this research. It should therefore be interpreted with appropriate caution.

3.5.3 Baseline Questionnaire 2 Exposure Variables

Running Behaviour

The specific question to assess current running (and used in the validation arm of this study) was as follows (Figure 43):

> Please complete the table below to outline details of your current average weekly running. Include duration, distance (identify units used) and surface for each session. If multiple runs are completed on a given day, calculate the daily distance and duration.

Figure 43: Running Exposure Question

This data is referred to as 'Current' running in the Validation analysis. For each run completed over a typical seven-day period, additional running data was requested (duration (time in hours/minutes), distance (kilometres or miles) and surface (ground type)).

A second question was then completed to identify historical running. Historical running in this circumstance relates to six months preceding completion date of the questionnaire (Figure 44).

Please complete the table below to outline details of your average weekly running for 6 months ago. Include duration, distance (identify units used) and surface for each session. If multiple runs are completed on a given day, calculate the daily distance and duration.

Figure 44: Historical Running Exposure

This question was completed in the same manner as the previous question, i.e. a grid for duration, distance and surface details. 'Average' running over a seven-day period rather than running over the last seven days was reported for several reasons. First, the runner may not have ran during that time frame, for a myriad of reasons including injury or lack of motivation. Second, due to the recruitment methods used in this research (i.e. recruitment at running events, including long-distance races), running during the week before might not be representative of normal running because of specific training and/or reducing the amount completed in preparation.

3.5.4 Follow-Up Questionnaire Exposure Variables

<u>Running Behaviours</u>

The following questions were used in the analyses at follow-up (Table 16). The wording at follow-up was consistent with questions in Baseline Questionnaire 1 and 2.

Question	Notes
Do you currently run?	Refers to running status during the previous 12 months
Are you running more or less than you were 12 months ago?	Categorical responses: A lot less A bit less About the same A bit more A lot more
On average, how many running sessions are you completing per week?	Number of running activities per week
On average, how long do these sessions last?	Units of time (hours:mins)

Table 16: Follow-up Questionnaire Running Behaviour Questions

3.5.5 Potential Confounders

Confounding can prevent the effect of exposure to be assessed correctly. Confounders are defined as:

> '*A predictor of the outcome, but is also associated with exposure.'*
>
> Baumann et al, 2002 p7

Potential confounders are those that are hypothesised to be indicated in the causal pathway (Greenland, Pearl & Robins, 1999). Confounders may distort the true relationship between an exposure and an outcome by negatively (underestimating exposure effect), positively or even reversing the effect of exposure on disease.

There are three conditions that are necessary, but not sufficient, for a factor to cause confounding. According to the criteria of McNamee (2003), the factor must:

1. Be a cause of the disease, or a surrogate measure of a cause, in unexposed people; factors satisfying this condition are called risk factors
2. Be correlated, positively or negatively, with exposure in the study population. If the study population is classified into exposed and unexposed groups, this means that the factor has a different distribution (prevalence) in the two groups
3. Not be affected by the exposure

McNamee (2003) p 228

Potential confounders and details about how they were identified in the questionnaire for this study are listed in Table 17 below.

Factor	Question	Response
Gender	What is your gender?	Binary
Age	What year were you born? (e.g. 1965)	Continuous (years)
BMI	What is your height? (without shoes) (feet and inches or centimetres)	Continuous (m/kg2)
	What is your current weight? (light clothing only) (stones and pounds or kilograms)	
Physical activity	We would like to know the type of and amount of physical activity involved in your work. Please tick which best corresponds with your present occupation from the following four possibilities	Categorical (sedentary, standing, manual, heavy manual)
	We would like to know the type of and amount of physical activity involved in your previous work if you have had more than one job / career. Please tick which best corresponds with the majority of your previous occupation(s) from the following four possibilities	Categorical (sedentary, standing, manual, heavy manual)
Injury	Have you ever sustained a significant injury that caused pain for at least most days during a one-month period and for which you consulted a medical professional or a healthcare provider such as a GP?	Binary
	Injury details	Body part, age at injury, type of injury, sport at time of injury, time to return to sport

Table 17: Potential Confounders

Gender

Females are at greater risk of, and more severely affected by, knee pain (especially anterior knee pain), knee OA and cruciate ligament injuries that could lead to OA. A systematic review and meta-analysis of risk factors for knee OA identified 11 papers looking at the role of gender. A pooled OR for female gender (1.68; 95% CI 1.37-2.07) was reported. Women generally describe greater pain compared to men despite the severity of radiographic OA being similar. It is not fully understood why gender differences exist, but they could relate to hormones, body composition, psychosocial characteristics, knee structure and neural processing (Silverwood et al, 2015). Gender was a binary choice, male or female.

Age

Prevalence and incidence of OA increases with age (Losina et al, 2013). It is hypothesised that this relationship is due to the cumulative effects of exposure to multiple risk factors throughout life in addition to other biological changes that occur in later life (e.g. reduced muscle strength) (Zhang & Jordan, 2011). Authors report that there is a non-linear association between age and incidence of severe knee OA. One study of Swedish males identified a steep increase above the age of 50 but then a decline in incidence after the age of 70. One potential mechanism is that susceptibility to OA is important and those at greatest risk will already have the disease by 70 (Jarvholm et al, 2005).

Age was calculated by subtracting the year of completion of the questionnaire from year of birth.

Body Mass Index (BMI)

Obesity has a deleterious effect on overall health, including risk of knee pain and OA. It is one of the greatest predictors of knee OA (Sharma et al, 2000). Excess bodyweight can be measured using BMI. BMI is a simple and easy assessment of to identify who is obese or overweight. It is widely used in research and clinical practice to assess obesity. A systematic review including 21 studies reported BMI was significantly associated with radiographic and symptomatic OA (RR 1.25 95%CI 1.17-1.35). For each five-unit increase in BMI, there was a 35% increased risk for knee OA (RR 1.35 95% CI 1.21-1.51) (Jiang et al, 2012). The knee may be more susceptible to the effects of higher BMI than the hip. This could result from the mediating factor of mechanical loading on the joint, for example, malalignment (Reijman et al, 2007)

BMI cannot differentiate between lean muscle mass and adiposity. Muscle and adiposity could have opposing effects lower limb joint health. Greater muscle mass may indicate higher levels of strength and function, whereas adiposity could influence local joint forces and systemic factors that raise risk of OA. BMI was calculated by using self-reported height and weight. Units for height were converted to metres and centimetres and to kilograms. BMI was calculated by dividing weight by height, then dividing this answer by height. BMI was

categorised according to a modification of the NICE (2014) guidelines for adults (Table 18):

Category	BMI Range
Underweight	<18.5
Normal	18.5-24.9
Overweight	25.0-29.9
Obese	30>

Table 18: BMI Categories

Occupation-Related Physical Activity

There is evidence that certain occupation types and specific activities are related to increased risk of knee OA, for example agriculture (Rossignol et al, 2003). Occupation is a contributor to overall PA. A review by Palmer (2012), concluded that occupational activities that physically load the joint - squatting, kneeling, heavy lifting, climbing and high workload - could contribute to the onset and progression of disease and symptoms.

The Short UK EPIC Physical Activity Questionnaire (Day et al, 1999) is a useful tool as it provides data for the previous 12-month period and therefore can be used appropriately throughout the annual follow-ups. Additionally, it provides data across occupation and other non-sporting activities (Espana-Romero et al, 2014).

Manual or heavy manual occupations were designated ‘high-risk occupations’. These were coded together, into a binary outcome, since data regarding

duration in each occupation was lacking. Obtaining enough additional detail to perform an analysis on occupational duration / type would have placed significant additional burden on the participants.

Injury

Previous injury has consistently been shown to be associated with increased risk of developing OA. It is plausible that damage to the internal structures within or surrounding the joint can influence biomechanics, deleteriously impact integrity and alter force distribution (Muthuri et al, 2011).

The wording of the injury question could have several impacts on this research and subsequent findings. The definition of injury used in this study - dependent upon pain for most days of a one-month period and consultation with a medical professional - sets a threshold designed to prevent the reporting of less severe injuries that may not have any relevance to long-term joint status. It is also hoped that by requiring more severe injuries to be recalled, this may increase accuracy. Furthermore, it is possible that by not limiting the recall of injury to a specific period, i.e. the previous ten years, that the accuracy of recall is reduced if injury occurred in early life for older participants. However, this was justified in the study design since injury may have occurred at any time and thus is relevant. Furthermore, injuries that occur throughout life may relate to different long-term outcomes. Injury was also not limited to those sustained during running. It is likely that significant injuries may also have occurred during

participation in other sports, pastimes, occupational activities. These could not be discounted since they could still impact on joint health.

Details of the injury were obtained via subsequent questions to try and elicit the type of injury. Specific injuries to the cartilage, meniscus and cruciate ligaments are most attributed to increased risk of OA and thus should be analysed separately (Roos et al, 2005).

Self-report injury is just one method of identifying injury. An alternative method would have been to use medical records. Accessing medical records in this circumstance would have confirmed attention by a medical professional (in line with the criteria of the definition included in the question). On the other hand, this may have limited the participation rate as informed consent would be necessary for the researchers to access these files. Ethics and governance issues would have been extremely strict, to protect the privacy of those involved. Further, there would have been significant issues since not all identifiers would have been removed from the data (i.e. it would not have been anonymous). In the case of longitudinal data, it would have been impractical to collect anonymous data and several safeguards would have been necessary. That is not to say that it would not have been possible, it just would have been extremely difficult in the time-frame for this thesis and placed significant burden on the researchers with the available resources.

Bias

The STROBE reporting tool requires discussion of potential bias in the methodology. This is presented below.

Bias relates to the prejudiced consideration of a research question. It can occur at any stage of research (e.g. design, data collection, analysis and publication (Pannucci & Wilkins, 2011). Bias is inherent in all research and unavoidable. Steps can be taken to minimise its effects and the extent to which the validity and reliability of results are affected (Smith & Noble, 2014). At various stages of this project, efforts have been made to reduce the impact of bias.

Design bias

Poor research design can create a gap between the stated aims and methods employed. Preconceptions of the authors (i.e. running has a specific health effect not synonymous with previous research findings) can also impair how the research is conducted since a particular outcome may be more desirable that supports said beliefs. To counter this, at the design stage, previous research was reviewed in collaboration with other senior academics to identify how previous work had been conducted and to critique the methods and results (Leech, Batt, Edwards, 2016; Timmins et al, 2017). An appraisement tool was used to ensure that the systematic review and meta-analysis was conducted objectively and reduce confirmation bias.

Selection bias

Selection bias refers to several sources of bias including loss to follow-up, incidence-prevalence bias, volunteer (consent) bias and non-response bias (Hernan, Hernandez-Diaz & Robins, 2004). The common consequence is that the association between the exposure and the outcome is different between those eligible for analysis.

Consent bias may lead to under or over estimation of incidence or prevalence of the condition of interest (Junghans & Jones, 2007). An ideal study design would include every runner, every person that had previously ran and everyone who in the future will run, followed up longitudinally but this is clearly unfeasible. In a practical sense, efforts were made to ensure that the eligibility to take part were maintained as open as possible. Furthermore, when educating potential participants that runners could take part regardless of the presence or absence of symptoms, but it cannot be assumed that equal numbers of runners with or without symptoms of interest were included.

The authors used paper copies of the questionnaire to facilitate responses from those that did not wish to use an online platform. There are no universally agreed criteria for acceptable follow-up rates (Fewtrell et al, 2008). Attrition may affect generalisability preventing incorrect conclusions to be drawn and the ability to apply these to the wider population 'external validity.'

To overcome potential selection bias, the researchers made every effort to recruit runners from a variety of backgrounds, regardless of whether they had symptoms and/or OA. This was emphasised in oral and written recruitment methods. The benefits of taking part were explained at each stage of the research process to encourage continued participation.

Data collection bias

Questionnaire administration can affect data quality (Bowling, 2005). There are several potential issues relating to electronic questionnaires, including high cognitive burden. Just because the survey is accessible does not mean that all people have the equivalent awareness and understanding of the components involved. Where appropriate, explanation of the terms or definitions were provided in the questions to assist the participants. Further, participants were able to contact the researcher should any questions remain.

It is assumed that because the participants can complete the survey in isolation at a time of their choosing and their responses known only to the researcher, the probability of social desirability bias (i.e. reporting in a manner that ensure they are viewed favourably rather than a true response) is reduced compared to an open forum.

Measurement bias

A potential source of bias with the use of a questionnaire is recall bias, for example failing to report instances of an outcome that didn't really occur or

providing inaccurate or erroneous responses). This may be particularly relevant for components that have a degree of subjectivity, such as symptoms (i.e. pain) and injury. For example, injuries that do not have a sudden onset could be hard to define for the participant (Figure 45). There is not a linear relationship between injury (pain) and time (Bahr, 2009). Previous studies that have relied upon retrospective analysis exploring knee symptoms and risk factors in OA have acknowledged this as a limitation. In addition, it is noted that time between events may increase imprecision of reporting. The use of multiple measures of outcomes is therefore important to enable these to be reported by the participant with greater sensitivity.

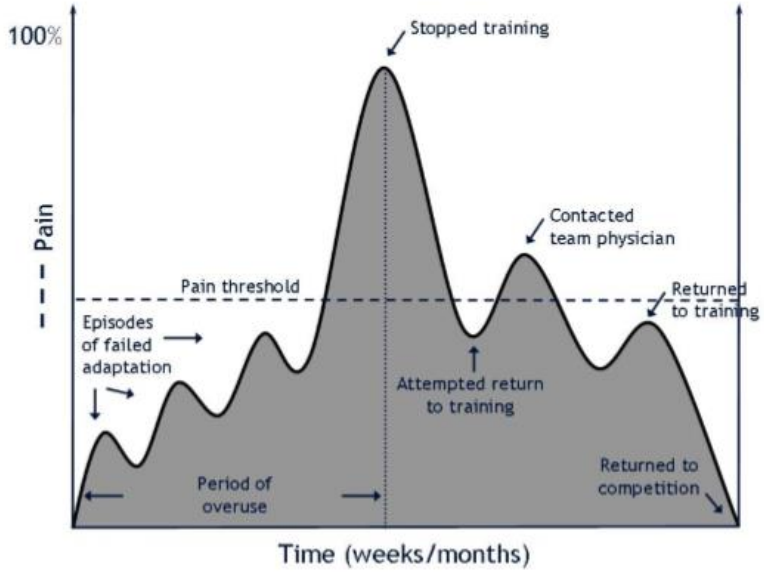


Figure 45: Hypothetical overview of the onset of tissue injury and pain in a typical overuse injury. Adapted from Leadbetter WB. Cell matrix response in tendon injury. Clin sports med 11: 533-578. In: Bahr (2009) p 967

A further issue may relate to misclassification bias which is reduced by using, where appropriate, validated tools for factors pertinent to the research

question. In the absence of objective measures (such as radiological findings), there is a reliance on self-report being accurate, which assumes that all participants have equivalent knowledge and provide a true answer. Previous research has reported that misclassification can lead to uncertainty and adversely affect sensitivity, due to coding errors or false reporting. Misclassification may also stem from poor/inaccurate diagnosis. This could therefore influence both exposure and outcome variables in this study.

Analysis bias

Like design bias, preconceptions or inherent bias within the researchers may lead to completion or presentation of certain analyses that support a pre-held belief. This could include:

- Data fabrication - reporting findings non-existing data
- Data elimination - removal or ignoring data that doesn't support the experimental hypothesis
- Statistical errors - using inappropriate tests or multiple tests until a significant outcome is found, regardless of hypothesis (Simundic, 2013).

To counter these potential sources of bias, the author has provided a detailed methodology using STROBE criteria for transparency. Justification for each decision made is provided at each step. The data will be maintained by other academics for future validation and continued analysis. Where appropriate, collaboration with other academics will ensure that the analyses are performed

accurately and appropriately. The aims, objectives and hypotheses are defined so that the appropriate tests are performed.

Publication bias

Publication bias can have an impact on research published in relation to OA, but the impact of this bias is unclear (Hansen et al, 2014). It is possible that data with a positive outcome is more likely to be of interest to journals. It could be proposed that positive (association between running and OA) and negative (no association between running and OA) are of equal clinical importance and therefore neither is more beneficial than the other to the editor. The importance of acknowledging this is that previous research was used to inform the present study design. However, the best available data was used, and in the absence of evidence to the contrary, this should be assumed to be an accurate representation of our knowledge.

Study Size

To generalise the findings to the wider population of runners (external validity), a large sample is required. The calculation for the number of people needed is comprised of four components (Noordzij et al, 2010):

1. Type I error - a false positive, i.e. the chances of falsely rejecting the null hypothesis. Alpha is most commonly fixed at 0.05, equivalent to <5% change of a false-positive conclusion being made

2. Power - a false positive i.e. the chance of falsely accepting the null hypothesis. Beta is most commonly fixed at 0.20, equivalent to <20% chance of a false negative conclusion being made.
3. Smallest effect of interest - the minimum difference considered clinically relevant and biologically plausible. This can be calculated using previous research for numerical continuous variables or binary outcomes. Sample size is inversely proportional to the square of the difference.
4. Variability - population variance estimated by the standard deviation of a continuous variable. Variability can be identified using previous research.

For the main thesis hypothesis testing, a difference in means sample size formula was used to identify the sample size using the KOOS (Noordzij et al, 2010). Using the previous research to identify the standard deviation of the outcome of interest (12.9) and the smallest difference in means important to detect (10), where $\alpha=0.05$ and $\beta=0.20$, a total of 35 participants per group would be required. (Roos, 2003; Roos, 2008).

To compare differences in OA prevalence in this cohort, recruitment of 3368 people was required in order to have sufficient power to determine a 1% difference (with standard assumptions of $\alpha=0.05$ and $\beta=0.2$) (van Belle, 2008).

For the training diary validation sub-group, based on statistical calculation proposed by Liao (2010), the number of participants required for agreement

studies, (with standard assumptions of α=0.05 and β=0.2), more than 32 participants were required.

For the function sub-group, based on a 95% confidence interval sample size calculation (Van Belle, 2008), using a conservatively estimated variance of 15 repetitions during the sit-to-stand protocol (during a 30-second testing period) with a low desired margin of error (3), 97 subjects (per country) would be required.

3.6 Data Analyses

Questionnaire Data Cleansing

Cleansing of questionnaire data (Baseline Questionnaire 1, Baseline Questionnaire 2 and Follow-up Questionnaire) was conducted to assess the quality and integrity of responses to maintain quality in the analyses. The rules applied were consistent across all questionnaires.

The rules for data cleansing have been divided into each relevant section for clarity of explanation. Demographic (Table 19) and running exposure variables were cleansed as follows (Table 20).

Question	Rules Applied	Justification
What **year** were you **born**? (e.g. 1965)	• If a two-digit number was entered (i.e. 56), rather than year of birth (i.e. 1960), the two-digit number was assumed to be their age at time of questionnaire completion.	The assumption for this question is that participants have misread what information was requested.
What is your **height**?	• Imperial units converted to metric units. • Metric units not in metres were converted, for example when given in cm or mm. • Where 'k' was entered as units, assumed to be 'kg'. • Weights accompanied by a comment e.g. 'About', 'estimate' or 'I think', these were accepted as defined. • If two values were provided (e.g. metric and imperial) that did not match, the lower of the two was used. • Where no units were used but numbers interrupted by decimal places, ':' or '/', e.g. 5.7, 5:7 or 5/7, these were identified as imperial figures. • Abnormally large values (e.g. '2.7') assumed to be 1.7 incorrectly typed.	Height was required to be in metric units for to use in the calculation for Body Mass Index (BMI). An NHS conversation chart was used to calculate metric values.
What is your current **weight**?	• Imperial units converted to metric. • Where part ounces were given, these were rounded up to the nearest full pound. • 'Half stone', '1/2 stone, '.5 stone' converted to 7 pounds	Weight was required to be in metric units for to use in the calculation for Body Mass Index (BMI). An NHS conversation chart was used to calculate metric values.

Table 19: Data cleaning rules applied to demographic data

Question	Rules Applied	Justification
How **long have you been running** for? (e.g. 3 years)	• Where no units given, the value given is assumed to be years (since the example in the question is in years). • Where years and months given (e.g. '3 years 10 months', converted to fraction of year. Values less than one year (e.g. '2 months') converted to fractions of a full year. • Where two values given (e.g. '8/9'), the mean of the two is calculated and used (e.g. 8.5). • Where a value is given but a break or interruption in running is implied (e.g. 'on and off for 30 years', '10 years this time'), the value given was taken as running duration. Where a break or interruption is indicated but no value is given regarding its duration (e.g. 'Started again this year,' 'Regularly in 80s & 90s'), the participants response was not included for analysis. • Where running duration was given inclusive of a break from running of a specified duration (e.g. '30 years with an 8 year break'), running history was calculated by subtracting the duration of the break from overall duration. In this example, the number of years running would be 22. • Where the duration is indicated to be an approximation or is indicated to be greater or less than a specified time period (e.g. '<1 year', 'Just over 3 years', '50+ years', value preceded by a '~'), the value given was used in analysis. • Answers such as 'Most of my life' without a figure were not included. • Where a date was given that they started running (e.g. 'Since June 2014', running duration was calculated from the difference between the stated date and the date the questionnaire was completed. • Where an age was given that which they started running (e.g. 'Since I was about 13…'), duration was calculated by subtracting their current age from the age given. Any reference to running as a child, teenager or at school (e.g. 'Since I could run. School running…') where no age was given, no value was entered for analysis.	Reponses should indicate an accurate representation of running history duration. Where this cannot be elucidated from the data provided, the data from this question was not included in the analysis.

Table 20: Data cleaning rules applied to exposure data

Question	Rules Applied	Justification
During the **previous 12 months** (or less if applicable), what has been your **average weekly running distance**? (e.g. 10 miles)	• Where a value was given but preceded by a '~', the given value has been used. • Where no units were reported in an answer to any question relating to running distance, the response was not included. • Where the same unit of distance (miles or km) are used in later questions that relate to running distance, the unit of measurement is extrapolated to other questions. • Where units differed, no assumptions could confidently be made about responses with missing units. In this instance, the response was not included in the analysis.	Consistency of units elsewhere in the questionnaire was justification for application of these units in other responses.
On average, how many **running sessions** are you completing **per week**?	• Where an answer was given as 'Other', these were reviewed, and a numerical figure attributed based on the reasoning (where indicated). For example, 'Less than one on average', a value of 1 was entered. • Where '0.5' was given, this response was retained for analysis. Where '0' entered (e.g. if injured), this was retained for analysis. • Where a range of values is given, the mean is calculated for analysis. • Where the response did not indicate a number ('Very dependent on what else I do weekly'), no value could be derived. • Where an average number of runs is given over a longer time period ('1 every four weeks', '7 per fortnight'), this was converted to a weekly value (0.25, 3.5).	Where no runs are currently being completed, this was retained since other factors may prevent current running (e.g. injury).
On average, **how long do these sessions last**? NB This refers to the previous question	• Where no units given but numbers include ':' (e.g. 1:15), assumed to be 1 hour 15 minutes and therefore converted to 75 minutes. • Where a value given but preceded by a '~', assumed to approximate a given value. The given value has been used. • Where a range of values given (e.g. 'from 30min to 2 hrs'), the mean is calculated. Where a range of values is given (e.g. 'varies from 30 minutes to a long run'), no value was used for analysis. • Where several runs have been defined (frequency and duration given) (e.g. '3x1 hour, the other 2-3 hours), the mean was calculated and included in analysis. If the information regarding the frequency or duration of several runs was insufficient to not enable this calculation to occur, no duration was reported. • Where a run duration was defined inclusive of warm-up and cool down, the sum of these was used for analysis.	A consistent metric (minutes) was necessary to report run duration. Where extra details were given, a calculation was completed to accurately identify the average (sum of all runs divided by number of runs).

Table 20: Data cleaning rules applied to exposure data cont.

IPAQ-SF

Interpretation of the IPAQ-SF was conducted according the instructions from the revised protocol (IPAQ, nd). IPAQ-SF METs were analysed as continuous rather than categorical outcomes.

The calculations for conversion of each activity to METs used are summarised in Figure 46;

Walking minutes/week = 3.3 x walking minutes x walking 'days
Moderate MET-minutes/week = 4.0 x moderate-intensity activity minutes x moderate days
Vigorous MET-minutes/week = 8.0 x vigorous-intensity activity minutes x vigorous-intensity days

Figure 46: IPAQ-SF Calculation

A sum of the above calculations gives an overall MET-minutes/week score used for analysis. The sitting question is not used for any calculation. Figures were converted to minutes. As per the instructions, if minutes and hours were placed in the wrong column by mistake, these were corrected. If 'Don't Know' was entered or data was missing for any value, this data was excluded from any analysis. If number of days exceeded 7, then this was noted. Any value greater than 9 was not allowed and the case removed. A minimum of 10 minutes activity was included in analysis. If it did not meet 10 minutes duration, this was recoded as zero. If total duration exceeded 16 hours for a specific activity (i.e. walking, moderate or vigorous activity, this case was removed from analysis). The 'truncation of data' rule was not applied. This proposed rule is included in

the guide but it is stated that it requires further testing. In this instance, all activities exceeding 240 minutes would be re-coded as a maximum of 240 minutes. The reason for not applying this cap is many of the runners are extremely active and would exceed this total.

Cleansing of Questionnaire Outcomes

Knee OA

A diagnosis of OA was reported as being made by either a physician (e.g. a general practitioner) and/or any other healthcare provider (e.g. a physiotherapist). Diagnosis by either healthcare professional group was given equivalent status and was not dependent on radiographic investigation. According to current NICE guidelines (2014), a diagnosis of knee OA can be made without radiograph.

Healthcare professionals were limited to allied health professionals (e.g. physiotherapists) Diagnosis by non-medically trained individuals (e.g. masseuse) were excluded.

The joint affected by OA was determined from the details provided in the table. The knee was used as an umbrella term for all articulations. 'Knee', 'patellofemoral' and 'tibiofemoral' are examples of terms that would be considered as inclusion for analysis of knee OA.

Joint Surgery

Details of joint surgery was provided according to the type (e.g. joint replacement), body area, age and indication for surgery. For joint replacement, a full or partial knee joint arthroplasty had to be indicated. As per the location of OA, the knee was an umbrella term for all articulations (i.e. the PFJ and TFJ were both included). The indication for surgery had to be OA for it to be considered as associated with the disease. 'Osteoarthritis' and 'wear and tear' are two examples of terms used that were accepted to indicated OA as the cause of joint replacement.

Knee Pain

The presence of knee pain was determined by asking whether pain had ever been present around the knee joint for most days during a one-month period. This was a binary question.

Injury Data

Significant injuries were defined as those that required consultation with a health professional and caused pain for most days during a one-month period. The Orchard Sports Injury Classification System (OSICS) is widely used in injury epidemiology research (Orchard et al, 2010). The latest version of OSICS (10.1) was used to classify injuries by a physiotherapist (RDL) based on the self-report diagnosis provided. Rules of interpretation anatomical information provided are listed in the table below:

Report	Interpretation / Classification
Gilmores Groin	Sportsman's hernia
Hamstring injury	Thigh injury not knee injury
Bursitis	Buttock injury not hip injury
Shin splints / lower leg stress	Other leg overuse injury
Neck	Cervical spine injury
Middle back / spine	Thoracic spine injury
Lower back / small of back	Lumbar spine injury
If 'probable'	Regarded as not definitive diagnosis
Upper leg	Thigh injury
Break	Fracture
Worn bones	OA
Heel	Foot injury
Skull/cheek/nose	Facial injury
Upper arm	Humerus
Lower arm	Forearm injury
Inflammation	'Not otherwise specified'
Inflamed tendon	Tendinopathy

Table 21: Data cleaning rules applied to injury data

Spelling errors were interpreted within the context of the specific report. If it could not be accurately ascertained from the information provided, the injury was classified appropriately according to what was legible. If necessary, it was reported as 'Not specified.' Where an injury was reported as OA, this was removed from the injury analysis. Medical conditions were also removed (e.g. gout). Participants were asked to report which (if any) activity they were completing when the injury occurred. An injury attributed to duathlon, triathlon (multi-discipline sports that includes running) or athletics where running was not explicitly specified as the cause were also classified separately. For example, an injury could have occurred in another athletic discipline (e.g. javelin). Obstacle and adventure races were not included as running injuries. Jogging and orienteering injuries were included within running injuries. Assault courses, fitness classes etc were not classified as running injuries.

For analysis, it is worth noting that this is self-reported injury and causality. As a result, the injuries should be considered as 'injuries attributed to running' rather than running injuries per se.

Questionnaire Validation

Once all the data had been input into the database prior to analysis, a second author (AG) reviewed the data from each participant. The completion dates of the questionnaire were identified (since these were the basis of calculation of the historical data from six month previous). Any specific running activities that did not appear correct compared with other activities recorded by the athlete were also highlighted and the original data source reviewed (i.e. runs that appeared excessively long or fast in comparison to other runs).

For validation section (comparing self-report running and contemporaneous/diary data), four categories of running behaviour were created. Previous studies have stratified runners according to metabolic equivalent (an expression of energy expenditure per minute, MET) (Williams, 2013). Using this calculation (Figure 47), running can be expressed as daily MET by:

$$\text{METhr/d} = \frac{\text{Running distance (km)} \times 1.07}{7}$$

Figure 47: Calculation for METs (running behaviour)

Using the above calculation, Williams (2013) used the following categories: <1.8 METhr/d, 1.8-3.6METhr/d, 3.6-5.4METhr/d and >5.4METhr/d in analysis of recreational runners (usual running) and risk of OA. These groups have been used in the present study. When requesting the diary, the same time periods that corresponded to the dates of questionnaire completion and six months prior. The diary data requested related to seven day, four-week and 12-week periods preceding the timepoint of interest.

Depending on the format of the diary data, participants may have provided additional data (for example, spanning a complete 12 months preceding questionnaire completion date). In this instance, the data relating to the dates of interest were extracted manually by identifying questionnaire completion date and calculating the date six calendar months from then.

It was not necessary for participants to provide data for all time-periods. When a diary was incomplete, participants were contacted to confirm why this was the case. For example, a device to measure running may have been purchased part-way through the period of interest. Where a diary was incomplete due to a reason that prevented running, for example, injury or illness, this diary was regarded as complete because actual running was still recorded. 'No Running' was recorded when a week period was blank during. In this instance, zero was input for weekly distance and weekly duration.

Where there was ambiguity, or no units were provided regarding run distance, efforts were made to contact the participants for clarification. Where a run was recorded with no units, but it was accompanied by a description of a specified distance event (i.e. a marathon), it was assumed that all other distances could be calculated accordingly. Miles were converted to kilometres (multiplied mileage by 1.61).

The questionnaire and diary data for each participant was combined into a single database. A collaborating researcher (AG) independently assessed its accuracy. Where inconsistencies were highlighted, the original data source of the data was reviewed by RL. If multiple runs on the same day were reported in either the questionnaire or the diary, these were combined. A daily total (the sum of each run distance and duration) was used in the analysis. For 7-day data, weekly running distance and running duration were calculated. Average running pace was calculated where both these factors were provided. Average running pace was calculated by dividing weekly running distance by running duration. For 4- and 12-week data, averages of running distance and running duration were calculated from the 4 and 12-week estimates respectively.

Functional Testing

All data were collected by a single physiotherapist (RDL). All participants completed the same protocol and tests were completed in the same order.

3.7 Statistical Analyses

The statistical tests for each analysis are described below. All comparisons were made with the largest sample of data available for each individual test. Data may be missing from some participants due to incomplete responses across all questions or sub-questions. This may mean variable *n* are reported at various points. Comparisons were considered significant at $p<0.05$.

3.7.1 Questionnaire Data (Baseline Questionnaire 1, Baseline Questionnaire 2 and Follow-Up Questionnaire)

Descriptive statistics are presented as proportions (percentages). The mean, standard deviation (SD) and range were calculated using SPSS. Parametric and non-parametric tests (as indicated) were used to assess differences between groups. Parametric tests are defined as:

> 'Statistical tests which assume that the continuous variables being analysed have a normal distribution.'
>
> Barton & Peat (2014) p376

Non-parametric tests are defined as:

> Statistical tests that have no assumptions about the distribution of data'
>
> Barton & Peat (2014) p375

Data distribution (i.e. normality) was analysed visually using a histogram and the Kolmogorov-Smirnov test. To determine whether there were statistical differences between the current runners and non-runners, chi-squared (categorical variables) and t-test (continuous variables) were used. Chi-squared was also used to identify the difference between two or more groups in analyses and binary outcomes (e.g. knee pain, knee OA). For example, in examination of runners-only, where the athletes were categorised into based on running behaviours (e.g. running duration per week (minutes), weekly running distance (km). Relative risk (RR) is the ratio of an outcome of interest (e.g. knee pain) and the difference in prevalence between groups. In this thesis, RR for knee pain was reported between runners. RR, rather than odds ratio (OR) were calculated since the outcomes under investigation (i.e. knee pain and OA) were not considered rare. It would therefore be inappropriate to use OR as this can inflate findings (Edwards, 2018). Multiple RR analyses were conducted. First, a crude RR for knee pain in runners with no adjustment. Second, RR for knee pain in runners was estimated with adjustment for gender, BMI and age. A RR analysis was conducted for knee OA in runners. This was conducted cognisant of other factors based on previous research (literature review). This includes demographic factors, lifestyle factors, history of injury and running behaviour). The assumptions of the tests are summarised below, assimilated by descriptions from Barton & Peat (2014) and Bland (2015)

Test	Type of Test	Assumptions
Chi-Square	Assessment of distribution of categorical variable in two or more groups	• Measurements are independent (one measurement per participant included) • Participants are included only once
t-test	Parametric	• Independent groups (each participant is in one group only) • Measurements are independent (one measurement per participant included) • The outcome variable is on a continuous scale and normally distributed in each group • Variances between the groups are approximately equivalent
Mann-Whitney-U	Non-parametric	• Data are randomly sampled from the population • Independent groups (each participant is in one group only)
Kruskal-Wallace	Relationship between two variables	• Ordinal data / nominal data • Interval data (not normally distributed)
Spearman's correlation	Non-parametric Rank correlation for two ordinal variables	• One variable has a continuous normal distribution • The other variable is categorical or non-normally distributed
Kendalls tau b	Non-parametric correlation	• Between two categorical variables or non-normally distributed variables

Table 22: Statistical Tests

3.7.2 Questionnaire Validation

Agreement between the diary and questionnaire running behaviour was investigated with Concordance Correlations and Limits of Agreement (Lin, 1989; Bland & Altman, 1986). The Concordance Correlation Coefficient is used to assess the agreement between paired readings (Lin, 1989). The Bland-

Altman Plot is a graphical representation of the agreement between quantitative measurements from two sources. The graph presents the difference in measurement between the paired data sources against the mean of the two measurements (Giavarina, 2015).

Comparison of agreement for the four categories of runners, (<1.8 METhr/d, 1.8-3.6METhr/d, 3.6-5.4METhr/d and >5.4METhr/d), according to the methods of Williams (2013), were completed with weighted (Kw) and unweighted kappas (K). The weight of Kw was $1 - \{(i-j)/(k-1)\}^2$ (Reichenheim, 2004).

Landis & Koch (1977) kappa coefficient thresholds were used to report the extent of agreement (table 23).

Interpretation	**K**
Poor	<0.00
Slight Agreement	0.01-0.20
Fair	0.41-0.60
Moderate	0.61-0.80
Almost Perfect	0.81-1.00

Table 23: Kappa coefficients thresholds

Although described as arbitary in the original paper, this classification system has become wiedely used and provides a useful benchmarks when presenting results (Landis & Koch, 1977).

3.7.3 Functional Testing

For comparison between groups, the student t-test was used to compare the means of independent groups (e.g. gender). The agreement between running behaviours (e.g. number of years running) and test performance was calculated with Spearman's Correlation Coefficient.

4.0 Results: The Validity of Self-Reported Running Behaviour

4.1 Introduction

Accurately measuring an exposure of interest is crucial to identify a dose-response relationship. No gold-standard of PA measurement exists for every research scenario. This is largely due to the inverse correlation between the practicality and accuracy of each tool (Ainsworth et al, 2015). Much of the research conducted relating to running and risk of OA has been reliant upon self-report running. This involves participants completing questionnaires, which are susceptible to imprecise reporting (under- or over- estimation) arising from recall difficulties and/or social desirability bias. Exposure inaccuracy could impair research conclusions and lead to false conclusions (e.g. failure to identify true associations, mistakenly reporting associations where none exist or erroneously estimation of the strength of associations).

The number of recreational athletes using 'tracking monitors' to contemporaneously monitor their training and performance is on the rise. Devices such as accelerometers, pedometers, heart rate monitors and global positioning systems (GPS) are commonly used (Butte, Ekelund & Westerterp, 2012). This provides an opportunity to assess the accuracy of recreational runners describing their own running behaviour against what they have recorded contemporaneously.

This section aims to identify the level of agreement between self-reported running in the baseline questionnaires and running recorded using user-owned contemporaneous measurement tools (e.g. GPS) in recreational athletes.

4.2 Demographic Characteristics

A total of 141 participants responded with diary data. Of the 141 participants, 139 had usable data which could be matched to questionnaire responses (Table 24)

Demographic Characteristic	n	%
Gender		
Female	57	41.3
Male	81	58.7
	Mean	**SD (range)**
Age (years)	51.1	10.8 (23.0-76.0)
History of Running (years)	12.26	11.81 (0.5-50)

Table 24: Validation Analysis - Participant Characteristics

Various formats of diary were submitted. There were 62 technological diaries, 19 handwritten diaries, 4 mixed different methods, and 39 did not specify. Examples of the different diary types are included below:

- Technological diaries; Strava, TomTom GPS
- Handwritten diaries; manual use of stopwatch, record from treadmill

4.3 Current Running

The descriptive statistics of questionnaire and diary running data is outlined in Table 25.

4.3.1 7-day Data

The difference in mean number of runs per week was greater in the questionnaire (by 41.15%) compared with diary data. The median number of runs per week was also greater in the questionnaire data (4) compared to the diary (2). For weekly running distance, mean and median running duration were also greater in the questionnaire by 46.05% and 49.04% respectively compared to the diary. On the other hand, average pace calculated from questionnaire and diary data were similar. The range (minimum-maximum) value was greatest in the questionnaire for weekly running distance and running duration.

4.3.2 4-Week Data

Like the 7-day data, the mean number of runs per week, weekly running distance, weekly running duration from 4-week data were all greater in the questionnaire than diary by 36.51%, 35.71% and 39.42% respectively. The mean and median pace calculations for the questionnaire and diary were similar.

4.3.3 12-week Data

Similarly, mean, median and maximum values of number of runs per week, weekly running distance and weekly running duration were all greater in the questionnaire. The mean difference between the mean number of runs reported in the diary and questionnaire data 46.33% greater when self-

reported. Average pace was similar in the questionnaire and diary (mean 6.11 vs 6.04; median, 6.00 vs 5.83).

		Number of Runs per Week		Weekly Running Distance (km)		Weekly Running Duration (mins)		Average Pace (mins/km)	
	Statistic	**Questionnaire**	**Diary**	**Questionnaire**	**Diary**	**Questionnaire**	**Diary**	**Questionnaire**	**Diary**
7 Day Data	**N**	137	137	122	122	98	98	81	81
	Mean	3.78	2.49	37.01	25.34	210.87	129.12	6.17	6.17
	SD	1.45	1.65	20.81	19.78	114.95	113.91	1.12	1.37
	Median	4.00	2.00	33.98	22.80	188.50	106.24	6.00	6.05
	Min-max	0-7.00	0-7.00	0-130.36	0-90.44	0-600.00	0-470.07	4.57-9.00	4.54-14.51
	IQR	2.00	3.00	23.17	25.96	133	141.15	1.53	1.17
4 Week Data	**N**	118	118	108	108	92	92	81	81
	Mean	3.79	2.62	36.90	25.72	212.79	142.72	6.11	6.04
	SD	1.47	1.45	19.49	18.30	114.40	104.25	1.09	0.90
	Median	4.00	2.50	33.98	23.76	200.50	130.02	6.00	5.83
	Min-max	0-7.00	0-6.50	0-95.03	0-74.87	0-600.00	0-480.74	4.57-8.80	3.87-9.53
	IQR	2.00	2.00	21.42	21.82	130.50	130.63	1.43	1.23

		Number of Runs per Week		Weekly Running Distance (km)		Weekly Running Duration (mins)		Average Pace (mins/km)	
	Statistic	**Questionnaire**	**Diary**	**Questionnaire**	**Diary**	**Questionnaire**	**Diary**	**Questionnaire**	**Diary**
12 Week Data	**N**	117	117	106	106	98	98	82	82
	Mean	3.79	2.59	37.02	23.57	213.71	123.15	6.17	6.13
	SD	1.47	1.30	19.61	15.54	113.63	87.13	1.12	0.95
	Median	4.00	2.58	33.98	21.83	200.50	114.82	6.02	5.91
	Min-max	0-7	0.25-6.58	0-95.03	0-65.18	0-600.00	0-369.86	4.57-8.80	4.61-9.58
	IQR	2.00	1.83	21.11	21.74	136.00	125.63	1.67	1.42

Table 25: Current Running – Analysis of Self-report and Questionnaire Running

4.3.4 Comparison of Current 7-Day Self Report Running and Diary Data

Concordance correlations for runs per week, weekly running distance, weekly running duration and average running pace were 0.45 (0.34-0.55), 0.52 (0.41-0.63), 0.53 (0.42-0.65) and 0.59 (0.46-0.73) respectively.

Average difference in number of runs completed per week between the two sources was 1.30 runs per week. Bland Altman Limits of Agreement (LoA) were -1.435-4.02 runs per week (Figure 48). For running distance, the average difference between the two sources was 11.67km (LoA -23.72-47.06km) (Figure 49). Average weekly running duration was overestimated in the questionnaire by approximately 82 minutes compared with the diary (LoA -100.52-264.02 minutes) (Figure 50). Average difference in running pace was -0.005 mins/km (LoA -2.22-2.21 minutes per km) (Figure 51).

Figures 48-51: 7-day Current Running Data Questionnaire and Diary Bland-Altman Plots

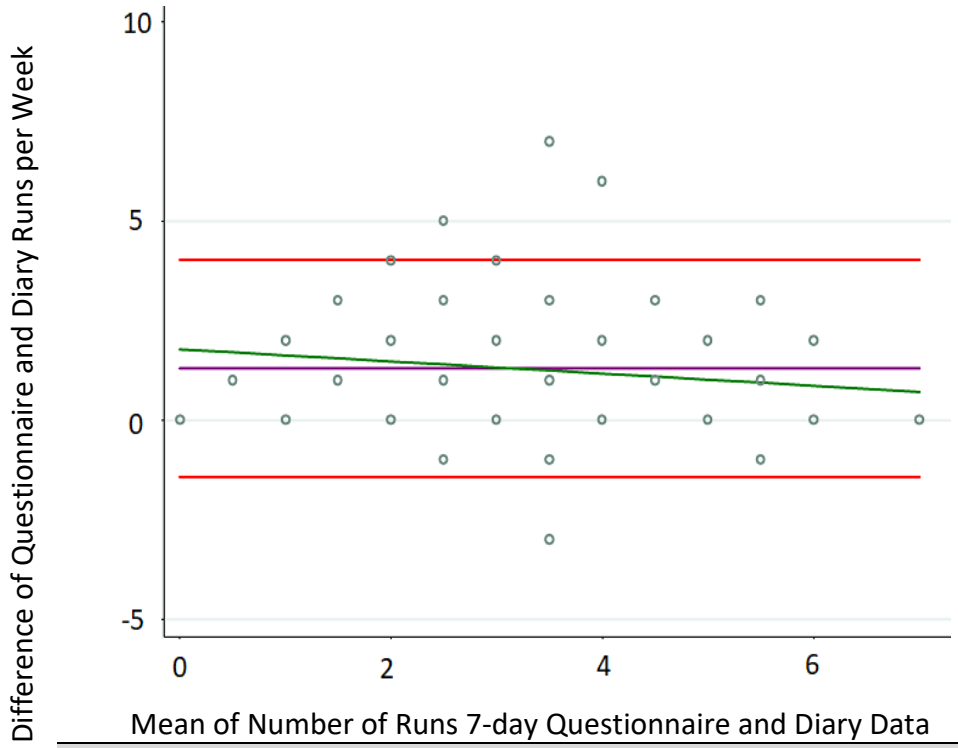


Figure 48

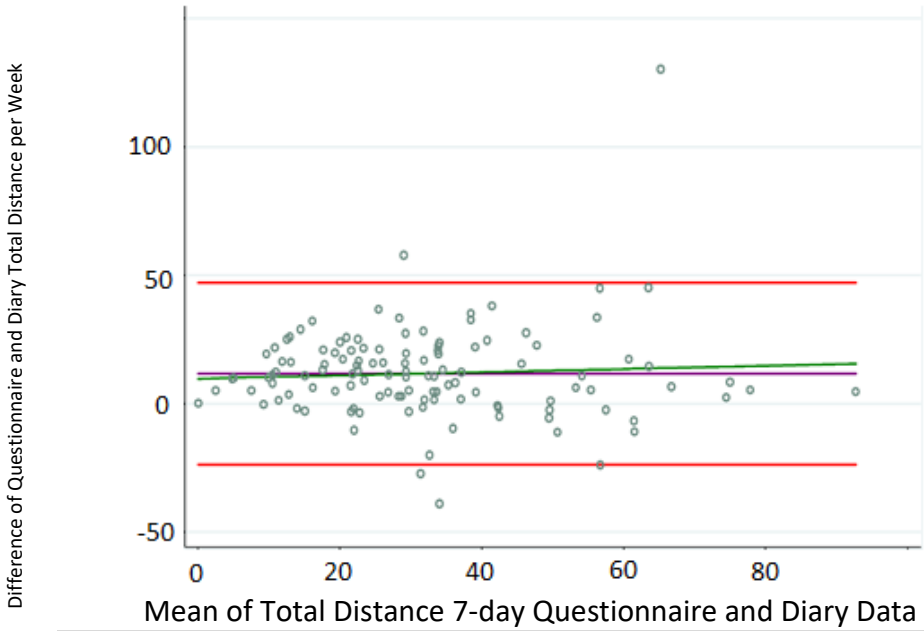


Figure 49

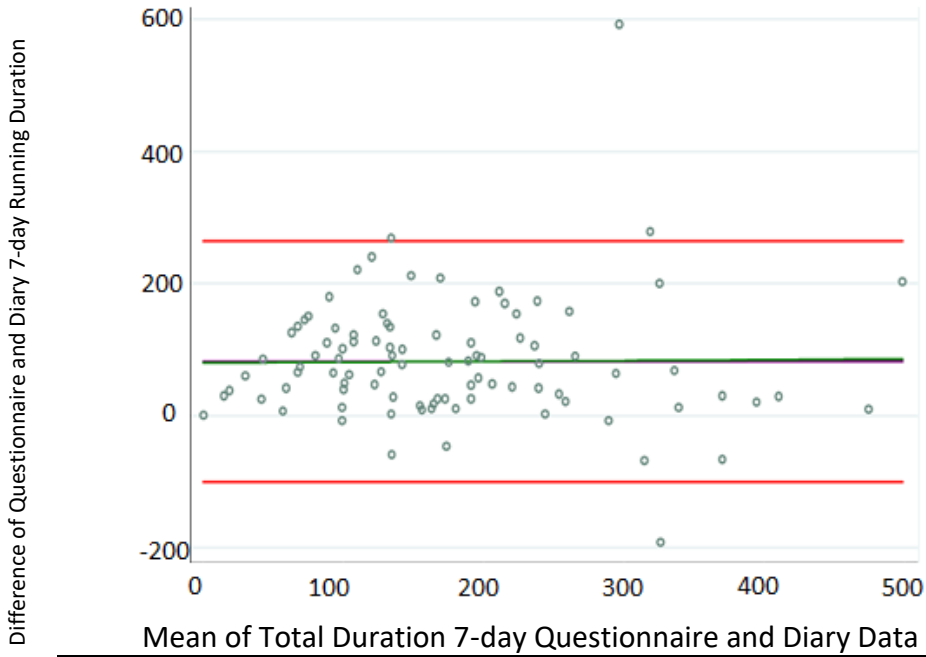


Figure 50

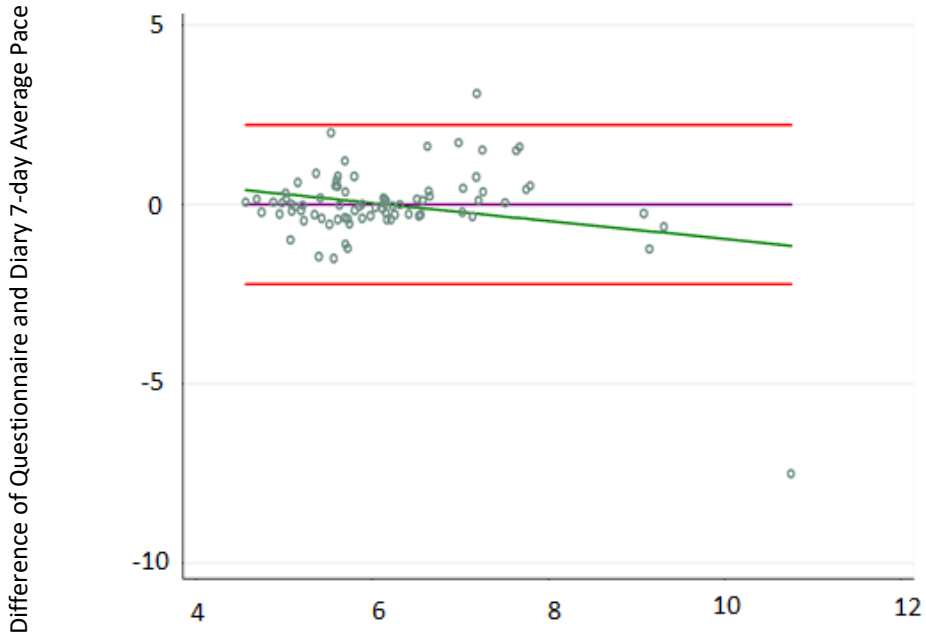


Figure 51

When agreement between the two sources were compared based on categorisation of runners (MET/hrs per day) revealed 'fair agreement' for unweighted kappa (K=0.24) and weighted kappa (Kw=0.46). Agreement was

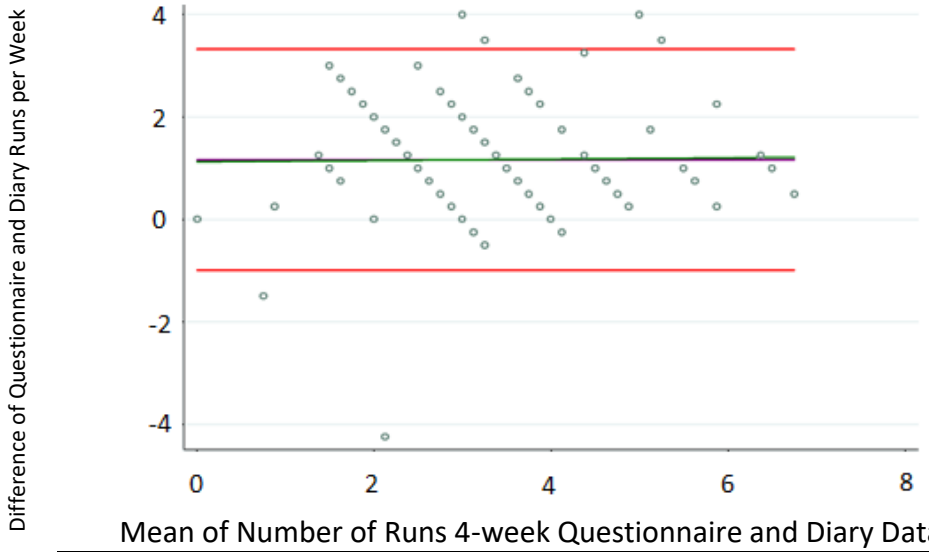
different across the categories of runners. Agreement was highest amongst the >5.4 MET/hrs per day runners (25/29 respondents, 86.21%).

4.3.5 Comparison of Current 4-Week Self Report Running and Diary Data

Concordance correlations for questionnaire running and 4-week diary-reported running were 0.54 (0.44-0.64) for weekly number of runs, 0.67 (0.58-0.76) for total weekly running distance, 0.62 (0.52-0.73) for total weekly run duration and 0.68 (0.56-0.79) for average run pace respectively.

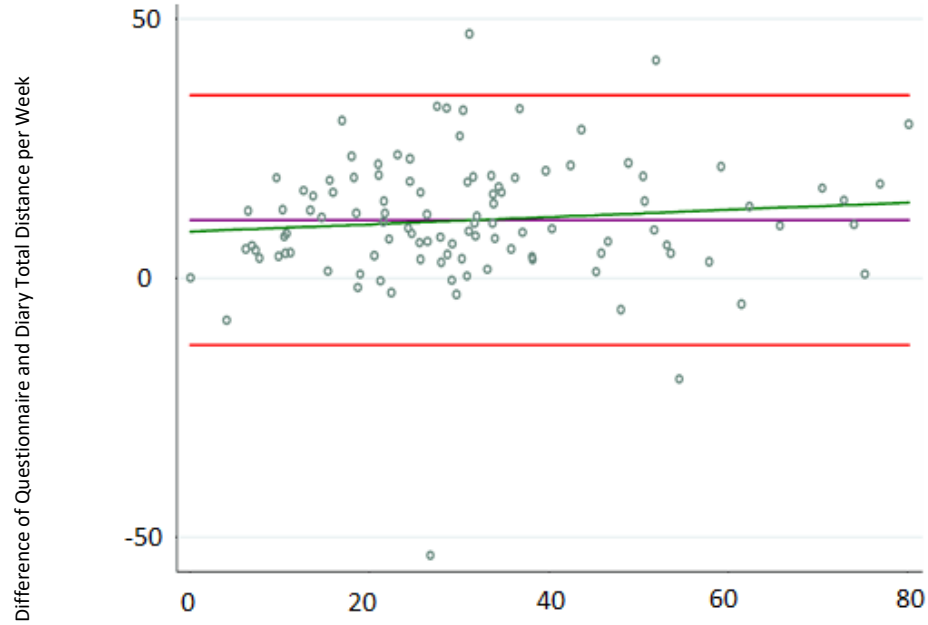
There was an over-estimation in the questionnaire (1.17 runs per week) (LoA -0.99-3.32) (Figure 52) for the number of runs per week completed compared to the diary. Further there was also greater values in the questionnaire for weekly distance (11.18km; LoA 12.96-35.32) (Figure 53) and weekly running duration (70 minutes (81.23-221.3) (Figure 54). Average difference in running pace was small (Figure 55) (0.07 minutes/km; LoA -1.51-1.64 minutes/km).

Figures: 52-55 4-Week Current Running Questionnaire and Diary Data Bland Altman Plots



Mean of Number of Runs 4-week Questionnaire and Diary Data

Figure 52



Mean of Total Distance 4-week Questionnaire and Diary Data

Figure 53

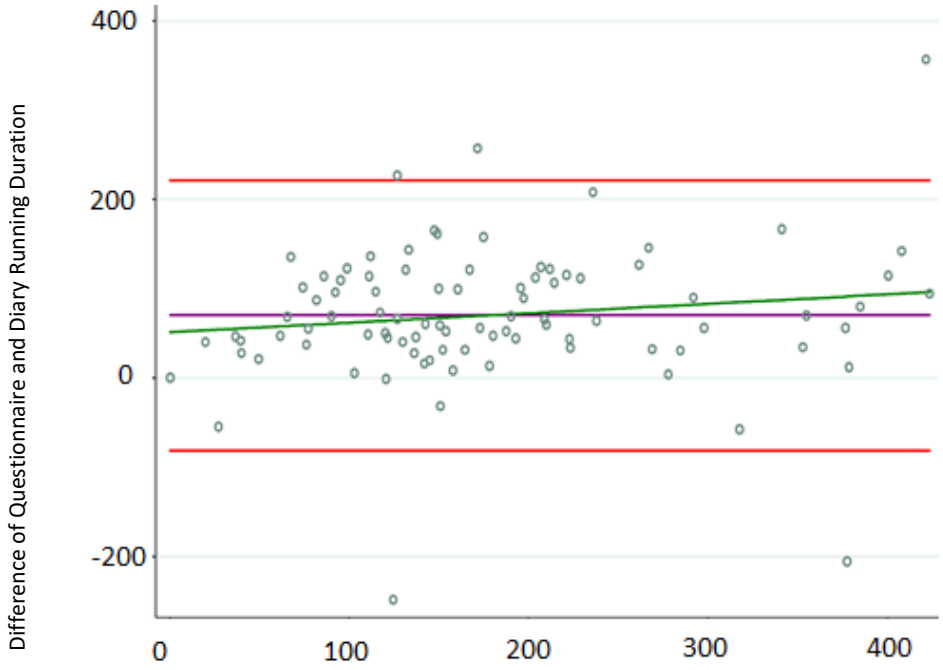


Figure 54

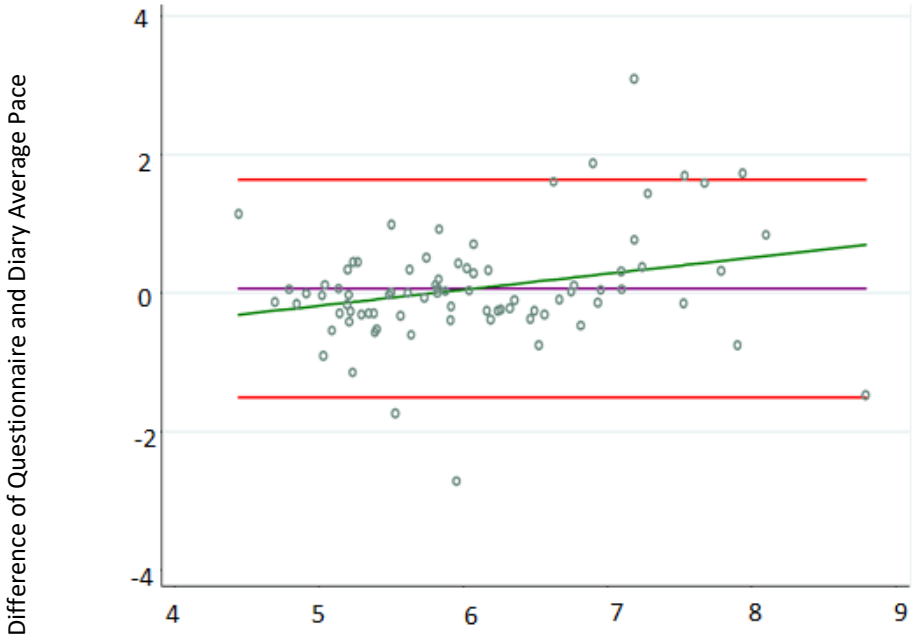


Figure 55

There was 'fair agreement' (K=0.26) for unweighted, and 'moderate agreement' (kw=0.53) for weighted analysis between the two sources.

MET categorisation of runners, as with 7-day data, was variable between different running intensities. For the lowest category of runners (<1.8MET/hrs per day), there was agreement in 8/31 (25.81%) of cases. For the highest running category (>5.4 MET/hrs per day, there was agreement in 22/23 cases (95.65%).

4.3.6 Comparison of Current 12-Week Self Report Running and Diary Data

The concordance correlations for questionnaire and 12-week training data were 0.51 (0.41-0.61), 0.56 (0.50-0.69), 0.46 (0.35-0.57) and 0.72 (0.62-0.82) for runs per week, weekly run distance, weekly run duration and average run pace respectively.

As shown with 7-day and 4-week diary data, again there was over-estimation in the number of runs (1.20) in the questionnaire. There was an average difference of 13.46km in weekly running distance when self-report and diary data were compared. Average pace different was minimal (0.04 minutes/km).

Figures 56-59: Twelve Week Current Running Questionnaire and Diary Data Bland Altman Plots

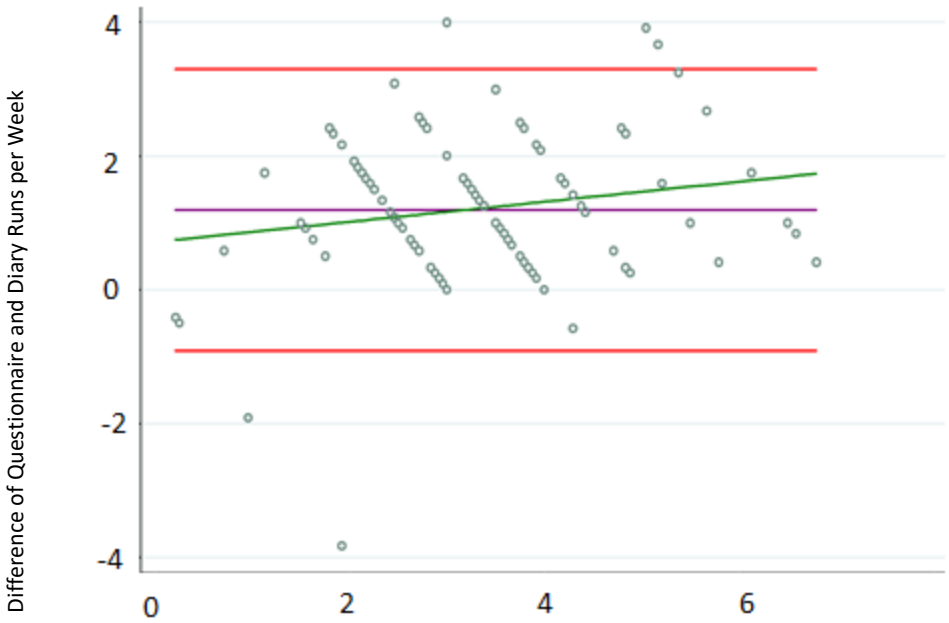


Figure 56

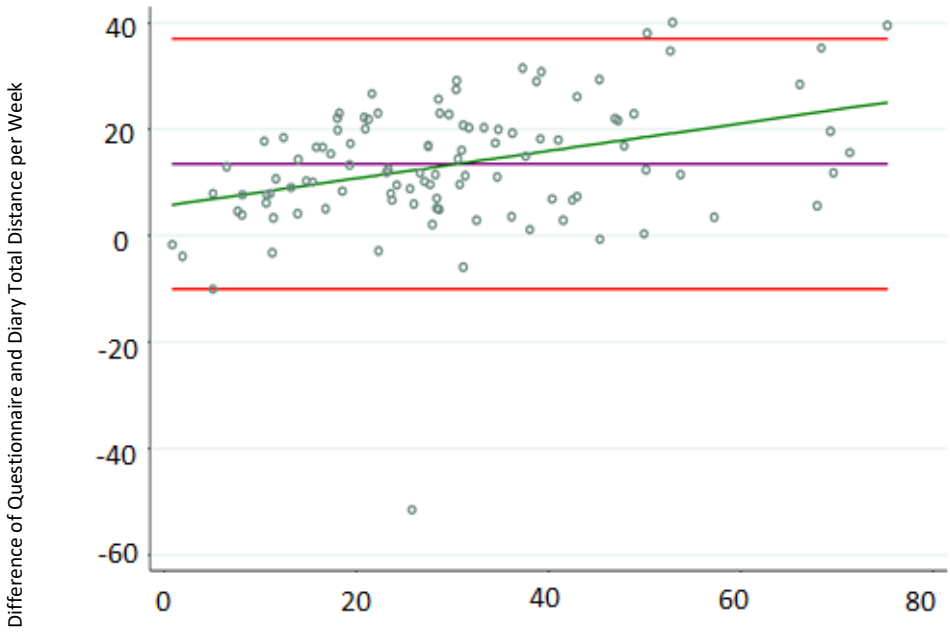
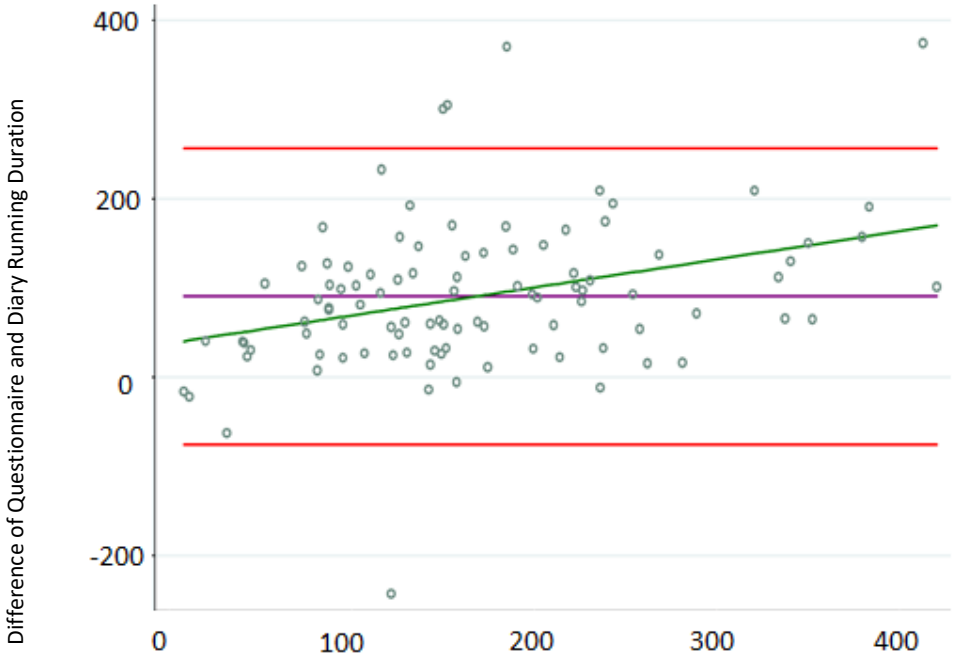
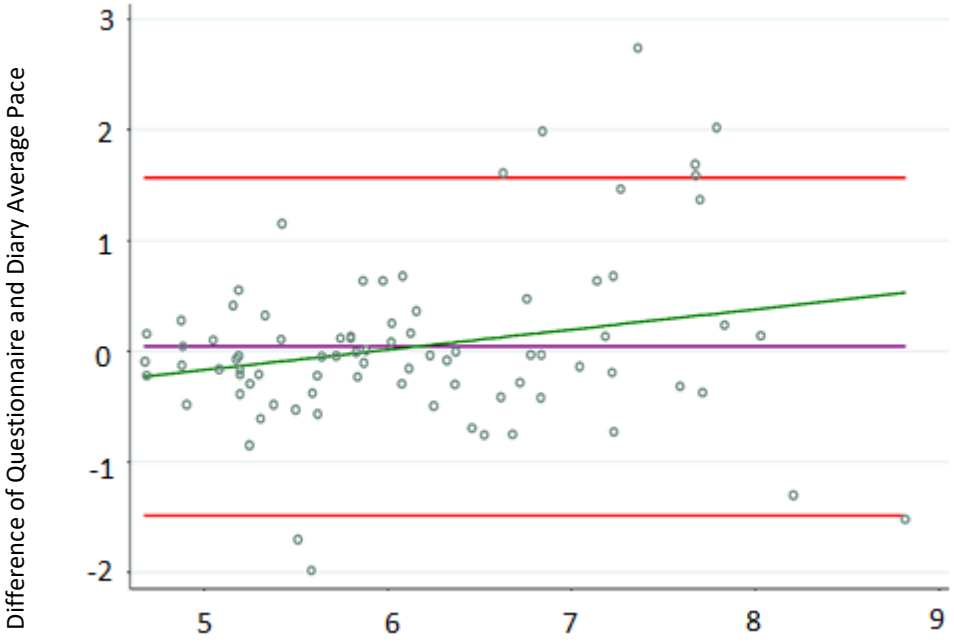


Figure 57



Mean of Total Duration 12-week Questionnaire and Diary Data

Figure 58



Mean of Average Pace 12-week Questionnaire and Diary Data

Figure 59

Agreement between running classifications were defined as ‘fair’ (K=0.33) and ‘moderate’ (Kw=0.49).

Greatest agreement was again observed in the runners in the >5.4 MET/hrs per day category, with 15/16 (93.75%) cases agreeing.

4.4 Historical Running

The descriptive statistics of questionnaire and diary running data is outlined in Table 18.

4.4.1 7-day Data

The difference in mean number of runs per week was greater in the questionnaire (by 41.15%) compared with diary data. The median number of runs per week was also greater in the questionnaire data (4 vs 2). For weekly running distance, the mean difference between the two sources was (41.60%). There was a 53.43% difference in mean values for questionnaire and diary reported weekly running duration. There was little difference in mean average pace from the two sources (6.08 and 6.04).

4.4.2 4-Week Data

Like the 7-day data, the mean number of runs per week, weekly running distance, weekly running duration from 4-week data were all greater in the questionnaire than diary by 36.51%, 35.71%, 39.42% respectively. Again, the

mean and median pace calculations for the questionnaire and diary were similar.

4.4.3 12-week Data

As for both 7-day and 4-week data, mean, median and maximum values for number of runs per week, weekly running distance and weekly running duration were all greater in the questionnaire. Average pace was similar in the questionnaire and diary (mean 6.11 vs 6.04; median, 6.00 vs 5.83).

		Number of Runs per Week		Weekly Running Distance (km)		Weekly Running Duration (mins)		Average Pace (mins/km)	
	Statistic	**Questionnaire**	**Diary**	**Questionnaire**	**Diary**	**Questionnaire**	**Diary**	**Questionnaire**	**Diary**
7 Day Data	**N**	116	116	102	102	92	92	75	75
	Mean	3.65	2.41	34.04	24.04	198.75	129.54	6.08	6.04
	SD	1.41	1.62	20.01	22.03	114.18	118.96	1.29	1.04
	Median	4.00	2.00	29.77	21.81	180.00	103.48	6.00	5.78
	Min-max	0-7.00	0-7.00	0-85.50	0-120.70	0-600.00	0-642.27	4.55-13.13	4.46-9.44
	IQR	1.00	3.00	25.06	29.28	136.00	157.39	1.17	1.43
4 Week Data	**N**	110	110	98	98	91	91	81	81
	Mean	3.69	2.52	35.24	25.45	205.64	142.65	6.23	6.14
	SD	1.39	1.41	20.29	20.59	111.44	129.18	1.47	1.22
	Median	4.00	2.25	30.79	21.71	180.00	118.14	6.00	5.92
	Min-max	0-7.00	0.25-7.00	0-85.50	0-113.46	0-515.00	0-950.60	4.55-13.13	3.23-11.30
	IQR	1.00	2.00	25.87	25.40	140.00	146.71	1.29	1.39

		Number of Runs per Week		Weekly Running Distance (km)		Weekly Running Duration (mins)		Average Pace (mins/km)	
	Statistic	**Questionnaire**	**Diary**	**Questionnaire**	**Diary**	**Questionnaire**	**Diary**	**Questionnaire**	**Diary**
12 Week Data	**N**	108	108	98	98	95	95	82	82
	Mean	3.65	2.41	34.83	21.96	204.23	115.50	6.20	6.38
	SD	1.31	1.40	20.02	16.51	109.81	89.63	1.50	2.25
	Median	4.00	2.25	30.66	18.96	180.00	98.81	6.00	5.91
	Min-max	0-7.00	0-6.83	0-85.50	0-78.12	0-515.00	0-442.72	4.55-13.13	3.29-22.25
	IQR	1.00	2.00	25.06	21.67	140.00	128.61	1.32	1.40

Table 26: Historical Running – Analysis of Self-report and Questionnaire Running

4.4.4 Comparison of Historical Self Report Running and Historical 7-Day Diary Data

Number of runs per week, weekly running distance and duration and average pace were all greater for self-report compared to diary. Concordance correlations were 0.38 (0.26-0.50), 0.57 (0.45-0.69), 0.49 (0.35-0.62) and 0.47 (0.30-0.65) for these factors respectively.

The mean over-estimation in the number of runs completed per week according to the questionnaire was 1.23 (LoA -1.73-4.20) (Figure 60). For weekly running distance, the average difference between the two sources was 10.01km (LoA -25.49-45.51) (Figure 61). Self-reported running duration was over-estimated by 69.22 minutes (LoA -142.13-280.56 minutes) (Figure 62). The mean difference in pace was 0.04 minutes/km (LoA -2.33-2.40 minutes/km) (Figure 78).

Figure 60-63: 7-day Historical Running Data Questionnaire and Diary Bland-Altman Plots

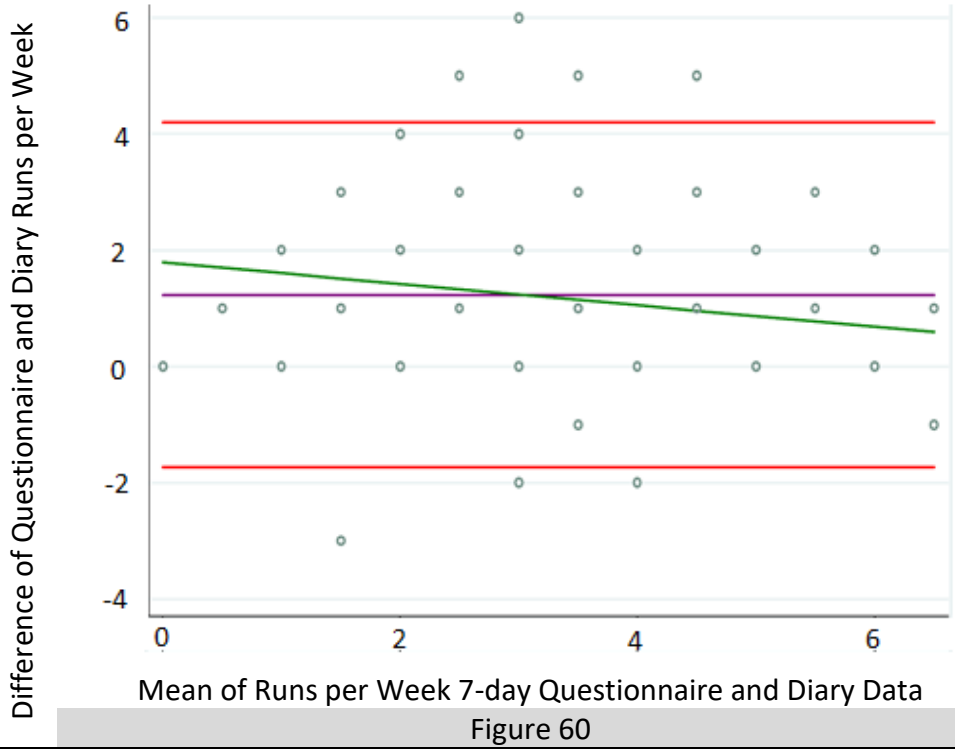


Figure 60

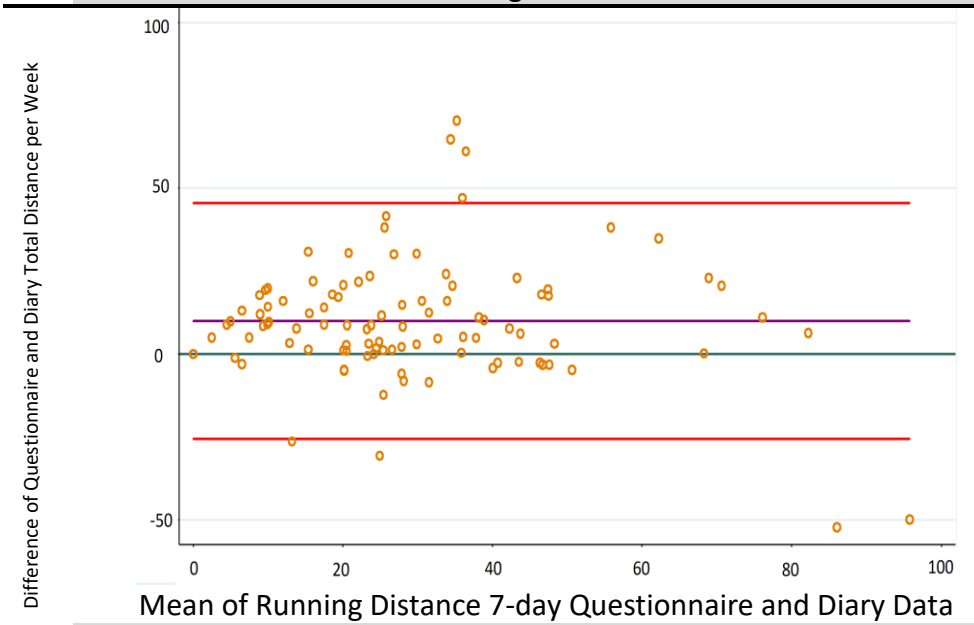
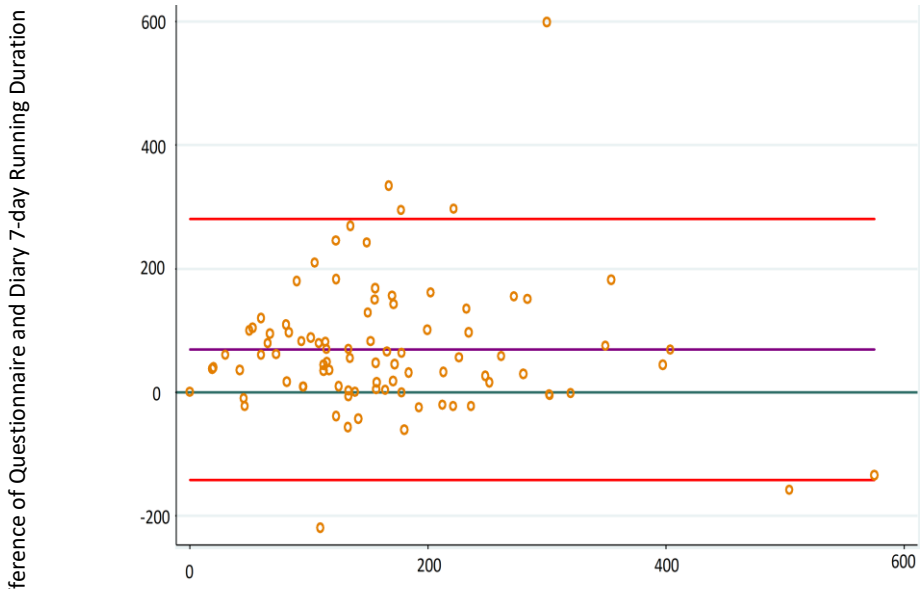
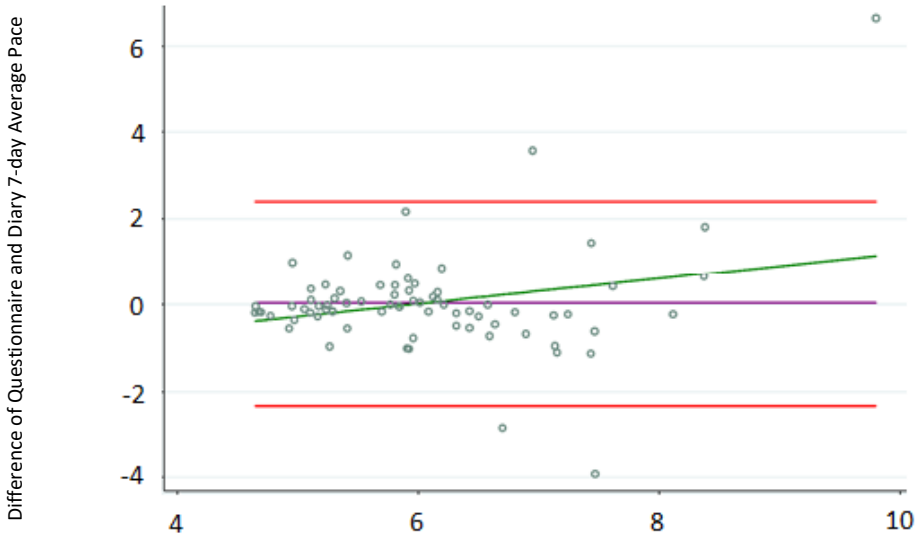


Figure 61



Mean of Running Duration 7-day Questionnaire and Diary Data

Figure 62



Mean of Running Pace 7-Day Questionnaire and Diary Data

Figure 63

Running classifications showed 'fair' (K=0.29) and 'moderate' (Kw=0.48) agreement for unweighted and weighted kappa's. In analysis of MET classifications, 8/38 (21.05%) cases agreed in the <1.8MET/hrs athletes. For the >5.4MET/hrs athletes, where there was agreement in 21/22 cases (95.45%).

4.5.5 Comparison on Historical Self Report Running and Historical 4 Week Diary Data

Concordance correlations for 4-week running were 0.46 (0.35-0.57), 0.68 (0.58-0.78), 0.58 (0.46-0.70) and 0.61 (0.47-0.74) for runs per week, weekly distance, weekly running duration and average pace respectively. Runs per week (1.18 per week), distance run (almost 9.79km) and run duration (62.99 minutes) were all greater in the self-report. The difference in pace between the two sources was 0.09 minutes/km (LoA -2.24-2.43 minutes/km) (Figure 67).

Figures 64-67: 4-Week Historical Running Questionnaire and Diary Data Bland Altman Plots

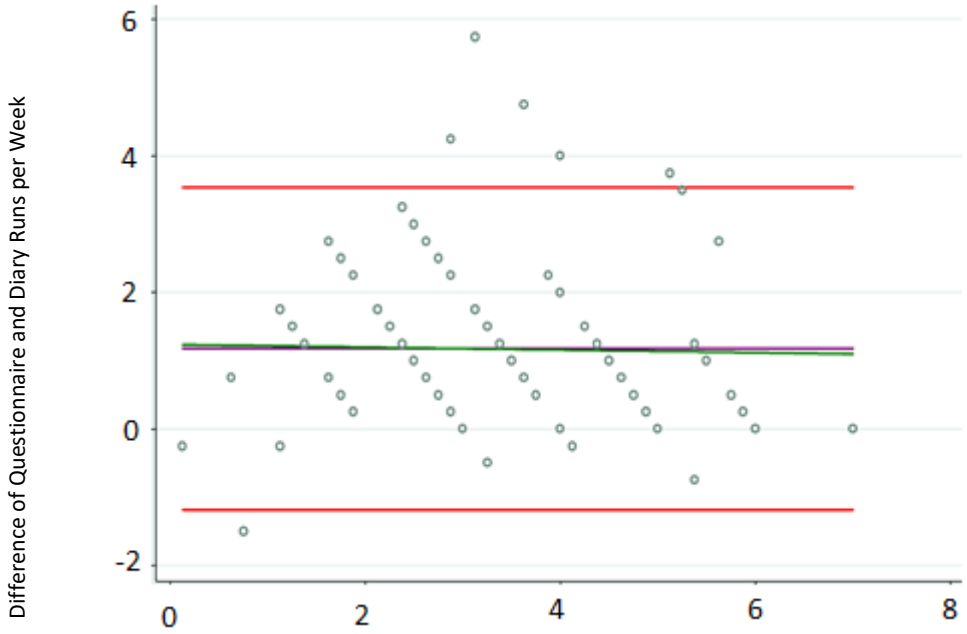


Figure 64

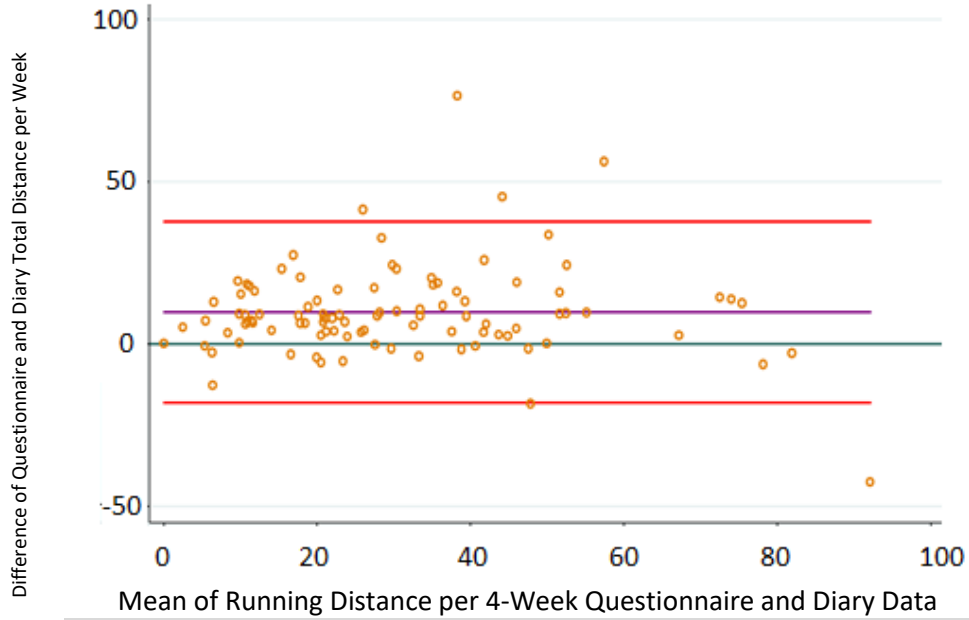


Figure 65



Figure 66

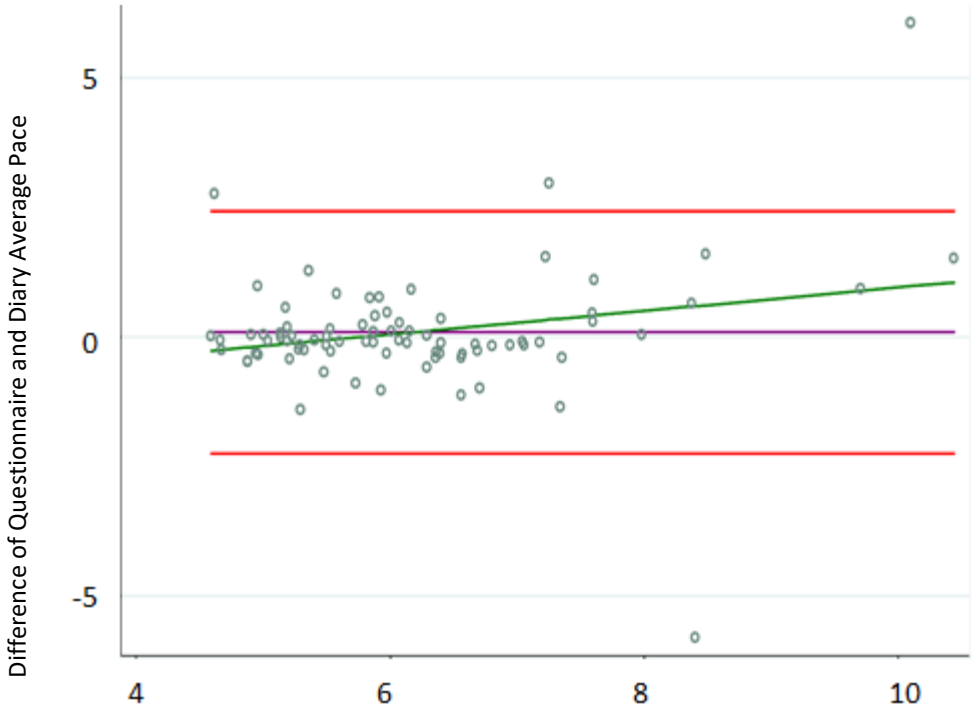


Figure 67

In the analysis of running classifications, the unweighted kappa showed 'fair' agreement (K=0.29), and the weighted kappa (Kw=0.63) showed 'substantial'

agreement. Like previous findings, the greatest agreement was observed in the >5.4 MET/hrs per day runners. There was agreement in 22/22 (100%) of cases.

4.6.6 Comparison of Historical Self Report Running and Historical 12 Week Diary Data

Concordance correlations were 0.45 (0.35-0.56), 0.58 (0.47-0.68), and 0.42 (0.30-0.54) for runs per week, weekly distance and weekly running duration respectively. There was over-estimation of number of runs by 1.24 in the self-report data (Figure 68). For weekly distance, there was over-estimation by 12.87km (LoA -14.00-39.75) (Figure 69). For running duration, there was over-estimation of 88.74 minutes (LoA -89.86-267.33) (Figure 70). Difference in average weekly pace was -0.14 mins/km (LoA -4.78-4.49 mins/km).

Figures 68-71: Twelve Week Historical Running Questionnaire and Diary Data Bland Altman Plots

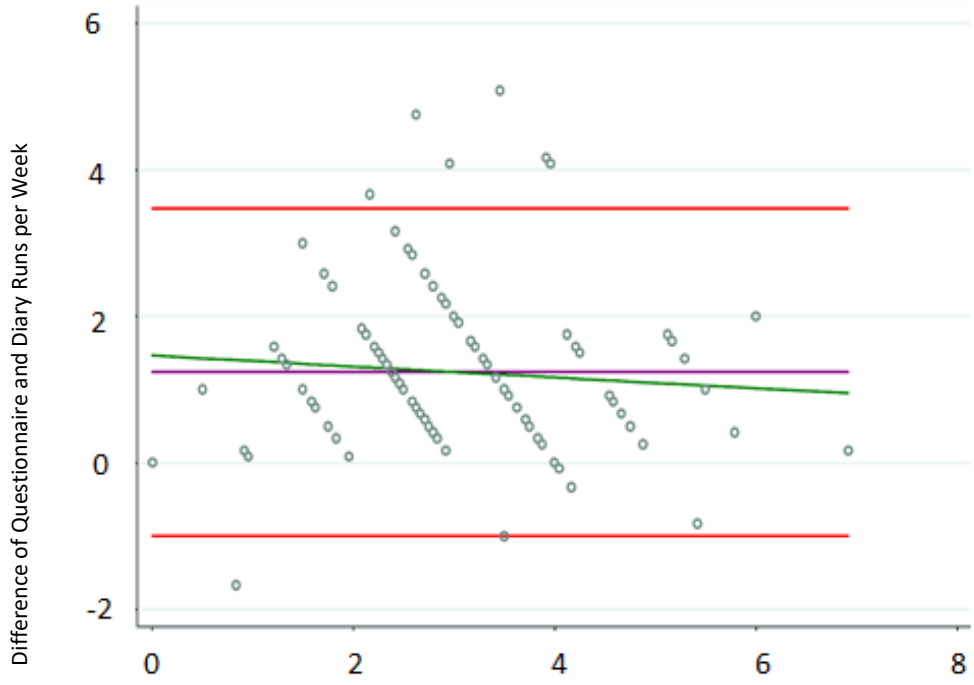


Figure 68

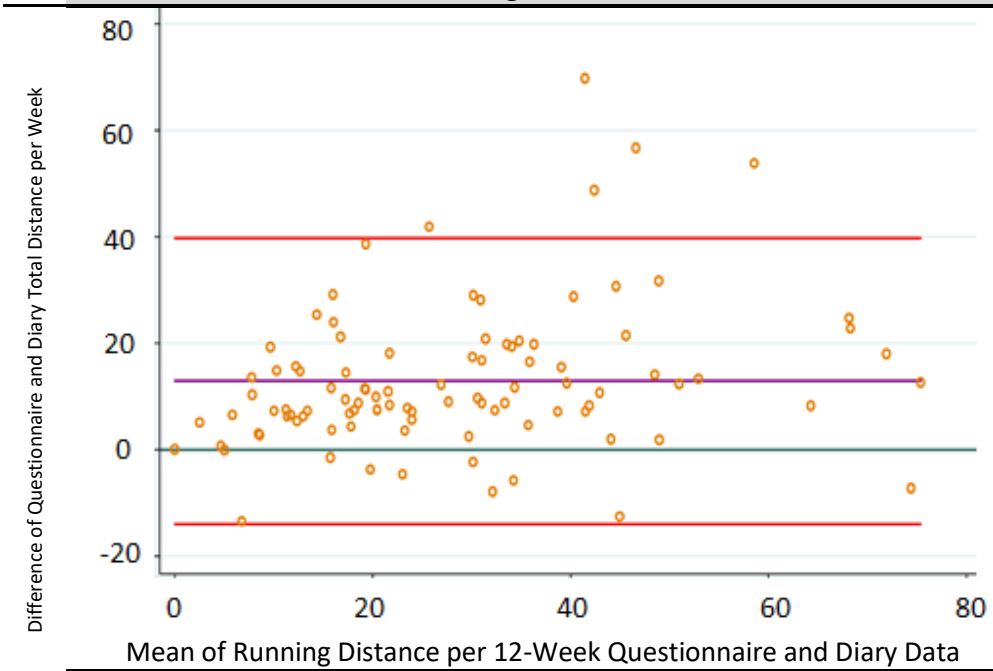


Figure 69

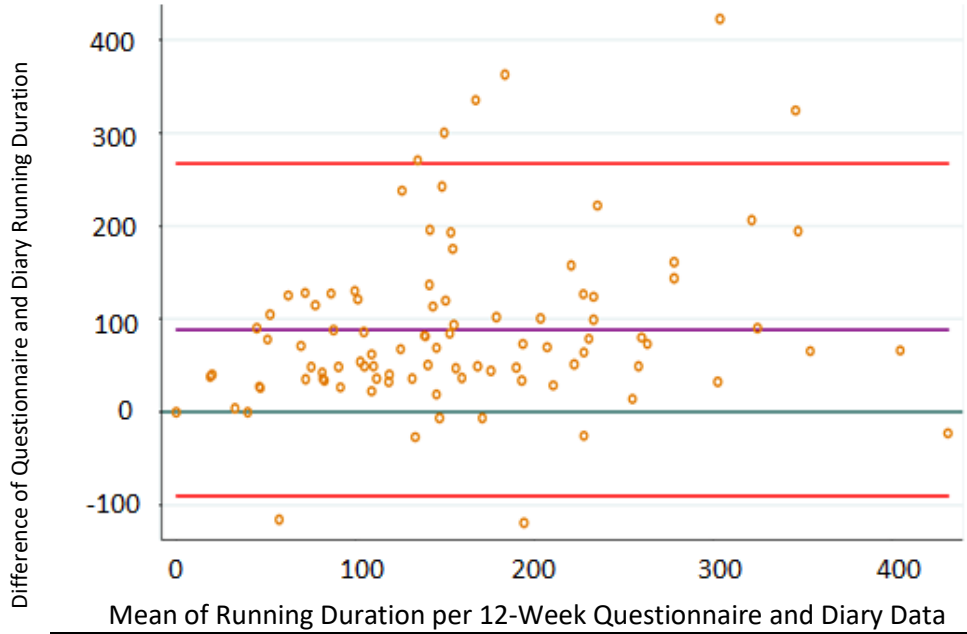


Figure 70

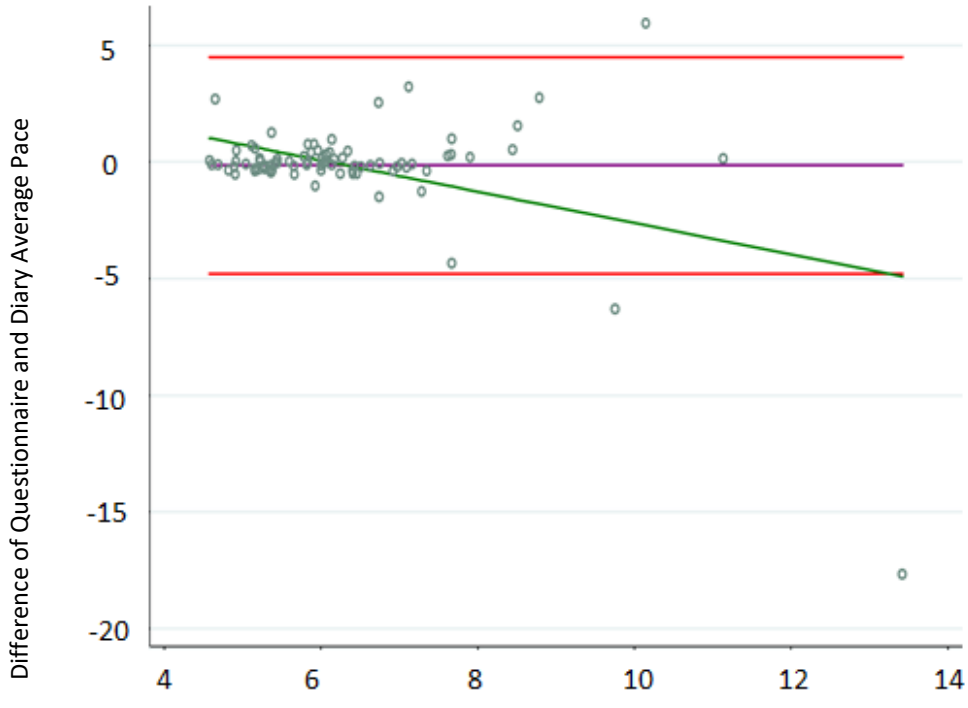


Figure 71

There was fair (K=0.21) and moderate (Kw=0.52) for running categorisation analysis. MET categorisation agreement in 7/29 (24.14%) of cases in the

<1.8MET/hrs athletes and in 15/16 (93.75%) of cases in the >5.4MET/hrs runners.

4.5 Results Summary

This analysis reported a comparison between self-report running and running diary. The results suggest that recreational athletes over-reporting in the questionnaire compared to actual running completed. This is

The reason for presenting this data before all other data is that it has significance in relation to how later results are interpreted. The consistent over-estimation of running with self-report may impact on the findings reported later and the association between the exposure and outcome may be affected.

5.0 Results: Markers of Knee Health in Recreational Runners and Non-Runners: A Cross-sectional Analysis

5.1 Introduction

Running is one of the most popular sporting pastimes in the UK. There is no evidence that running increases risk of OA (Timmins et al, 2017). However, injuries are common in sport and this is one of the greatest risk factors associated with OA (Roos et al, 2005). Research advocates the use of interventions that reduce the incidence of injuries across multiple sports, but there is a lack of data for recreational runners. Injury surveillance is regarded as the first stage of implementing appropriate injury prevention strategies (van Mechelen, 1992).

The aim of this section is to describe the prevalence of musculoskeletal injury, other markers of joint health (e.g. pain) and OA in recreational runners and non-runners.

5.2 Cohort Characteristics

This section reports the characteristics of all participants within the cohort, regardless of running status.

3687 questionnaires were completed. Nine participants were removed as they were aged <18. 29 participants completed the questionnaire more than once and were thus removed. Six participants completed the questionnaire from ineligible territories.

In total, 3,643 Baseline Questionnaire 1's were analysed. Also included in this section is data from Baseline Questionnaire 2 (n=1470).

The demographics of the cohort are summarised in Table 27.

	Total		**Runners**		**Non-Runners**	
Total (n)	**3643**		**3446**		**197**	
	Count (%)		Count (%)		Count (%)	
Gender (female)	2045 (56.1)		1900 (55.1)		145 (73.6)	
Ethnicity (white) Count (percentage)	3400 (93.3)		3235 (93.8)		165 (83.8)	
	Mean	**SD; min-max**	**Mean**	**SD; min-max**	**Mean**	**SD; min-max**
Age	45.9	12.7; 18-81	46.3	12.4; 18-81	40.4	16.6; 18-79
BMI	23.8	3.8; 13-63	23.7	3.6; 13-63	26.1	5.8; 16-63
Age (years) mean (SD,min-max)	45.9	12.7; 18-81	46.3	12.4, 18-81	40.4	16.6; 18-79
Body Mass Index (kg/m^2) Mean (SD,min-max)	23.84	3.8; 13-63	23.7	3.60; 13-63	26.06	26.06 5.84; 16-63

Table 27: Cohort Characteristics

Within the cohort, there was a greater proportion of females (56.14%) than males. The mean age was almost 46 (range 18-81 years). Runners were slightly older than non-runners. Mean BMI (23.84kg/m^2) is within the healthy weight

range. Runners had a lower mean BMI (23.71 kg/m^2) compared to non-runners (26.06kg/m^2) (Table 28). Most of the population was white, with all other ethnicities combined accounting for less than 10% of the total. Almost three quarters of the population have never smoked.

A small proportion (7.90%) work in either manual or heavy manual work. Over two thirds of the cohort population had a sedentary occupation, but this was slightly lower for the non-runners (54.96%).

Most of the cohort considered themselves either a little bit or a lot more active than other people of the same age and gender in the general population (90.26%). The perception of PA levels of generally greater amongst the runners, with over 60% reporting that they were a lot more active than others in the population. This is compared to non-runners, where under 20% perceived themselves the same.

	Total	Runners	Non-Runners
Total	**n 3643**	**n 3446**	**n 197**
Current Occupation Count	3515	3324	191
Heavy manual work Count (%)	36 (1.02)	34 (1.02)	2 (1.05)
Manual work Count (%)	242 (6.88)	224 (6.74)	18 (9.42)
Sedentary work Count (%)	2358 (67.08)	2253 (67.78)	105 (54.97)
Standing occupation Count (%)	879 (25.01)	813 (24.46)	66 (34.55)
Perceived Activity Levels (vs others of same age and gender)	3635	3439	196
A lot more active Count (%)	2188 (60.19)	2153 (62.61)	35 (17.86)
A bit more active Count (%)	1093 (30.07)	1033 (30.04)	60 (30.61)
About as active Count (%)	254 (6.99)	205 (5.96)	49 (25.00)
A bit less active Count (%)	75 (2.06)	38 (1.10)	37 (18.88)
A lot less active Count (%)	25 (0.69)	10 (0.29)	15 (7.65)

Table 28: Descriptive Data for Lifestyle Physical Activity in Cohort

The BMI categorisation of runners and non-runners is shown in Figure 72. Seventy-percent of runners were a healthy weight. In contrast, only 43% of non-runners were a healthy weight, whilst over half were either overweight or obese. Just 5% of runners were obese.

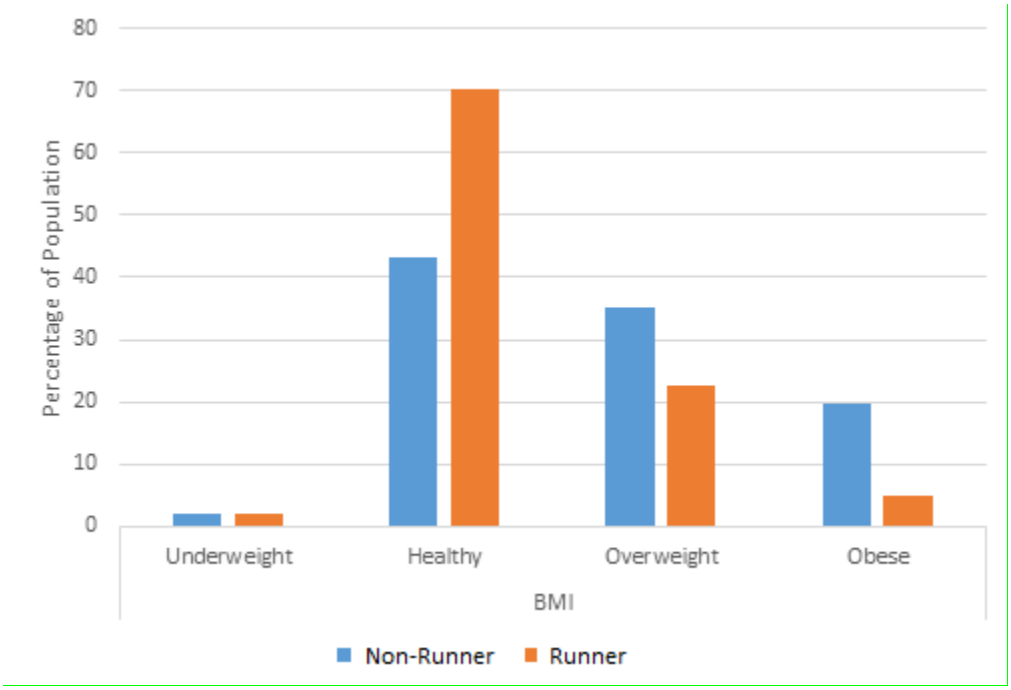


Figure 72: BMI categorisation of runners and non-runners

5.3 History of Injury

Table 29 below summarises the proportion of runners and non-runners that have sustained significant injury, significant knee injury and those attributed to running. Intra-joint (ligamentous and cartilaginous) injuries are reported separately due to their specific relevance to joint health and OA. Injury (any cause/location) were common amongst the population. Over half the entire cohort reported a history of injury. There was a statistically significant difference between the runner and non-runners when these rates were assessed. Perhaps unsurprisingly, almost 1/3 of the runners reported a

significant running-attributed injury compared to just 6.60% of non-runners. However, this is notable since it suggests that some non-runners in this cohort had run at some point in their life.

	All n (%)	Runners n (%)	Non-Runners n (%)	x2 (p)
History of Significant Injury	2103 (57.70)	2009 (58.30)	94 (47.70)	8.554 (0.003)
History of Significant Knee Injury	726 (19.93)	696 (20.20)	30 (15.23)	2.883 (0.090)
History of Significant Ligament Injury	201 (5.52)	189 (5.48)	12 (6.09)	0.132 (0.717)
History of Significant Cartilage Injury	170 (4.67)	165 (4.79)	5 (2.54)	2.121 (0.145)
History of Significant Running Injury	988 (27.12)	975 (28.29)	13 (6.60)	44.374 (<0.0001)

Table 29: Injury history of runners and non-runners

The prevalence of history of joint surgery (any, knee-specific and knee arthroplasty) are summarised in table 30. The difference in prevalence between runners and non-runners did not achieve statistical significance for any type of surgery.

	All n (%)	Runners n (%)	Non-Runners n (%)	x^2 (p)
Joint Surgery	458 (12.60)	428 (12.40)	30 (15.20)	1.337 (0.248)
Knee Surgery	235 (6.45)	221 (6.41)	14 (7.11)	0.148 (0.700)
Knee Joint Arthroplasty	18 (0.49)	16 (0.46)	2 (1.02)	1.150 (0.283)

Table 30: Surgery history of runners and non-runners

Incidentally, there were 17 cases of hip arthroplasty reported (14 in runners and 3 in non-runners. The difference in the prevalence of hip OA between the two groups (runners and non-runners) was not statistically different (x^2 5.002, p=0.025).

5.4 Prevalence of Knee Symptoms in Runners and Non-Runners

Pain, crepitus, morning stiffness and reduced ROM in runners and non-runners are presented in table 31. A similar proportion of runners (28.48%) and non-runners (29.44%) reported knee pain. More non-runners reported knee crepitus (p 0.001), morning stiffness (not statistically significant) and reduced range of movement (not statistically significant).

Outcome	Running Status		X^2 (p)
	Runner (n=3445)	Non-Runner (n=197)	
Knee Pain	981 (28.48)	58 (29.44)	0.085 (0.770)
Knee Crepitus	403 (11.70)	39 (19.80)	11.462 (0.001)
Knee Morning Stiffness	1001 (29.06)	63 (31.98)	0.770 (0.380)
Knee Reduced ROM	382 (11.09)	30 (15.23)	3.183 (0.074)

Table 31: Symptom history of runners and non-runners

Mean age of first onset of knee pain was higher in runners (age 36.92, SD 14.01, range 9-75) compared to non-runners (age 32.74, SD 17.39, range 8-78) (Figure. The difference in knee pain onset age does not differ significantly

between the runners and non-runners (Mann-Whitney U Test, p 0.013) (Figure 73).

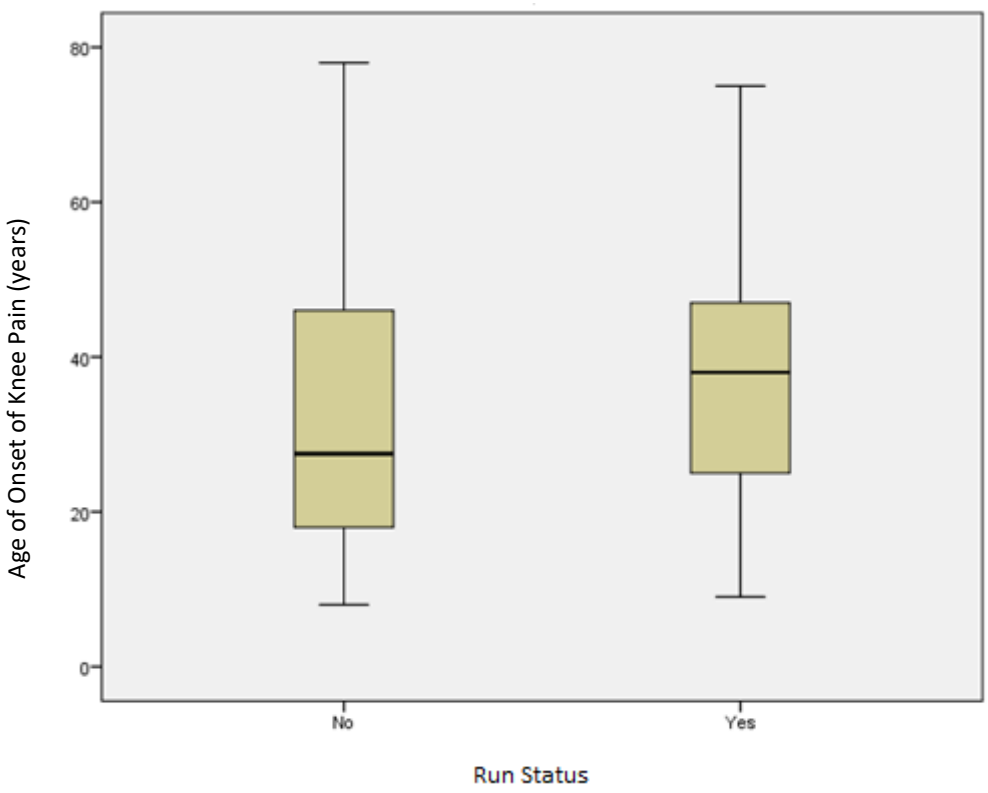


Figure 73: Age of Onset Knee Pain

Running Status and Knee OA

There was no statistically significant difference in the prevalence of knee OA diagnosis (made by a clinician or other healthcare professional) (Table 32). Relatively few participants in either group had a diagnosis of knee OA.

Running Status	Knee OA Diagnosis n (%)	X^2 (p)
Non-Runner	16 (8.12)	1.592 (0.207)
Runner	204 (5.92)	

Table 32: Prevalence of OA Diagnosis

5.5 Running Status and KOOS Values

A comparison of mean KOOS values for each of the five domains for runners and non-runners is summarised in table 34. For each of the five domains, for both legs, runners consistently reported higher KOOS values. For example, for the Pain outcome, runners reported 95.67 and 95.18 respectively for right and left knee responses. In runners, these were 84.93 and 89.56 respectively for right and left knee responses. Knee Quality of Life was lowest for both groups, but the non-runners reporting values of 76.76 and 81.64 for these outcomes for right and left knees.

Mann Whitney U test analyses were performed on each of the five domains to test the thesis hypothesis. The results are summarised in table 33. The data suggests that the null hypothesis for this study should be accepted for all outcomes (except for R knee quality of life). All of these tests show that there is no statistically significant difference in the distribution of KOOS values between runners and non-runners.

KOOS Domain	Mann Whitney U Test Significance (p)
R Pain	0.168
L Pain	0.674
R Symptoms	0.111
L Symptoms	0.677
R Activity of Daily Living	0.060
L Activity of Daily Living	0.380
R Sport	0.489
L Sport	0.995
R Quality of Life	0.040
L Quality of Life	0.211

Table 33: Mean KOOS values of runners and non-runners

Table 34		KOOS Domains									
Run Status		R Symptoms	L Symptoms	R Pain	L Pain	R Activity	L Activity	R Sport	L Sport	R QoL	L QoL
No	Mean	84.20	86.69	84.93	89.56	88.77	93.45	81.29	87.42	76.76	81.64
	N	33	33	33	33	33	33	31	31	32	32
	Std. Deviation	19.93	20.31	22.47	18.93	21.57	15.13	30.41	25.91	29.87	27.45
Yes	Mean	91.45	92.12	94.67	95.18	97.40	97.61	92.06	92.64	90.09	90.64
	N	1383	1383	1382	1382	1376	1376	1367	1367	1367	1367
	Std. Deviation	11.14	10.53	9.58	9.11	6.70	6.31	14.00	13.58	14.76	15.05

5.6 Recreational Runners

This section describes the running characteristics of recreational athletes in this cohort. These relate to the specific metrics of assessing running load (Section 3.5.2). These are reported according to factors such as distance and frequency of activity.

Running Behaviour

Self-described primary running participation type is shown in Figure 74.

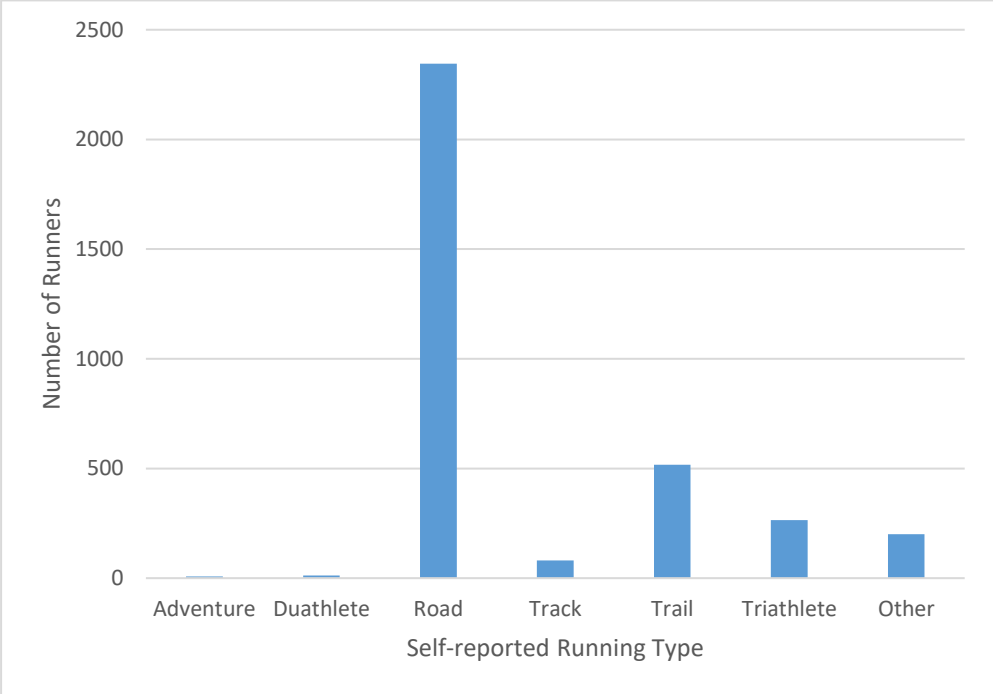


Figure 74: Self-reported running type

The vast majority self-reported that they were a road runner. Mean number of years running (n=3331) was years 11.07 (SD 12.10 min 0(1week)-65.00years). There was a statistically significant relationship between age and years running

(r= 0.42, p=<0.0001). Higher ages were associated with a greater number of years running.

The mean weekly running distance (n=3272) was 23.83km (SD 16.84km). The range was 0-170.59km. Mean weekly running distances were further for males (n=1466, 26.71km SD 17.47km) than females (n=1806, 21.48km SD 15.93km).

There was a high degree of variability, but the mean weekly running distance running did not fluctuate greatly between age-groups (Table 35, Figure 75). Males in each age band ran further on average than females with the exception being the youngest and eldest athletes.

Age of Runner (years)	N	Mean Weekly Running Distance (km)	Standard Deviation	Range
<24.9	120	19.66	19.37	110.04
25.0-29.9	228	21.18	17.16	103.00
30.0-34.9	281	23.49	20.02	113.24
35.0-39.9	316	22.49	16.21	78.86
40.0-44.9	468	24.34	15.87	88.51
45.0-49.9	526	23.79	16.05	112.65
50.0-54.9	491	24.59	17.41	169.59
55.0-59.9	374	24.12	15.48	88.40
60.0-64.9	231	25.57	16.38	106.63
65.0-69.9	136	25.25	16.30	80.46
70.0+	101	26.08	16.25	78.86

Table 35: Age of runners and Running Distance

Change in running (n=3438) showed recreational athletes in the cohort were running ‘About the same’ (n=1012) and ‘Slightly more’ (n=940) or ‘A lot more’ (n=790). A much smaller proportion were either running ‘A bit less’ (n=493) or ‘A lot less’ (n=203).

Number of runs per week was reported by n=3437 athletes. The mean runs per week was 3.21 (SD 1.42) and the range 0-14 runs per week. As for average weekly running distance, males performed a greater number of runs per week compared to females, apart from in the youngest and eldest age groups.

5.6.2 BMI and Running Behaviour in Recreational Athletes

Tables 36-38 identify the running behaviours according to BMI. On average, obese individuals had run for fewer years, and completed less distance and duration on average per week compared to other BMI categories. In fact, for each assessment of running, there was a trend for Underweight runners to complete the greatest amount of running.

Running years and BMI

BMI Category	N	Years Running (Mean)	SD	Range
Underweight	69	13.30	11.92	50.80
Healthy Weight	2343	11.59	11.99	65.00
Overweight	752	10.07	12.54	62.90
Obese	163	7.20	10.50	57.00

Table 36: Running years and BMI

Running average weekly km and BMI

BMI Category	N	Weekly Run Distance KM (Mean)	SD	Range
Underweight	70	34.05	23.90	109.44
Healthy Weight	2292	25.40	17.20	114.84
Overweight	747	19.90	14.32	170.59
Obese	160	14.50	10.63	50.00

Table 37: Running average weekly km and BMI

Average weekly total run duration and BMI

BMI Category	N	Weekly Run Duration Minutes (Mean)	SD	Range
Underweight	68	217.40	146.93	675.00
Healthy Weight	2341	174.72	114.83	1200.00
Overweight	762	143.72	87.83	600.00
Obese	167	129.67	79.63	480.00

Table 38: Average weekly total run duration and BMI

5.6.3 Prevalence of Injury in Recreational Runners

Figure 75 shows the percentage of each age group reporting a history of injury (all injuries, any cause). There is a trend for a greater proportion of each age group to have been afflicted by injury as age rises. For example, in the <24.9 age group, 49% reported a history of serious injury, by age 45-49.9, 60% reported a history of injury and in the 70+ age group, this percentage reached 73%.

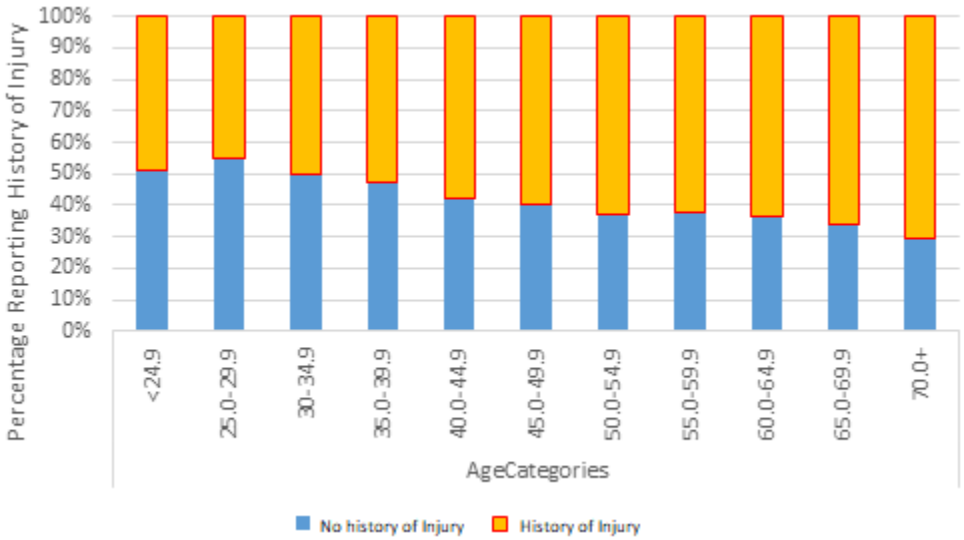


Figure 75: Injury History Prevalence in Runners

The graph (Figure 76) below shows the percentage of each age band afflicted by running-attributed injury. Generally, there was a trend for increased prevalence as age increases. In the youngest age group (<24.9), 15% had sustained a running-attributed injury, in the 45-49.9 age group 28% had sustained an injury. In the oldest age group (70+), 43% had previously sustained a running attributed injury.



Figure 76: Running Injury Prevalence in Runners

A total of 1491 running injuries were reported (19 orienteering injuries) in 988 runners. A further 142 injuries were attributed to multiple causes including running and there were 60 triathlon injuries. When exclusions were removed (OA n=24), post-surgical complications (n=1) and medical illness (n=1), 1,465 running injuries were identified with an additional 19 attributed to orienteering. Triathlon (n=60) and causes of injury where more than one activity including running was identified as the cause (n=142) are considered separately within this results section, since the attributable cause cannot be determined to be running. Running-attributed injuries affected every anatomical region of the body. A majority (86.39%) of running injuries affected the lower limb (hip and groin, pelvis, thigh, knee, lower leg, ankle and foot) (Table 39). 73 injuries could not be fully assigned to a specific region or diagnostic classification, primarily because of insufficient information being provided.

Parent / Type	Attributable Cause n, (% of total)			
	Running	Orienteering	Triathlon	Running plus Other
Ankle	283 (19.32)	4 (21.05)	6 (10.00)	22 (15.49)
Foot	231 (15.77)	2 (10.53)	9 (15.00)	16 (11.27)
Hip and Groin	77 (5.26)	-	3 (5.00)	8 (5.63)
Knee	353 (24.33)	8 (42.11)	12 (20.00)	36 (25.35)
Lower Leg	165 (11.26)	-	6 (10.00)	6 (4.23)
Pelvis	90 (6.14)	-	3 (5.00)	11 (7.75)
Thigh	70 (4.78)	-	6 (10.00)	1 (0.70)
Lower Limb Injuries	1269 (86.62)	14 (73.68)	45 (75.00)	100 (70.42)
All Attributed Injuries	**1465**	**19**	**60**	**142**
Total Running Injuries	**1484**		**-**	

Table 39: Self report running injuries

The knee was the most affected region, accounting for almost a quarter of all running injuries (24.33%). The ankle was the second most affected joint.

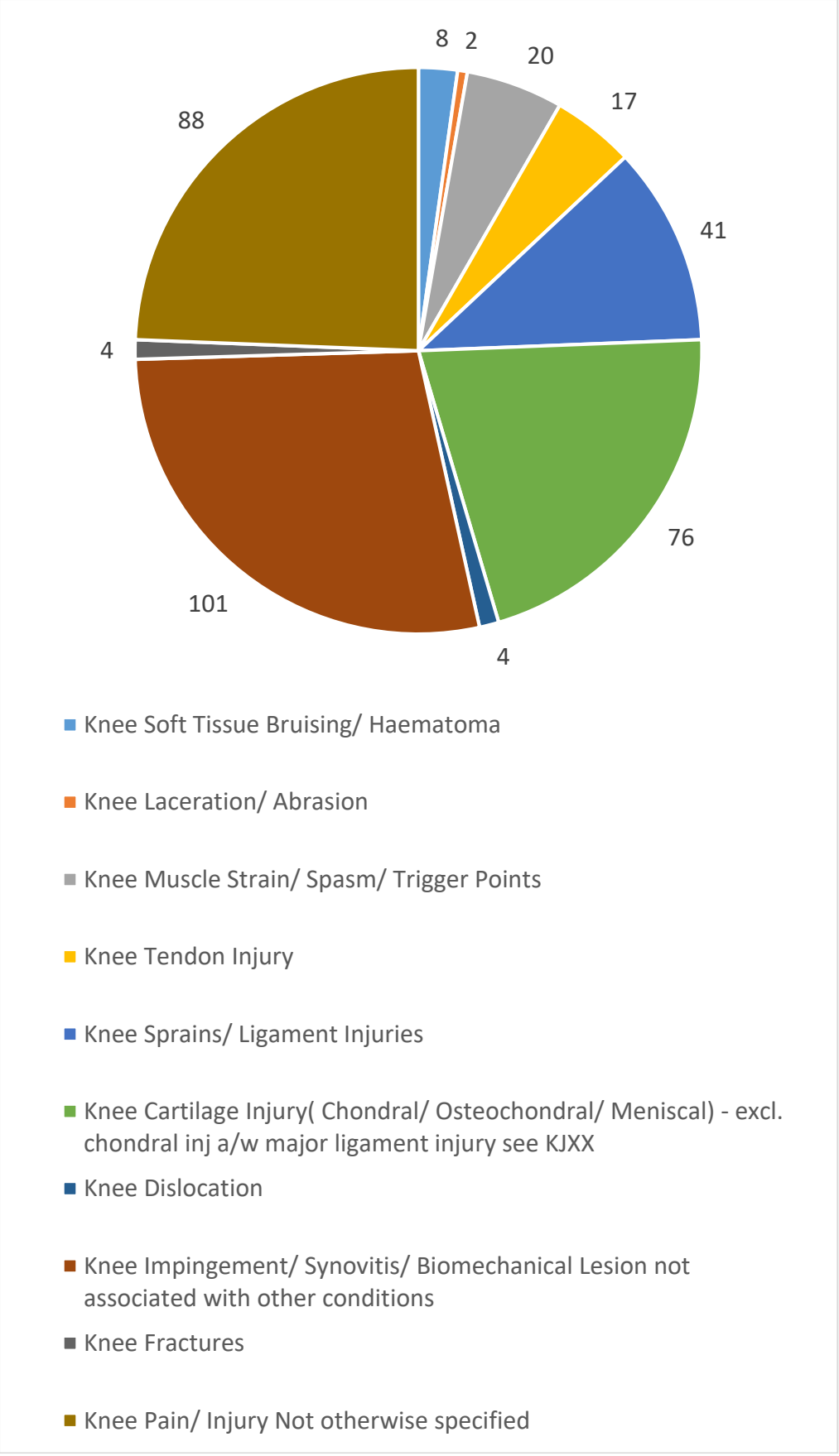


Figure 77: Type of Knee Injuries

Of the knee injuries reported, 'Impingement/synovitis and biomechanical lesions' were the most common, followed by 'knee pain/injury not otherwise specified' and 'Cartilage (chondral/osteochondral/meniscal)' injury (Figure 77).

Change in Running and Running Injury

When running behaviour is characterised according to self-reported change in running between now and previous activity, there is a statistically significant difference between the prevalence of injury in these groups (x^2 44.539, p <0.0001) (Figure 78). For those athletes running a lot less, the proportion of those afflicted by previous running injury is 35.96%. The lowest proportion of those with a previous running injury were in the category completing 'A lot more' running (19.62%).

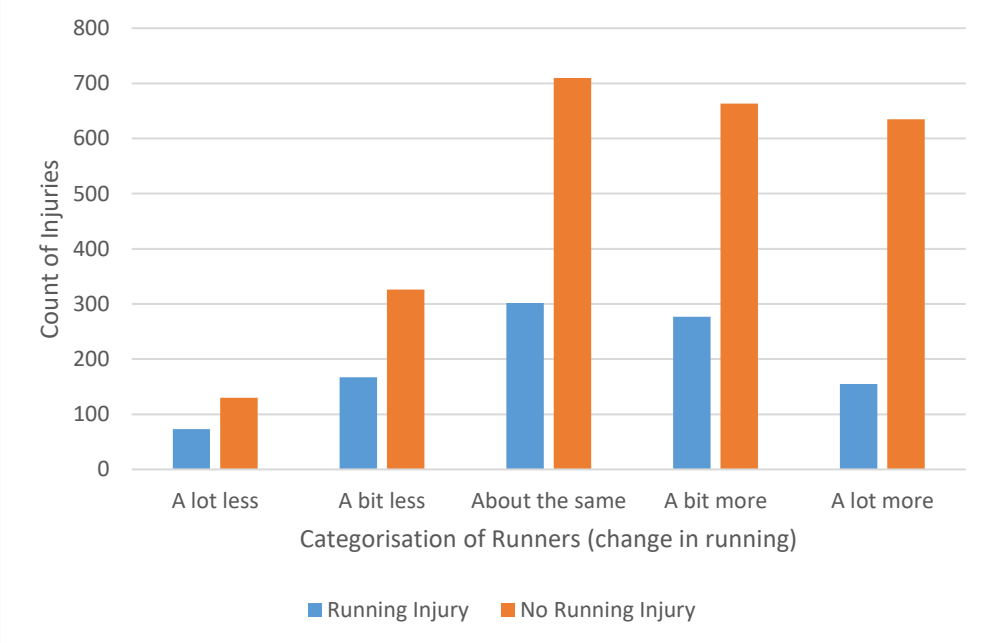


Figure 78: Change in Running Behaviour and Injury

5.6.4 Knee Symptoms in Male and Female Runners

Pain

Prevalence of a history of knee pain (any cause) was greater in male (30.85%) than in female runners (26.54%) (Figure 79).

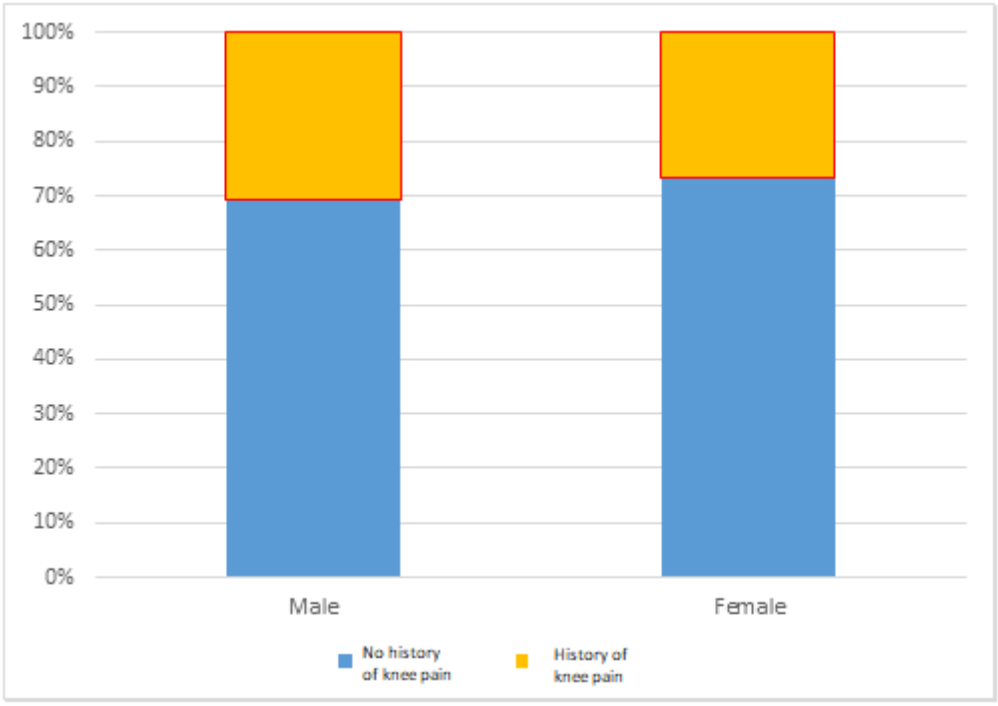


Figure 79: Distribution of Knee Pain in Male and Female Runners

The distribution of the knee pain (any cause) in male and female runners is statistically significant (x^2 8.005, p 0.005) (Figure 80). There was no statistically significant difference in the prevalence of morning knee joint stiffness in females (11.12%) and males (12.45%) (x^2 1.465, p 0.226).

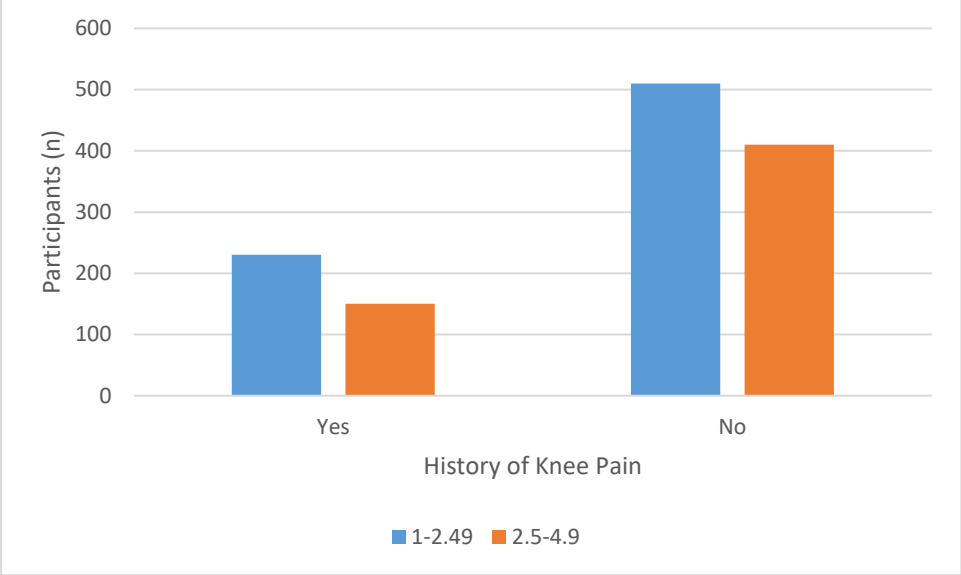


Figure 80: Prevalence of Knee Pain. Male and female runners

Figure 81 shows the gender distribution of knee joint crepitus in males and female runners. In males, 25.56% of runners report a history knee crepitus. In females, 31.93% report a history of knee crepitus. The x2 test identified that the difference in distribution between males and females is statistically significant (x^2 16.780, p <0.0001).

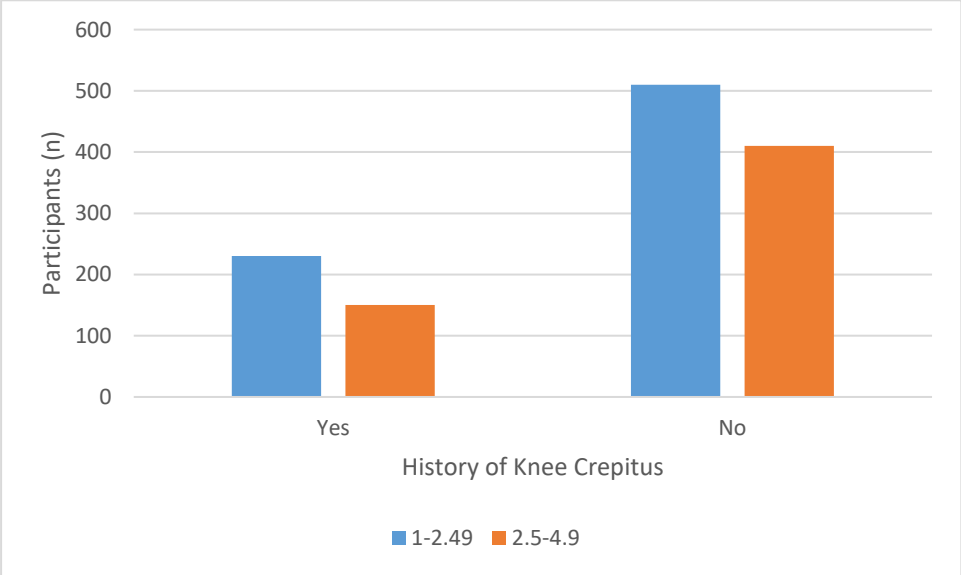


Figure 81: Prevalence of Knee crepitus. Male and female runners

For reduced knee ROM (Figure 82), 9.80% of females and 12.65% of male runners reported this outcome. The x^2 6.997 approached but did not achieve statistical significance (p 0.008).

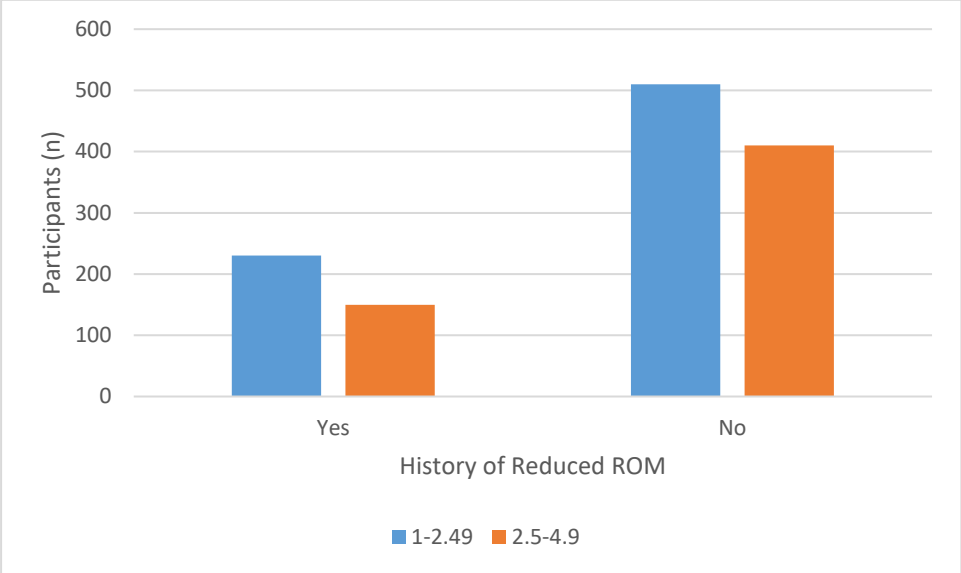


Figure 82: Prevalence of Knee reduced ROM. Male and female runners

Age Group Analysis of Runners and Knee Symptoms

When the runners were categorised by age group (n=3,444), the prevalence of a history of knee pain was variable (Table 40). The lowest prevalence was in the 65.0-74.9 age group, followed by those aged <24.9. Prevalence of morning joint knee joint stiffness was similar between all age groups. There was a trend for prevalence of knee crepitus to reduce as age increased. In the younger groups (<24.9, 25-34.9 and 35.0-44.9) the proportion affected was 34.34%, 30.39% and 32.32% respectively. By contrast in the three eldest groups (55.0-64.9, 65.0-74.9 and 75>, the prevalence of crepitus was 23.86%, 17.54% and 23.08% respectively. For reduced joint ROM, prevalence was low and remained relatively stable until 65-74.9 age group when it increased to 16.23. In the 75>,

it increased to 19.23%. Crepitus was the only marker of joint health where the distribution of the variable reached statistical significance.

Age Group	n	Knee Pain n (%)		Morning Stiffness n (%)		Crepitus n (%)		Reduced ROM n (%)	
		No	Yes	No	Yes	No	Yes	No	Yes
<24.9	131	99 (75.57)	32 (24.43)	117 (89.31)	14 (10.69)	86 (65.65)	45 (34.34)	119 (90.84)	12 (9.16)
25.0-34.9	533	385 (72.23)	148 (27.77)	490 (91.93)	43 (8.07)	371 (69.61)	162 (30.39)	485 (90.99)	48 (9.01)
35.0-44.9	823	569 (69.14)	254 (30.86)	720 (87.48)	103 (12.52)	557 (67.68)	266 (32.32)	741 (90.04)	82 (9.96)
45.0-54.9	1066	779 (73.08)	287 (26.92)	951 (89.21)	115 (10.79)	737 (69.14)	329 (30.86)	950 (89.12)	116 (10.88)
55.0-64.9	637	440 (69.07)	197 (30.93)	540 (84.77)	97 (15.23)	485 (76.14)	152 (23.86)	556 (87.28)	81 (12.72)
65.0-74.9	228	173 (75.88)	55 (24.12)	200 (87.72)	28 (12.28)	188 (82.46)	40 (17.54)	191 (83.77)	37 (16.23)
75>	26	18 (69.23)	8 (30.77)	23 (88.46)	3 (11.54)	20 (76.92)	6 (23.08)	21 (80.77	5 (19.23)
X^2 (p)	3444	8.814 (0.184)		16.071 (0.013)		31.648 (<0.0001)		13.536 (0.035)	

Table 40: Prevalence of Knee Symptoms in Runners, by age group

BMI Category Analysis of Runners and Joint Health

Distribution of knee OA is statistically significant in different categories of BMI in runners (Table 41). The highest prevalence was in the 'Overweight' BMI category (8.96%). In contrast, the lowest prevalence was in the 'Underweight' category (2.82%).

BMI Category	Total n	Knee OA n (%)	
		No	Yes
Underweight	71	69 (97.18)	2 (2.82)
Healthy Weight	2414	2294 (95.03)	120 (4.97)
Overweight	781	711 (91.04)	70 (8.96)
Obese	174	162 (93.10)	12 (6.90)
X^2 (p)	3440	18.382 (<0.0001)	

Table 41: Distribution of knee OA in runners by BMI category

Table 42 summarises the prevalence of joint health markers from 3,440 runners categorised by BMI. For knee pain, the proportion of those affected rose with each increase in BMI category. This was consistently shown across the other markers of joint health (crepitus, reduced knee ROM and morning stiffness). The difference in distribution of each marker was statistically significant for all outcomes, except for crepitus.

BMI Category	n	Knee Pain n (%)		Morning Stiffness		Reduced Knee ROM		Crepitus	
		No	Yes	No	Yes	No	Yes	No	Yes
Underweight	71	59	12 (16.9)	65	6 (8.5)	65	6 (8.4)	55	16 (22.5)
Healthy Weight	2414	1753	661 (27.4)	2171	243 (10.1)	2173	241 (9.9)	1740	674 (27.9)
Overweight	781	534	247 (31.6)	664	117 (14.9)	678	103 (13.2)	535	246 (31.6)
Obese	174	113	61 (35.)	137	37 (21.3)	143	31 (17.8)	110	64 (36.8)
X^2 (p)	3440	13.6 (0.004)		30.2 (<0.0001)		14.9 (0.002)		10.3 (0.016)	

Table 42: Distribution of knee symptoms in runners by BMI category

5.6.5 Running Behaviour and Symptoms

5.6.5.1 Knee Pain

Runners with knee pain have been running marginally longer (mean 11.24 years, SD 12.69 v 11.00 years, SD 11.86). The difference between the groups did not achieve statistical significance (Mann-Whitney U Test, p 0.448).

Data from 3,330 recreational athletes shows that the proportion of runners with knee pain is relatively consistent across each group of runners when categorised by history of running (number of years). The greatest proportion of knee pain was in the athletes that had run for less than 2.49 years (30.48%) (Figure 83). The distribution of knee pain between the groups is not statistically significant (x^2 4.207, p 0.379).

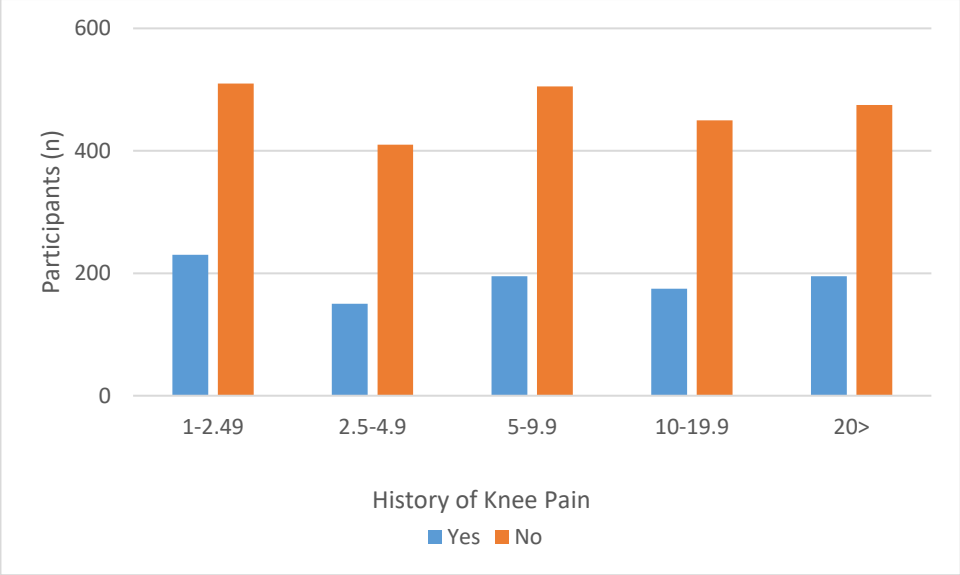


Figure 83: Knee Pain in runners, stratified by number of years running

Current Weekly Running and Knee Pain

3,266 recreational runners reported knee pain and weekly run distance (km) (Figure 84). When categorised on current, average running distance per week, distribution of knee pain was not statistically significant (x^2 1.642, p0.642). Prevalence of a history of knee pain was lowest (as a percentage) in the 30+ km per week group, (27.13%).

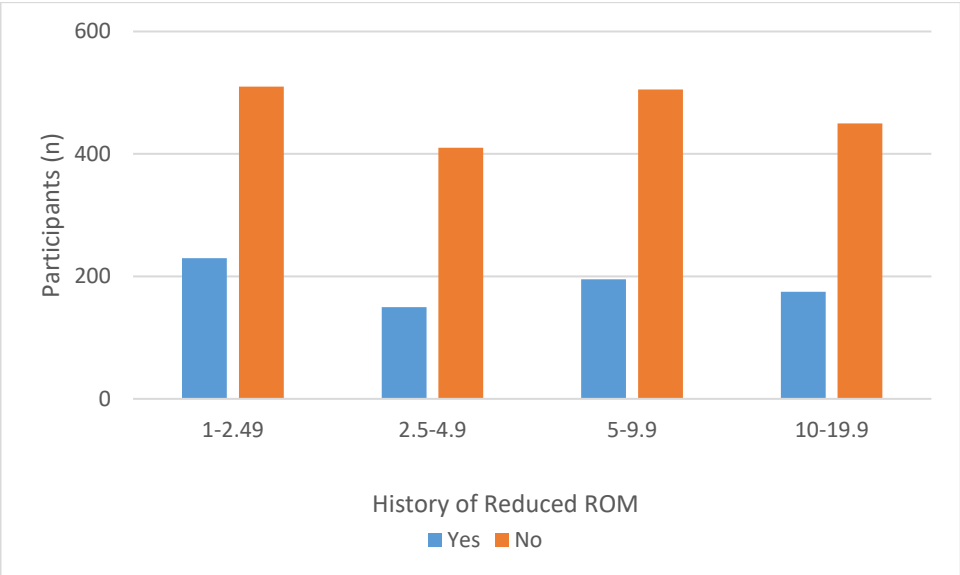


Figure 84: Knee Pain in runners, stratified by average weekly distance (km)

Run minutes per week

Of the runners completing up to 60 minutes of running per week, 35.65% report knee pain. Across the other categories (increasing duration), there was a trend for reducing prevalence of knee pain as run duration per week increased (28.10%, 27.69%, 26.71%) (Figure 85). The difference between groups did not meet statistical significance (x^2 9.936, p 0.019). Of the runners currently not running (n=25), 40% had a history of knee pain.

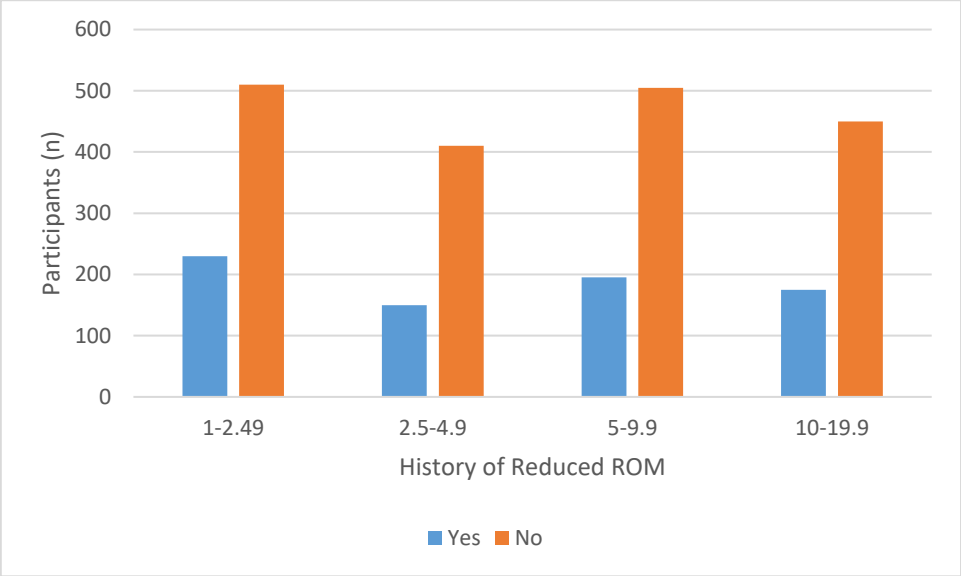


Figure 85: Knee Pain in runners, stratified by average weekly run duration (mins)

Change in Running Behaviour and Knee Pain

There is a statistically significant difference in the distribution of knee pain in different groups categorising change in running behaviour (current compared with previous running volume) (x^2 40.763, p <0.0001). Figure 86 reveals that, for those runners that state they are completing 'A lot less' (45.81%) or 'A bit less' running (32.45%), a history of knee pain is more prevalent than other

groups where runners were either running ‘About the same,’ ‘A bit more,’ or ‘A lot more’ (26.48%, 25.24%, 27.85% respectively).

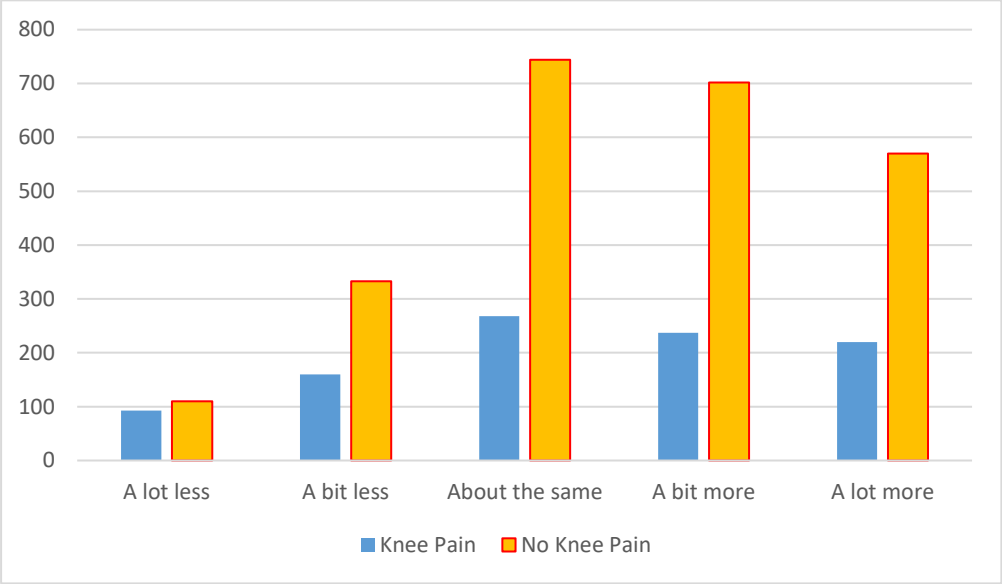


Figure 86: Knee Pain in runners, stratified by change in running

5.6.5.2 Risk Factors for Knee Pain in Runners

Crude and adjusted risk ratios for knee pain are described in the tables below (Table 43 and Table 44). For knee pain, being overweight or obese was associated with higher risk of knee pain in recreational runners. Previous serious knee injury and previous running injury were also associated with increased risk. When adjusted for age, gender and BMI, injury the association with knee pain remained statistically significant. Neither history of running (duration in years) nor weekly run distance were associated with increased risk of knee pain.

Factors	Risk Ratio (crude)	P value	95% Confidence Interval
Demographics			
Female Gender	0.86	0.006	0.78-0.96
Age >45	0.96	0.47	0.86-1.07
Overweight or obese BMI	1.20	0.001	1.07-1.35
High Risk Occupation	1.02	0.846	0.87-1.18
Family history of OA	1.14	0.019	1.02-1.27
Injury			
Previous Knee Injury	3.55	<0.0001	3.24-3.90
Running Injury	1.51	<0.0001	1.35-1.67
Running Behaviour			
Running >5 years	1.00	0.972	0.90-1.11
Running >10km per week	0.92	0.193	0.82-1.04

Table 43: Risk Factors for knee pain in runners (unadjusted)

Adjusted for Gender, BMI and Age

Factors	Risk Ratio (adjusted)	P value	95% Confidence Interval
Knee Injury	3.56	<0.0001	3.24-3.91
Running Injury	1.52	<0.0001	1.37-1.70
Running >5 years	0.99	0.919	0.89-1.11
Running >10km per week	0.92	0.165	0.81-1.04

Table 44: Risk Factors for knee pain in runners (adjusted)

5.6.6 Runners and OA

There was a statistically significant different distribution of knee OA diagnosis between the age groups (Table 45). As age increased, the number of participants reporting knee OA in each group increased.

Age Group	n	OA Diagnosis n (%)	
		No	Yes
<24.9	131	131 (100)	0 (0)
25.0-34.9	533	528 (99.06)	5 (0.94)
35.0-44.9	823	789 (96.87)	34 (4.13)
45.0-54.9	1066	1004 (94.18)	62 (5.82)
55.0-64.9	638	571 (89.50)	67 (10.50)
65.0-74.9	228	197 (86.40)	31 (13.60)
75+	26	21 (80.77)	5 (19.23)
X^2 (p)		93.160 (<0.0001)	

Table 45: Distribution of OA in runners, stratified by age

5.6.6.1 Risk Factors for Knee OA in Runners

Significant risk factors for knee OA in recreational runners are age >45, overweight or obese BMI, family history of OA, knee injuries. When adjusted for age, gender and BMI neither running greater than 5 years nor running more than 10km per week were significantly associated with knee OA risk (table 46-47).

Factors	Risk Ratio (crude)	P value	95% Confidence Interval
Demographics			
Female Gender	0.99	0.945	0.76-1.29
Age >45	3.22	<0.0001	2.28-4.53
Overweight or obese BMI	1.78	<0.0001	1.36-2.34
High Risk Occupation	1.09	0.634	0.76-1.58
Family history of OA	1.61	<0.0001	1.23-2.10
Injury / Pain			
Previous Knee Injury	5.88	<0.0001	4.50-7.68
Ligament Injury	2.86	<0.0001	1.98-4.11
Cartilage Injury	6.12	<0.0001	4.61-8.12
Running Injury	1.64	<0.0001	1.25-2.14
Knee Pain	7.73	<0.0001	5.67-10.54
Running Behaviour			
Running >5 years	1.61	0.001	1.22-2.13
Running >10km per week	1.14	0.446	0.82-1.58

Table 46: Risk Factors for knee OA in runners (unadjusted)

Adjusted for Gender, BMI and Age

Factors	Risk Ratio	P value	95% Confidence Interval
Knee Injury	3.56	<0.0001	3.24-3.91
Running Injury	1.51	0.002	1.16-1.98
Running > 5 years	1.30	0.078	0.97-1.75
Running >10km per week	1.10	0.561	0.80-1.53

Table 47: Risk Factors for knee OA in runners (adjusted)

5.5.7 KOOS Values in Runners

Data from a sub-cohort of runners is described below relating to outcomes measured by the KOOS (Table 48). Males in the 55-64.9 age group reported the lowest scores for all five domains in both knees (n=128-131, depending on the analysis). There are negative correlation coefficients for pain, activity sports and quality of life domains of the KOOS with age in recreational runners (Table 49). However, the majority of these did not achieve statistical significance (kendalls correlation).

Table 48			KOOS Domain									
Age	Gender		R Symptoms	L Symptoms	R Pain	L Pain	R Activity	L Activity	R Sport	L Sport	R QoL	L QoL
<44.9	Female	Mean	90.9	91.6	94.8	95.1	97.8	98.0	92.4	92.7	90.3	90.7
		N	335	335	334	334	332	332	331	331	330	330
		Std. Deviation	10.5	9.6	9.7	9.1	6.1	5.8	14.1	13.1	15.1	14.7
	Male	Mean	92.5	92.9	95.4	95.5	97.7	97.5	93.1	92.6	91.6	91.1
		N	186	186	186	186	186	186	186	186	186	186
		Std. Deviation	9.8	9.3	8.7	9.6	6.	6.981	13.045	13.990	13.112	15.728
45-54.9	Female	Mean	90.8	91.7	95.3	95.7	98.1	98.4	92.9	94.5	90.2	91.9
		N	254	254	255	255	255	255	254	254	252	252
		Std. Deviation	10.2	9.8	7.6	7.7	4.6	3.7	11.8	10.8	13.0	12.5
	Male	Mean	92.0	92.3	94.7	95.6	97.4	97.8	92.6	93.1	89.9	91.0
		N	182	182	181	181	179	179	178	178	178	178
		Std. Deviation	10.5	11.3	9.3	8.3	6.6	5.6	13.4	12.4	14.6	14.3
55-64.9	Female	Mean	91.1	92.4	93.3	95.4	96.3	97.6	90.7	93.1	88.8	90.9
		N	158	158	158	158	157	157	155	155	156	156
		Std. Deviation	14.1	11.6	12.4	8.6	9.8	5.8	16.2	12.7	17.3	15.6
	Male	Mean	90.5	90.6	93.0	92.3	96.1	95.7	89.1	87.7	87.9	85.4
		N	130	130	131	131	130	130	128	128	128	128
		Std. Deviation	13.5	12.5	11.1	12.4	8.4	9.9	16.8	19.5	16.9	19.4
65>	Female	Mean	91.6	94.6	94.2	96.1	97.6	97.2	90.9	92.5	91.4	93.2
		N	41	41	40	40	40	40	40	40	40	40
		Std. Deviation	13.4	9.5	10.7	7.9	5.8	7.4	16.9	14.6	15.1	13.1
	Male	Mean	93.5	93.6	95.7	95.9	97.2	97.1	92.1	92.6	90.9	90.9
		N	97	97	97	97	97	97	95	95	97	97
		Std. Deviation	8.9	11.6	7.9	8.6	5.8	7.2	12.1	13.3	13.6	14.7

KOOS Domain	Right Knee			Left Knee		
Symptoms	**Correlation Coefficient**	**Sig. (2-tailed)**	**N**	**Correlation Coefficient**	**Sig. (2-tailed)**	**N**
	0.031	0.117	1383	.052	0.008	1383
Pain	**Correlation Coefficient**	**Sig. (2-tailed)**	**N**	**Correlation Coefficient**	**Sig. (2-tailed)**	**N**
	-0.03	0.138	1382	-0.006	0.771	1382
Activity	**Correlation Coefficient**	**Sig. (2-tailed)**	**N**	**Correlation Coefficient**	**Sig. (2-tailed)**	**N**
	-.053	0.01*	1376	-0.031	0.135	1376
Sport	**Correlation Coefficient**	**Sig. (2-tailed)**	**N**	**Correlation Coefficient**	**Sig. (2-tailed)**	**N**
	-0.031	0.13	1367	-0.008	0.706	1367
Quality of Life	**Correlation Coefficient**	**Sig. (2-tailed)**	**N**	**Correlation Coefficient**	**Sig. (2-tailed)**	**N**
	-0.029	0.16	1367	-0.016	0.426	1367

Table 49: Correlation of age and KOOS in runners

Classified by positive or negative history of knee injury, KOOS values of runners are shown in the table below (Table 50). Each of the sub-sections of the KOOS are reported separately for the left and right limbs. For all five domains, the mean KOOS values were lower for both the left and right knee in those with a history of knee injury compared to those without a history of knee injury. All five outcomes for each joint (left and right) were statistically significant (Mann-Whitney U test, $p < 0.0001$). Subsequent analysis of runners with cartilage and ligament injuries also revealed similar trends (i.e. injury affected KOOS on both limbs) (Table 51-52). There is a statistically significant difference (MWU $p<0.0001$) in KOOS scores for all domains on both limbs for those with a diagnosis of knee OA. The findings of each group are summarised below.

Table 50		KOOS Domain									
Knee Injury History		R Symptoms	L Symptoms	R Pain	L Pain	R Activity	L Activity	R Sport	L Sport	R QoL	L QoL
No	Mean	92.6	93.3	95.4	96.2	97.9	98.3	93.4	94.2	91.9	92.7
	N	1099	1099	1097	1097	1091	1091	1084	1084	1082	1082
	Std. Deviation	9.9	8.9	8.8	7.7	5.7	5.02	12.4	11.2	12.8	12.6
Yes	Mean	87.0	87.6	91.8	91.4	95.5	95.1	86.8	86.9	83.0	82.7
	N	284	284	285	285	285	285	283	283	285	285
	Std. Deviation	14.3	14.3	11.65	12.48	9.23	9.4	17.9	19.2	18.9	20.2

Table 51		KOOS Domain									
Knee Ligament Injury		R Symptoms	L Symptoms	R Pain	L Pain	R Activity	L Activity	R Sport	L Sport	R QoL	L QoL
No	Mean	91.8	92.5	94.9	95.4	97.5	97.8	92.4	92.9	90.6	91.1
	N	1307	1307	1306	1306	1300	1300	1292	1292	1291	1291
	Std. Deviation	10.8	9.9	9.5	8.70	6.7	5.8	13.9	12.8	14.5	14.3
Yes	Mean	85.4	86.20	91.4	91.07	96.5	94.7	87.1	86.7	82.6	83.2
	N	76	76	76	76	76	76	75	75	76	76
	Std. Deviation	14.6	16.4	10.6	13.8	6.9	11.9	14.7	22.2	17.7	23.2

Table 52		KOOS Domain									
Cartilage Injury		R Symptoms	L Symptoms	R Pain	L Pain	R Activity	L Activity	R Sport	L Sport	R QoL	L QoL
No	Mean	91.9	92.5	94.9	95.4	97.6	97.8	92.6	93.1	90.7	91.2
	N	1309	1309	1308	1308	1302	1302	1293	1293	1293	1293
	Std. Deviation	10.4	9.8	9.2	8.8	6.3	5.9	13.2	13.0	14.2	14.5
Yes	Mean	83.0	85.3	88.9	90.6	94.1	94.5	82.5	85.3	79.9	80.6
	N	74	74	74	74	74	74	74	74	74	74
	Std. Deviation	17.9	17.5	13.8	12.3	11.4	10.1	21.9	20.1	19.8	20.6

Table 53		KOOS Domain									
Knee OA		R Symptoms	L Symptoms	R Pain	L Pain	R Activity	L Activity	R Sport	L Sport	R QoL	L QoL
No	Mean	92.3	93.0	95.2	95.7	97.7	98.1	92.9	93.6	91.1	91.9
	Std. Deviation	10.0	9.1	8.9	8.2	6.0	5.3	12.9	11.9	13.5	13.3
	n	1300	1300	1299	1299	1293	1293	1284	1284	1284	1284
Yes	Mean	78.3	78.1	86.9	86.2	92.5	90.6	78.3	77.2	74.1	71.7
	n	83	83	83	83	83	83	83	83	83	83
	Std. Deviation	17.8	18.6	15.1	15.6	12.5	13.0	21.5	23.9	22.6	24.8

Kendall's tau-b correlation was used to determine the relationship between different running behaviours and the domains of KOOS (Table 54). For all outcomes, the relationship was positive, but very weak. This means that as the behavioural exposure increased, the KOOS value also increased but the gradient denoting the strength of the association was low. For many of the variables, (denoted by a *), the test achieved statistical significance (<0.05).

Table 54	Running Factor							
	Number of Years Running		Mean Weekly Run Distance		Mean Run mins per week		Mean runs per week	
KOOS Pain	**R**	**L**	**R**	**L**	**R**	**L**	**R**	**L**
Correlation Coefficient	0.049	0.038	0.055	0.070	0.042	0.046	0.025	0.036
p	0.018*	0.071*	0.008*	0.001*	0.045*	0.030*	0.266	0.104
KOOS Symptoms	**R**	**L**	**R**	**L**	**R**	**L**	**R**	**L**
Correlation Coefficient	0.038	0.036	0.043	0.048	0.052	0.054	0.025	0.036
p	0.066	0.075	0.034*	0.018*	0.011*	0.008*	0.247	0.097
KOOS Activity	**R**	**L**	**R**	**L**	**R**	**L**	**R**	**L**
Correlation Coefficient	0.038	0.031	0.041	0.058	0.031	0.046	0.011	0.046
p	0.076	0.148	0.054*	0.007*	0.154	0.034*	0.633	0.045*
KOOS Sport	**R**	**L**	**R**	**L**	**R**	**L**	**R**	**L**
Correlation Coefficient	0.020	0.020	0.078	0.057	0.064	0.043	0.051	0.045
p	0.237	0.351	<0.0001	0.007*	0.002*	0.041*	0.023*	0.044*
KOOS QoL	**R**	**L**	**R**	**L**	**R**	**L**	**R**	**L**
Correlation Coefficient	0.037	0.017	0.104	0.092	0.082	0.068	0.068	0.056
p	0.074	0.426	<0.0001	<0.0001	<0.0001*	0.001*	0.002*	0.012*

5.6.8 Pain After Running (within 48 hours)

Of those currently running (n=1431, 21 runners not currently running), 57% reported pain following running (within 48 hours of completion). Almost 65% of those with a history of running injury reported pain after running compared to 53% of those without a history of running injury (x^2 31.628 <0.0001) (Figure 87). However, previous injury was not associated specifically with knee pain after running (x^2 0.009 p 0.923). Once knee injuries were analysed separately, there was a statistically significant association with prevalence of knee pain after running (Figure 88) (x^2 43.696 p<0.0001) (Figure 88). This was trend was also the case when history of knee surgery was analysed (i.e. when surgery had occurred, pain was more prevalent), but the number of cases of knee surgery was small (n=106) (x^2 16.377, p<0.0001). (Figure 89). When the presence or absence of knee OA and prevalence of knee pain after running was reported, those with knee OA were more likely to report pain (Figure 102, x^2 41.763, p<0.0001) (Figure 90).

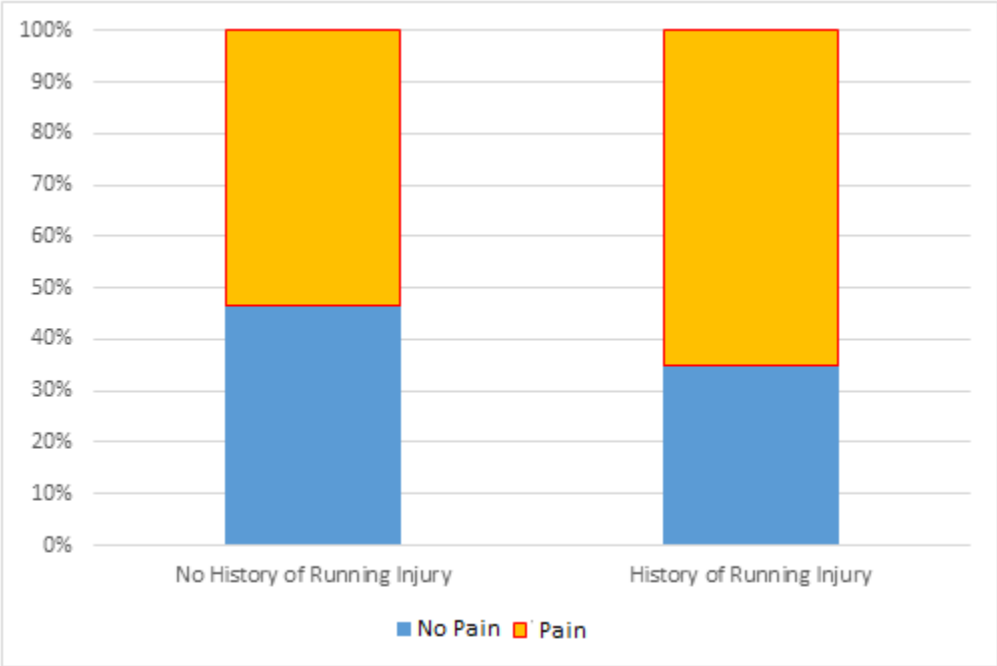


Figure 87: Body Pain after running, comparison of injured and non-injured

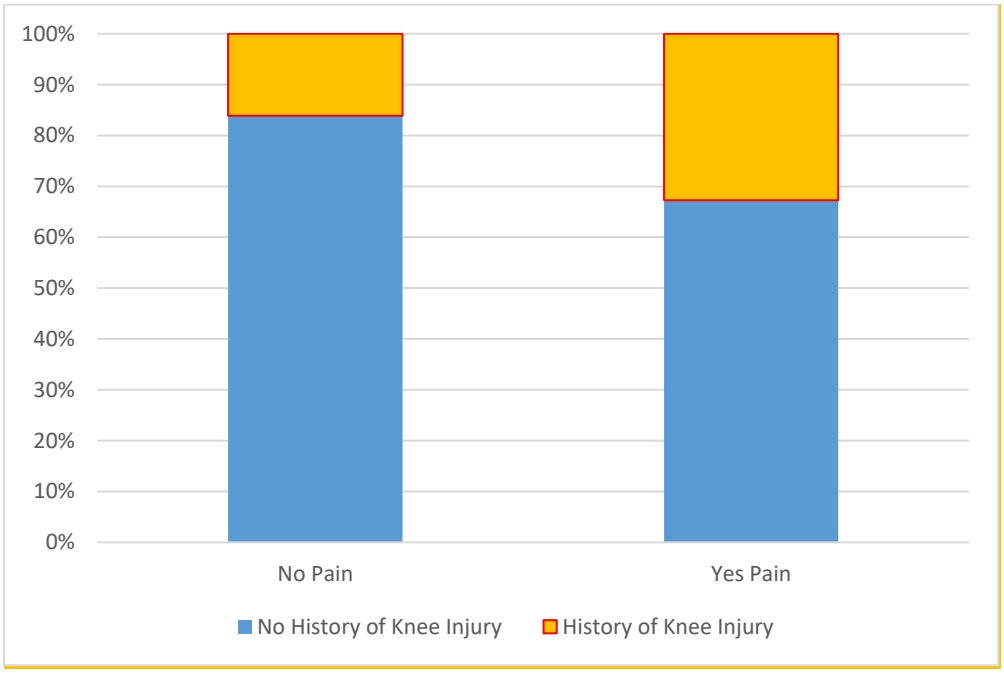


Figure 88: Knee Pain after running, comparison of runners with and without history of knee injury

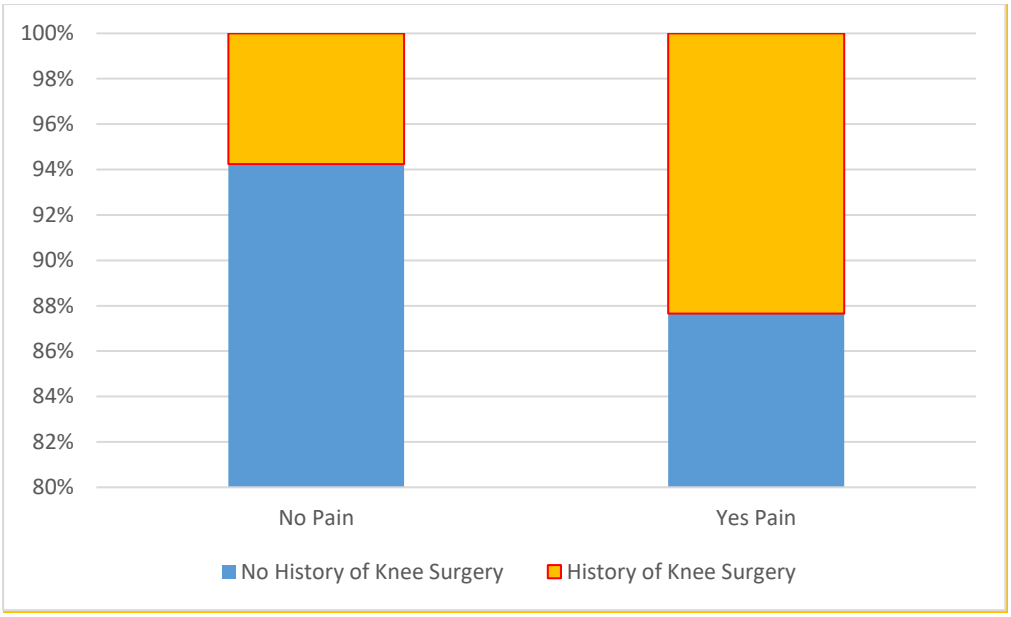


Figure 89: Knee Pain after running, comparison of runners with and without history of knee surgery

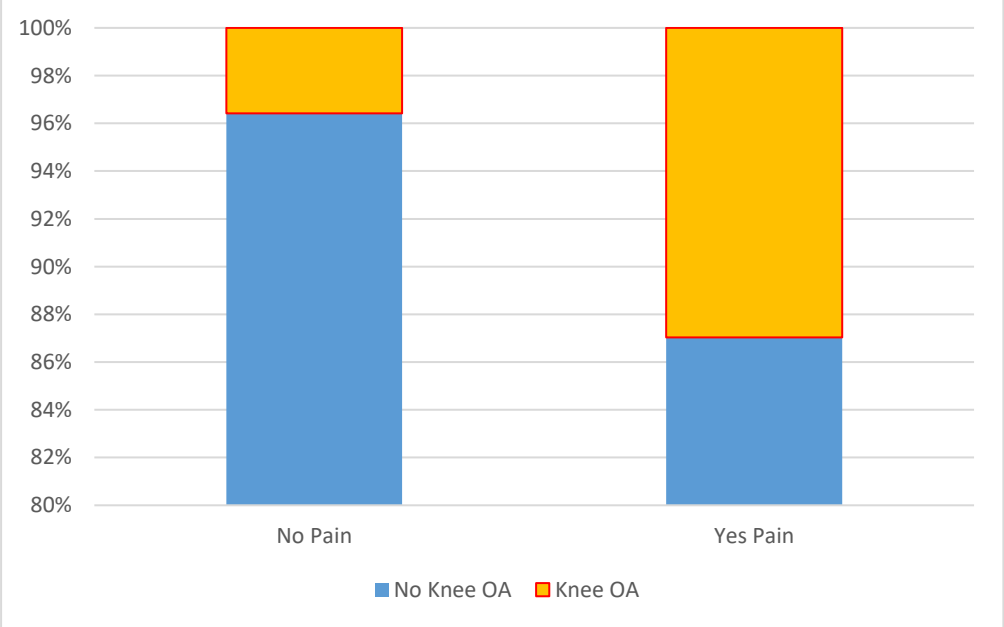


Figure 90: Knee Pain after running, comparison of runners with and without history of knee OA

5.6.9 Running and Health (EQ-5D-5L)

For runners with complete EQ5D data (n=3063), their responses are outlined in Table 55 below.

EQ5D Domain	Response	n (%)
Mobility	I have no problems in walking about	2857 (93.3)
	I have slight problems in walking about	180 (5.9)
	I have moderate problems in walking about	19 (0.6)
	I have severe problems in walking about	7 (0.2)
	I am unable to walk about	0
Self-Care	I have no problems washing or dressing myself	3031 (99.0)
	I have slight problems washing or dressing myself	27 (0.9)
	I have moderate problems in washing or dressing myself	2 (0.1)
	I have severe problems in washing or dressing myself	1 (0.0)
	I am unable to wash or dress myself	2 (0.1)
Usual Activities	I have no problems doing my usual activities	2848 (93.0)
	I have slight problems doing my usual activities	175 (5.7)
	I have moderate problems doing my usual activities	30 (1.0)
	I have severe problems doing my usual activities	5 (0.2)
	I am unable to do my usual activities	5 (0.2)
Pain / Discomfort	I have no pain or discomfort	1757 (57.4)
	I have slight pain or discomfort	1154 (37.7)
	I have moderate pain or discomfort	133 (4.3)
	I have severe pain or discomfort	16 (0.5)
	I have extreme pain or discomfort	3 (0.1)
Anxiety / Depression	I am not anxious or depressed	2345 (76.6)
	I am slightly anxious or depressed	552 (18.0)
	I am moderately anxious or depressed	134 (4.4)
	I am very anxious or depressed	23 (0.8)
	I am extremely anxious or depressed	9 (0.3)

Table 46: Responses by runners to EQ-5D-5L

In mobility, self-care and usual activities, the clear majority (over 93% in each case) reported no problems. Over 40% reported pain or discomfort. Almost 25% of runners reported anxiety or depression.

When change in running over the previous 12 months is analysed (Kruskal-Wallis), the distribution of EQ5D health score is significantly different

(p<0.0001) between the categories (Table 56). There was a trend for lower mean values in the athletes running less.

Running Change (n)	Mean (SD)
A lot more (694)	84.10 (14.40)
A bit more (835)	86.27 (12.44)
About the same (912)	86.61 (13.89)
A bit less (441)	83.26 (15.69)
A lot less (177)	79.32 (16.49)

Table 56: Responses by runners to EQ-5D-5L, stratified by running change

For 'pain and discomfort' and 'anxiety and depression', running behaviours were analysed to assess the distribution of number of years running and average weekly running distance across the outcomes. Run history was equally distributed between categories of pain and discomfort (Kruskal-Wallis, p 0.832) but was not equally distributed with anxiety and depression (Kruskal-Wallis, p 0.000). For average weekly running distance, the distribution was not the same between categories for pain and discomfort or anxiety and depression (Kruskal-Wallis, p < 0.000).

The distribution of outcomes for EQ5D 'Pain and Discomfort' and history of running injury and knee injury are presented below (table 57 and table 58).

More participants without a history of running injury have no pain or discomfort. Fewer than half of the participants with a history of running injury are free of pain and discomfort. Distribution of the outcomes across the categories was statistically significant (x^2 41.437, p<0.0001). For the same exposure, there was no difference in the distribution of outcomes when analysing anxiety and depression (x^2 6.085, p 0.193).

There was a statistically significant difference in the distribution of outcomes between the categories for runners with a history of knee injury (x^2 72.291, p 0.000). Just over 40% of runners with a history of knee injury are pain free. Almost half report slight pain or discomfort.

EQ5D Pain or Discomfort						
Status		**I have extreme pain or discomfort n (%)**	**I have severe pain or discomfort n (%)**	**I have moderate pain or discomfort n (%)**	**I have slight pain or discomfort n (%)**	**I have no pain or discomfort n (%)**
History of Running Injury	**No (n=2383)**	2 (0.1)	9 (0.4)	92 (3.9)	842 (35.3)	1438 (60.3)
	Yes (n=948)	2 (0.2)	10 (1.1)	51 (5.4)	423 (44.6)	462 (48.7)

Table 57: History of running injury and EQ-5D-5L (pain or discomfort)

EQ5D Pain or Discomfort						
Status		**I have extreme pain or discomfort n (%)**	**I have severe pain or discomfort n (%)**	**I have moderate pain or discomfort n (%)**	**I have slight pain or discomfort n (%)**	**I have no pain or discomfort n (%)**
History of Knee Injury	**No (n=2639)**	4 (0.15)	11 (0.42)	96 (3.64)	931 (35.28)	1597 (60.52)
	Yes (n=679)	0 (0.00)	8 (1.18)	47 (6.92)	329 (48.45)	295 (43.45)

Table 58: History of knee injury and EQ-5D-5L (pain or discomfort)

5.6.9.1 EQ-5D-5L Analogue Health Score

For all participants, regardless of running status (n=3069), there is a statistically significant correlation for age ($p<0.0001$) and BMI ($p<0.0001$) with Health Score (Table 59). These relationships were weak, but with increasing age, health score increased. There was a negative correlation between BMI and health score.

Factor (n)	Spearmans Correlation	p
Age (3073)	0.144	<0.0001
BMI (3069)	-0.188	<0.0001

Table 59: Correlation between age and BMI with EQ-5D-5L health score

Table 60 shows the correlation between two running factors and EQ5D health score. For both number of years run and current average weekly distance there was a small, positive correlation.

Factor (n)	Kendall's tau b	p
Years Running (3059)	0.096	<0.0001
Average Weekly Distance (3059)	0.112	<0.0001

Table 60: Correlation between running with EQ-5D-5L health score

Conclusion

In summary, this section has reported the prevalence of knee pain and knee OA in a cohort of recreational runners and non-runners. The prevalence of knee pain is similar between runners and non-runners, but a greater proportion of

non-runners reported knee OA. Knee injuries – a key risk factor for knee OA - are the most common type amongst runners. Further longitudinal data is required to define the long-term effects of running on knee joint health, including the onset and progression of OA.

6.0 Results: Lower Limb Function in Recreational Runners

6.1 Introduction

Knee OA can have a detrimental effect on joint function and could prevent participation in PA such as running. Tests have been developed to review lower limb function (Dobson et al, 2013). Such tests have been recommended to compliment subjective measures and can be used in both research and clinical settings. Self-report data were the outcomes used in the previous chapter. The addition of clinical assessment of participants from this cohort strengthens the conclusions drawn as it provides extra insight. As previously discussed, it was impractical to assess every participant due to finite resources.

This assessment provides objective measure of functional, everyday tasks (ambulatory transitions, walking (short and long distances) and stair negotiation). The importance of understanding the average performance of tests, particularly in the absence of OA, will provide a threshold against which the effects of the disease (i.e. change with onset and progression) can be judged longitudinally. Test performance in recreational runners may vary compared to the normal values indicated in the research. If different types of PA affect test performance, it might be beneficial to identify population norms based on PA, in addition to age and gender.

The purpose of this section is to measure lower limb function in recreational runners of tests that assess lower limb function. A comparison against the test norms in the literature are provided.

6.2 Cohort Characteristics

In total, 152 participants were contacted to take part and 56 participants were tested (response rate, 36.84%). The study participants are described in Table 61. One participant had not run recently due to injury; therefore, their running behaviour data is not included below.

Over half the sample were female and mean BMI values show that the population is 23.68 which is in the healthy BMI range for adults (NICE, 2014).

In comparison to the larger cohort of recreational runners from which this sample was derived, this sample was fairly similar in terms of average age (mean 46.31 years), proportion of females (55.14%) and mean BMI (23.71kg/m^2). The rate of significant injury was also comparable.

Females were slightly older than the males (47.70 years compared to 45.42 years). The youngest male was 18, the eldest 73 years old. For females, the youngest was 25, the eldest 72 years old. Females also had lower BMI (mean 23.36 vs 24.05kg/m^2).

	All, n (%)
Age (years), mean (SD)	46.64 (14.6)
Gender, female n (%)	30 (53.6)
BMI (kg/m^2), mean (SD)	23.68 (4.8)
Ethnicity (white), count (%)	49 (87.5)
Weekly METS, mean (SD)	4062.44 (3897.6)
History of running (years), mean (SD)	9.91 (11.6)
Current number of mean weekly runs (SD)	3.26 (1.5)
Current average weekly distance (km), mean (SD)	24.73 (16.2)
Current average weekly run duration (minutes), mean (SD)	159.73 (108.7)
Significant Running Injury (n, %)	18 (32.1)
Hip	1 (1.8)
Knee	14 (25.0)
Ankle	7 (12.5)
Knee Surgery	3 (5.4)
Knee OA Diagnosis	3 (5.4)
Ankle OA Diagnosis	1 (1.8)

Table 61: Cohort Characteristics

6.3 The OARSI Tests

The OARSI test scores achieved by the participants are outlined in Table 62. These are categorised into male and females

Test	All; mean, (SD, range)	Males; mean (SD, range)	Females; mean (SD, range)	p
30s-CST (reps)	18.04 (4.08, 9-28)	18.12 (3.79, 9-26)	17.97 (4.38, 11-28)	0.893
40mFPWT (secs)	21.72 (2.54, 16.28-29.28)	21.94 (2.52, 16.96-29.28)	21.54 (2.59, 16.28-25.90)	0.559
SCT (secs)	5.81 (1.60, 3.50-11.32)	5.48 (1.37, 3.50-9.47)	6.09 (1.74, 3.50-11.32)	0.153
TUG (secs)	7.17 (1.30, 4.97-11.12)	7.29 (1.25, 5.44-10.22)	7.07 (1.35, 4.97-11.12)	0.533
6MWT (m)	666.95 (93.36, 504.65-908.65)	659.32 (99.41, 504.65-840.43)	673.57 (88.97, 534.86-908.50)	0.574

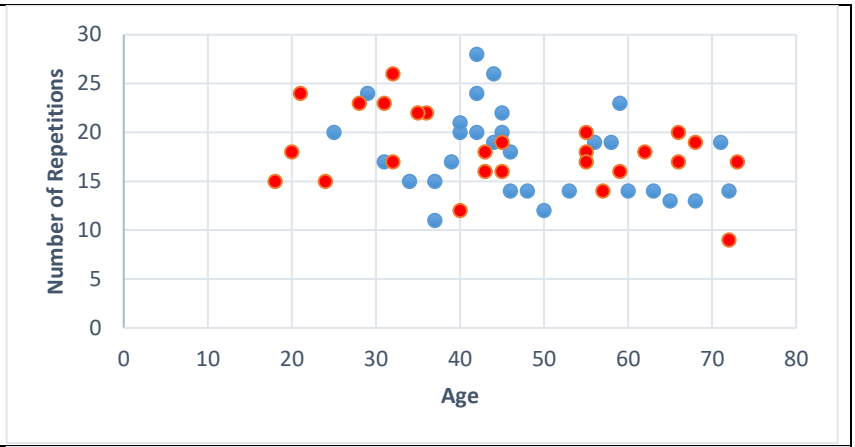
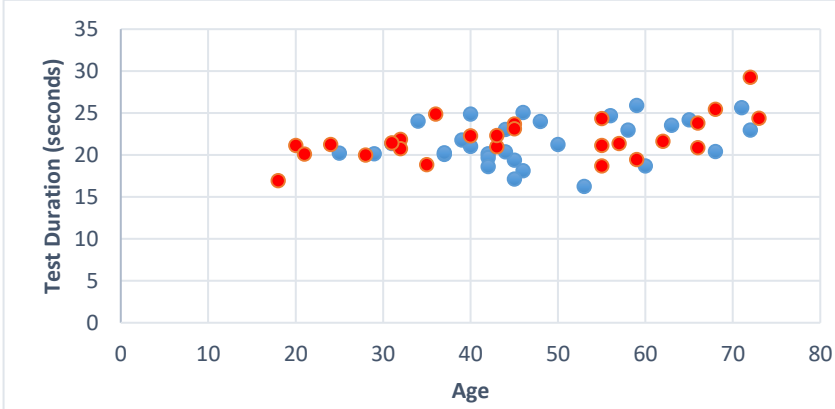
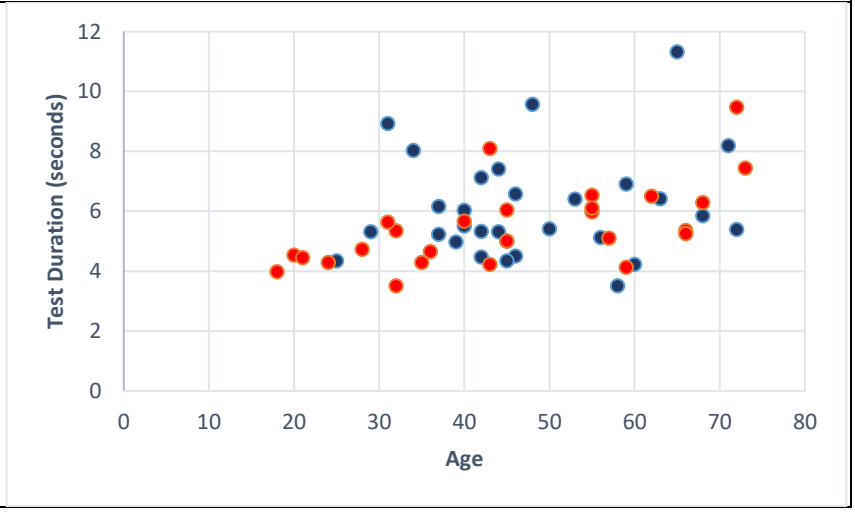
Table 62: OARSI Test Results

Males performed better than females at the 30s-CST and the SCT, but females achieved better scores in the three remaining tests. The difference in performance by males and females did not achieve statistical significance for any tests.

The mean performance of all OARSI tests declines with age for in males and females (Figure 91). Blue dots are male participants, red dots are female participants.

The directionality of performance is important to note on the graphs:

- For the 30sCST, a greater number of repetitions is better.
- For the 40mFPWT, a quicker time is better
- For the SCT, a quicker time is better
- For TUG, a quicker time is better
- For 6MWT, a further distance is better

30sCST (reps)	
40mFPWT (secs)	
SCT (secs)	

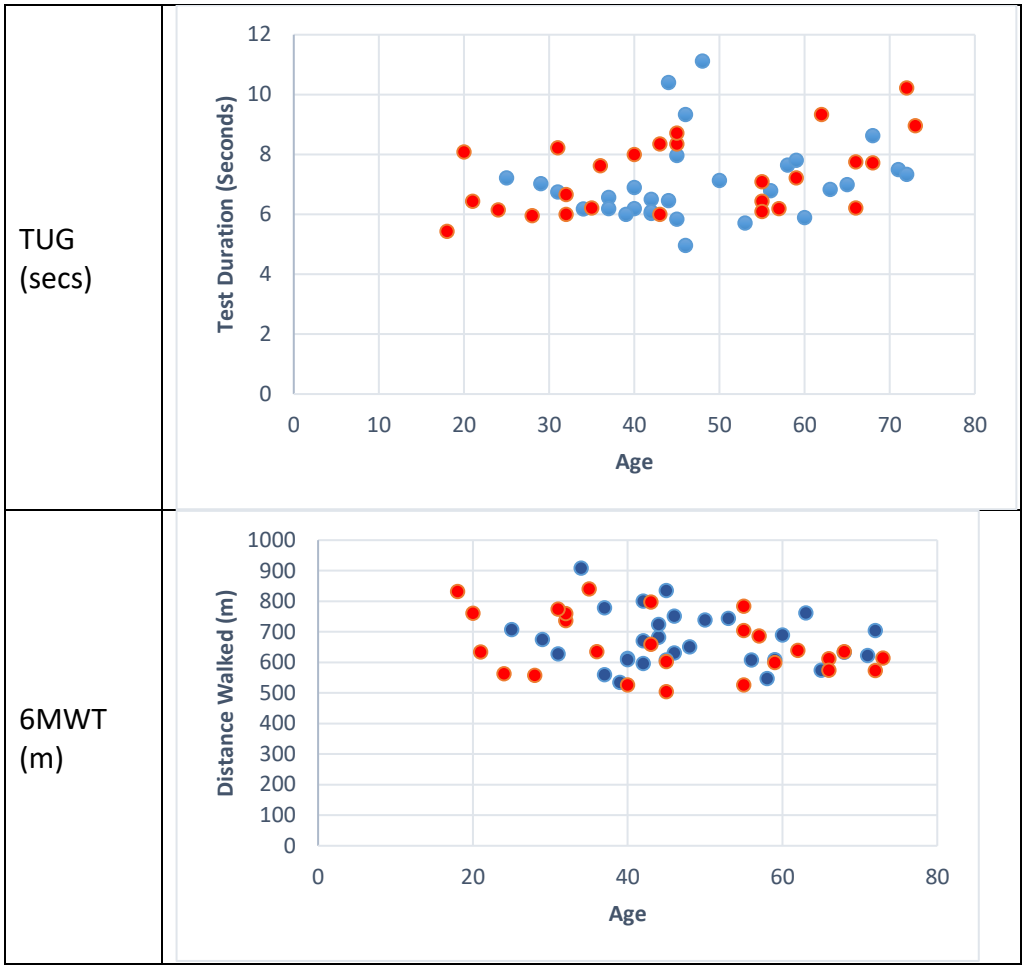


Figure 91: Age-related performance of OARSI tests.
Key: Males – red; Females – blue

Because of the relatively small sample, there were few subjects within each age and gender group for comparison with normative values in OARSI data. For certain tests (40mWT and TUG), equivalent values are available (Table 63).

Test	Age	OARSI Normative Values	Recreational Runners (n)	Mean Performance (seconds, SD)	Difference in Performance (secs)	Difference in Performance (%)
40m (4 x 10m) Fast Paced Walk Test (seconds)	40s	16.26	17	21.41 (2.39)	5.15	26.34
	50s	19.32	10	21.61 (2.96)	2.29	11.19
	60s	20.73	8	22.33 (2.28)	1.60	7.43
	70s	19.24	4	25.57 (2.70)	6.33	28.25
Timed Up and Go Test (seconds)	60-69	8.1	8	7.42 (1.17)	0.68	8.76
	70-79	9.2	4	8.50 (1.35)	0.70	7.91
	80-99	11.3	-	-	-	-

Table 63: Runners and Normative OARSI values

Recreational runners in their 40s (n=17) performed worse that then the normative values. This was trend for runners performing worse was consistently observed in all age groups at this test. The largest differences were in the 40s and 70s age groups. For the TUG, the recreational runners performed better (i.e. performed the test quicker) than the OARSI normative values.

6.4 Performance Tests

Results of the performance tests are summarised in Table 64. On average, female runners performed better than their male counterparts on both limbs completing the star test. The difference between males and females did not achieve statistical significance. Males performed significantly better than females at the triple hop on both legs. On the final test, UPDB, there was no clear difference between genders, with males and females outperforming each other on different limbs.

Test	Male mean (SD)		Female mean (SD)		P
	Left	Right	Left	Right	
Star Test (sum of distance)	648.27 (87.43)	661.92 (96.78)	686.03 110.41	676.50 (106.58)	R 0.597 L 0.116
THFD (longest trial)	399.73 (93.25)	420.92 (105.61)	348.73 (109.27)	344.43 (93.89)	R 0.006 L 0.062
Balance (longest trial)	4.0 (2.22)	3.80 (1.71)	4.57 (2.69)	3.65 (1.72)	R 0.742 L 0.392

Table 64: Performance Tests, males and females

Age-related test performance is shown in Figure 92. The decline in performance that was observed in the OARSI tests is also shown for the THT and UPSLB.

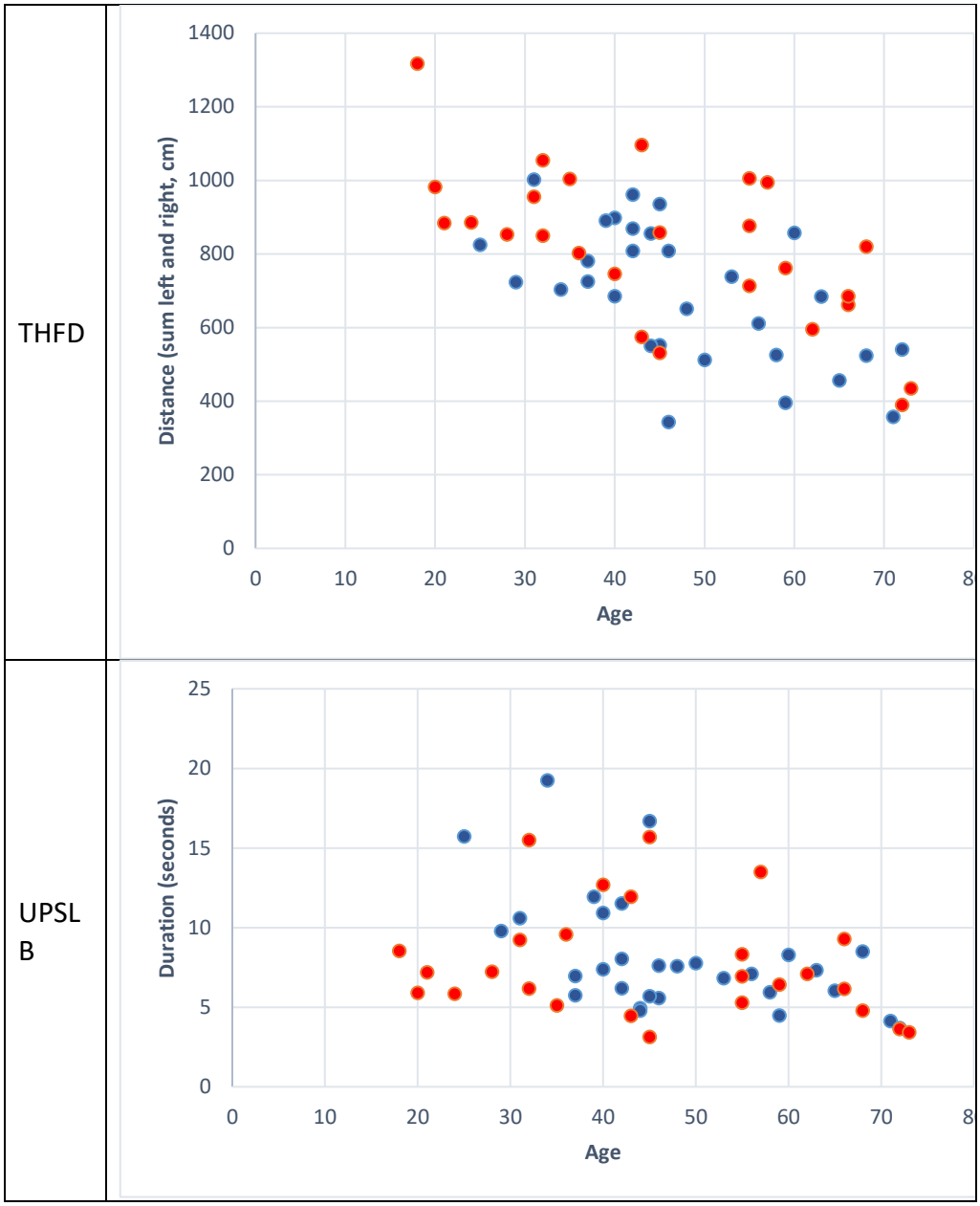


Figure 92: Age-related performance of THT and UPSLBT. Key: Females – blue; Males - Red

6.5 Running Behaviour and OARSI Test Performance

Participant running behaviour and OARSI test performance are described in Table 65. With one exception (number of years running and 30sCST), there was a weak positive correlation between all running behaviours and performance of the tests. Because of the testing methodologies, this does not equate to

improved performance, since lower times on 40mFPWT, SCT and TUG are indicative of better results for those tests.

r value	**30sCST correlation coefficient, (p value for trend)**	**40mFPWT correlation coefficient, (p value for trend)**	**SCT correlation coefficient, (p value for trend)**	**TUG correlation coefficient, (p value for trend)**	**6MWT correlation coefficient, (p value for trend)**
Mins running per week	0.111 (0.428)	0.139 (0.320)	0.293 (0.033)	0.132 (0.346)	0.056 (0.691)
Years Running	-0.029 (0.836)	0.102 (0.467)	0.168 (0.229)	0.176 (0.208)	0.070 (0.621)
Average Run Duration	0.130 (0.362)	0.123 (0.391)	0.158 (0.269)	0.175 (0.218)	0.098) (0.495)

Table 65: Correlation between running and OARSI tests

6.6 Injury History and Test Performance

A summary of test performance in those with and without a history of injury are summarised in Table 66. Participants that reported a significant running injury or a significant knee injury performed better in all the tests. For the triple hop test, there was less of a difference within participants (i.e. comparing left and right) than there was in those who had never had a knee injury or a significant running injury. When the distances recorded by the left and right leg are summed, there was no statistically significant difference, but those with a knee injury and a significant running injury recorded a greater distance compared to those without. The difference in overall distance was 7.61% greater in those with a knee injury compared to those without. Findings were similar for the start test, that is, those with a history of running injury or knee injury recorded a greater average difference on both limbs compared to those

without a history of injury. The UPDBT results also show runners with a history of injury perform better than those without.

Triple Hop	**R mean (SD)**	**L mean (SD)**	**Sum mean (SD)**	**R mean (SD)**	**L mean (SD)**	**Sum mean (SD)**	**p**
	Significant Knee Injury (n=14)			**Non-knee Injury (n=42)**			
	396.6 (75.6)	399.2 (71.7)	795.8 (145.7)	374.4 (114.4)	363.1 (111.2)	737.4 (222.7)	Of sum: 0.365
	Significant Running Injury (n=18)			**No Significant Running Injury (n=38)**			
	409.9 (88.3)	405.4 (81.0)	815.3 (167.1)	365.7 (111.4)	356.3 (109.8)	722.1 (218.4)	Of sum 0.116

Star Test	**R Sum of Distance**	**L Sum of Distance**	**R Sum of Distance**	**L Sum of Distance**	
	Significant Knee Injury (n=14)		**No knee Injury (n=42)**		
	685.2 (80.6)	672.0 (72.4)	664.6 (107.9)	667.3 (109.9)	Of sum: 0.485
	Significant Running Injury (n=18)		**No Significant Running Injury (n=38)**		
	702.9 (89.1)	683.2 (65.2)	654.0 (104.3)	661.6 (114.7)	Of sum: 0.348

Balance	**R mean (SD)**	**L mean (SD)**	**Sum mean (SD)**	**R mean (SD)**	**L mean (SD)**	**Sum mean (SD)**	
	Significant Knee Injury (n=14)			**Non-knee Injury (n=42)**			
	3.97 (1.7)	5.4 (3.3)	9.4 (4.1)	3.64 (1.70)	3.94 (2.04)	7.6 (3.4)	Of Sum: 0.110
	Significant Running Injury (n=18)			**No Significant Running Injury (n=38)**			
	4.0 (1.9)	4.9 (2.6)	8.9 (3.8)	3.6 (1.6)	3.9 (2.4)	7.6 (3.5)	Of sum: 0.180

Table 66: Test performance and injury history

There was no consistency in the results regarding whether previous injury (running-attributable or knee-specific) had a negative effect on OARSI test performance. None of the differences between groups were statistically significant. For most tests, the difference was very small, for example SCT (5.51 vs 5.95 seconds) and TUG (7.14 vs 7.18 seconds) (table 67).

	Significant Running Injury (n=18)	**No Significant Running Injury (n=38)**	**p**
30s-CST	19.61 (4.26)	17.29 (3.83)	0.46
40mFPWT	21.68 (1.83)	21.74 (2.84)	0.940
SCT	5.51 (1.00)	5.95 (1.80)	0.334
TUG	7.14 (1.22)	7.18 (1.35)	0.915
6MWT	661.10 (98.31)	669.73 (92.16)	0.750
	Significant Knee Injury (n=14)	**Non-knee Injury (n=42)**	
30s-CST	16.57 (3.78)	18.52 (4.10)	0.122
40mFPWT	21.83 (2.48)	21.69 (2.59)	0.863
SCT	5.74 (1.04)	5.83 (1.75)	0.864
TUG	6.73 (0.92)	7.32 (1.38)	0.147
6MWT	677.54 (105.85)	663.43 (89.94)	0.629

Table 67: OARSI test performance and injury history

Summary

This chapter showed:

1. There is weak correlation between the performance of functional tests (OARSI and/or other tests of balance and force production) and different running behaviours.

2. Functional test performance of OARSI tests declines with age. Neither gender consistently outperformed the other on the tests.
3. There does not appear to be a detrimental effect of injury (either running related nor knee-specific) on test performance. Instead, there was a trend for recreational runners with a history of injury to perform better than those without a history of injury.

7.0 Results: Joint Health in Recreational Runners: A 12-month Report

7.1 Introduction

Prospective data is required to identify causation in epidemiology. It is a prerequisite that factors/behaviours must precede an outcome to result in appropriate assumptions of causality. It is within the scope of this thesis to present 12-month data relating to the cohort recruited at baseline. The aim of this section is to report the change in knee joint health in recreational runners over a 12-month period.

7.2 Cohort Description

In total, 820 participants completed the 12-month questionnaire. Fourteen participants could not be related to their participant ID number, for example, because they entered an erroneous ID number. Of those that described themselves as runners at baseline, 784 provided data at follow-up.

7.3 Running Behaviour of Baseline Runners at Follow-Up

Change in running behaviour in baseline runners over the previous 12 months at follow up is summarised below (Table 68).

A lot less	A bit less	About the same	A bit more	A lot more
100	138	299	165	58

Table 68: Change in Running over previous 12 months

Running behaviour at follow-up is described below (table 69):

Characteristic	N	Mean (SD)
Weekly runs	742	3.24 (1.44)
Average duration of run (mins)	720	52.37 (23.77)

Table 69: Running behaviour at follow-up

7.4 Joint Health

The number of cases of OA to have been diagnosed and the incidence of joint symptoms that have occurred during the previous 12 months are described in table 70. There were 28 cases of newly diagnosed knee OA during the past 12 months.

Factor	Yes n (%)	No n (%)
Knee Pain	104 (13.30)	678 (86.70)
Morning Joint Stiffness	66 (8.44)	716 (91.56)
Crepitus	173 (22.12)	609 (77.88)
Reduced ROM	49 (6.27)	733 (93.73)

Table 70: Joint Health Outcomes in previous 12 months

<u>Incidence of Pain after Running in last 12 months</u>

Pain after running was reported by 428 runners at follow-up. There were 309 runners that have not had pain during the past 12 months after running. There were 35 runners at baseline that were not running at follow-up.

7.4.1 Incidence of Injury

Serious injury during the previous 12 months was reported by 246 participants (No injury n= 536). A total of 189 running injuries were occurred in the previous 12 months. One case of knee OA was removed from this analysis (table 71).

Location	Number of Injuries
Ankle Injuries	46
Chest Injury	2
Foot Injuries	36
Head Injuries	2
Hip and Groin Injuries	9
Injuries Location Unspecified or Crossing Anatomical Boundaries	4
Knee Injuries	39
Lower Leg Injuries	16
Lumbar Spine Injury	2
Neck Injuries	1
Pelvis/ Buttock Injuries	13
Shoulder Injuries	4
Thigh Injuries	11
Thoracic Spine Injury	1
Trunk and Abdominal Injury	1
Wrist Injuries	2

Table 71: Injuries in previous 12 months

The top three most common locations for injury to occur were the ankle (n=55), knee (n=54) and foot (n=41).

7.5 Repeat KOOS Scores

The baseline and follow-up mean KOOS performance for recreational runners is shown in table 72 below.

Table 72		KOOS Domain									
		R Symptoms	L Symptoms	R Pain	L Pain	R Activity	L Activity	R Sport	L Sport	R Quality of Life	L Quality of Life
Baseline	Mean	91.4	92.1	94.7	95.2	97.4	97.6	92.1	92.6	90.1	90.6
	N	1383	1383	1382	1382	1376	1376	1367	1367	1367	1367
	Std. Deviation	11.1	10.5	9.6	9.1	6.7	6.3	14.0	13.6	14.8	15.1
Follow-Up	Mean	93.2	93.7	95.9	96.2	98.1	98.2	93.5	94.2	91.8	92.4
	N	777	777	777	777	774	774	768	768	772	772
	Std. Deviation	9.8	9.5	8.7	8.1	5.6	5.2	13.0	12.7	14.7	14.4

At follow-up, for each of the five domains, mean KOOS values were higher compared with baseline. The following table (Table 73) reports the statistical difference and the associated paired samples of data are shown in the diagrams below. The greatest proportion of respondents reported no change in KOOS scores on either leg. Relatively few reported a negative difference (i.e. worsening knee health) but the domain with the greatest number reporting a negative difference was symptoms.

KOOS Domain	n	Positive difference	No difference	Negative difference	p
R Symptoms	479	184	187	108	<0.0001
L Symptoms	479	171	196	112	0.010
R Pain	478	158	239	81	<0.0001
L Pain	478	117	276	85	0.317
R Activity	474	102	306	66	0.062
L Activity	474	84	319	71	0.656
R Sport	465	128	247	90	0.010
L Sport	465	120	269	76	0.067
R Quality of Life	474	152	241	81	<0.0001
L Quality of Life	474	126	269	79	0.056

Table 73: Distribution of change in KOOS

7.5.1 Change in KOOS and Baseline Running Behaviour

The correlation between running behaviour at baseline and change in KOOS domains is summarised in Table 74.

KOOS Domain	Baseline Weekly Running Distance (Kendalls, p)	Baseline Run minutes per week	Baseline Number of Runs per week (Kendalls, p)
R Symptoms	-0.12 (0.733)	-0.001 (0.982)	0.038 (0.289)
L Symptoms	0.012 (0.953)	0.005 (0.890)	0.032 (0.380)
R Pain	-0.002 (0.518)	-0.016 (0.641)	0.038 (0.289)
L Pain	0.064 (0.070)	0.077 (0.028)	0.081 (0.031)
R Activity	0.023 (0.519)	0.014 (0.703)	0.025 (0.505)
L Activity	0.117 (0.001)	0.097 (0.007)	0.084 (0.028)
R Sport	-0.037 (0.298)	-0.016 (0.657)	0.002 (0.967)
L Sport	0.032 (0.375)	0.048 (0.178)	0.021 (0.591)
R Quality of Life	-0.078 (0.027)	-0.046 (0.192)	-0.050 (0.181)
L Quality of Life	-0.003 (0.936)	0.033 (0.356)	0.023 (0.550)

Table 74: Correlation of Baseline Running and Change in KOOS

For baseline running characteristics, there were few that achieved statistical significance. There were no strong associations in either direction (positive or negative).

7.5.2 Change in KOOS and Change in Running over Previous 12 months

The following graphs (Figures 93 and 94) identify the change in KOOS from baseline to follow-up and change in running volume. The left and right knees are reported separately.

For runners completing a lot less running compared to 12-months ago, there was a trend for mean reduction in KOOS values in some (right knee) or all (left knee) domains of the KOOS. There was a trend for runners that were completing 'About the same amount' or 'A bit more' running to have slightly greater KOOS values in each of the five domains. This trend was more pronounced on the left knee.

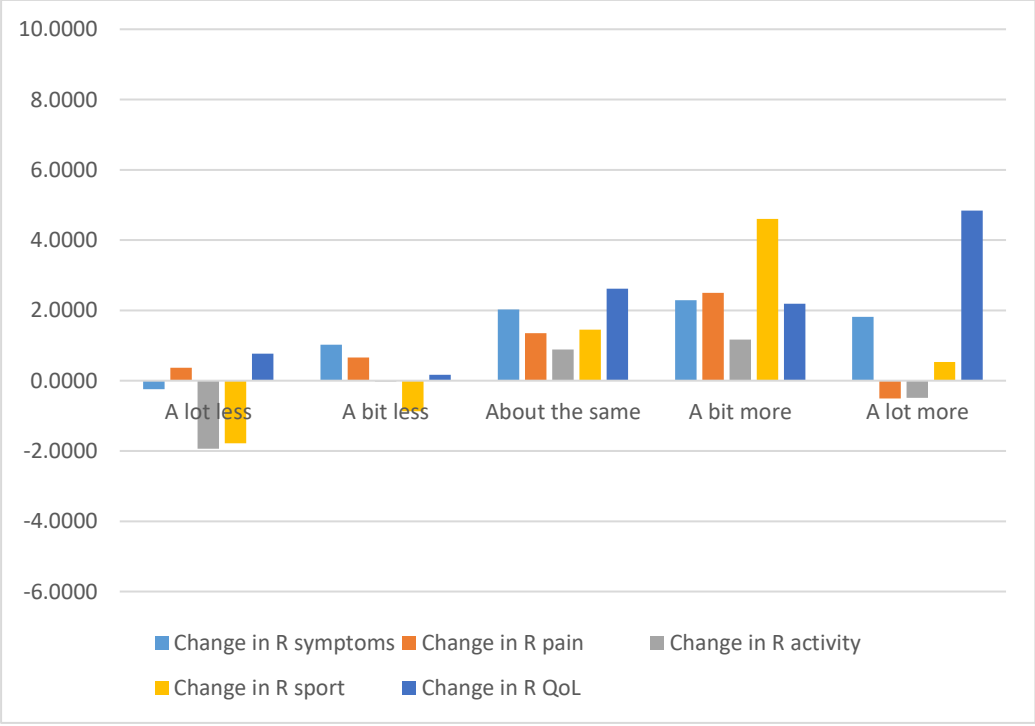


Figure 93: Change in Running and R KOOS

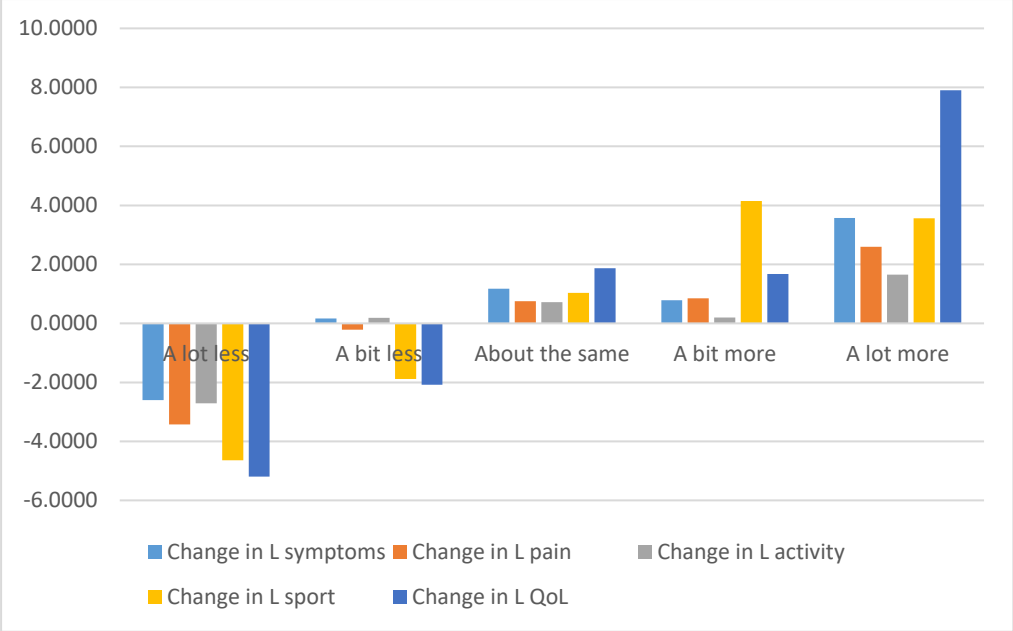


Figure 94: Change in Running and L KOOS

7.5.3 Change in KOOS and Baseline Joint Health Status

The correlation between baseline joint health status and change in KOOS domains is summarised in Table 75.

KOOS Domain	Knee Injury History (mann whitney U)	Knee Surgery (mann whitney U)	Knee OA (mann whitney U)
R Symptoms	0.735	0.932	0.002
L Symptoms	0.655	0.365	0.874
R Pain	0.399	0.536	0.310
L Pain	0.267	0.651	0.588
R Activity	0.523	0.292	0.070
L Activity	0.011	0.842	0.861
R Sport	0.520	0.905	0.033
L Sport	0.055	0.720	0.185
R Quality of Life	0.128	0.285	0.881
L Quality of Life	0.194	0.927	0.076

Table 75: Change in KOOS and baseline knee surgery, knee injury and knee OA

The table above shows that none of the joint health markers (injury, surgery or OA) were associated with change in KOOS. This suggests that knee health, as measured by the KOOS does not alter significantly over a 12-month period.

8.0 Discussion

8.1 Results Synopsis

Previous research has failed to provide definitive evidence of an association between running and knee OA. The aim of the current study was to explore the knee joint health of runners. In summary, the results show:

1. Knee injuries are the most common reported by recreational runners. The most commonly affected joint is the knee.
2. The prevalence of knee OA and knee pain in a cohort of recreational runners is not greatly dissimilar to non-runners.
3. Risk factors for OA and knee pain in recreational runners in this cohort are consistent with previous research (e.g. increasing age, BMI and previous joint injury). Previous knee injury was associated with knee pain in recreational runners (RR 3.55, 3.24-3.90).
4. The analysis of the self-report and contemporaneous running diary data suggests that runners over-estimate running behaviours. Agreement varied between athletic groups - there was a trend for greater agreement in runners completing more running.
5. Performance of functional tests appears to decline with age in recreational runners. There was no significant difference between runners with injury history and those without.

In relation to the thesis hypothesis, there was no statistically significant difference in mean KOOS values for runners and non-runners. There was a trend for runners to report greater KOOS values, but the findings here are limited by the small sample of non-runners that completed all KOOS domains sections. In order to elaborate these findings, a larger sample of non-runners would be needed.

8.2 Discussion of Joint Health in Runners and Non-Runners Results

Running and Injury

The current study identified the knee joint as the most common anatomical site of injury in runners, which is consistent with previous evidence (Taunton et al, 2002). van Gent et al (2007) identified in their systematic review that the knee is the predominant site of injury in runners although the incidence varied widely (incidence range 7.2% - 50%). This is perhaps indicative of a lack of standardised definitions for what constitutes an injury, the different data collection methods and heterogeneity of running behaviours of subjects.

In the current study, injury was defined as one that caused pain for greater than one month and for which healthcare intervention was required. Evidence from a survey conducted in 497 marathon runners concurs with the findings of the current study by identifying the knee as the most common site of injury sustained during training for the event, although no questionnaire details or definitions were provided in the methodology (Maughan & Miller, 1983). All

marathon entrants were invited to take part and the response rate was 52%. Of 358 injuries, 100 affected the anterior knee and 13 affected the posterior knee. Another key finding from this paper was that more than half the injured runners did not seek medical attention. These results have implications when interpreting the present study. First, the definition for injury may mean a significant proportion of runners have sustained an injury but it did meet the threshold for reporting due to the definition used. Second, although the findings suggest the knee was most common site, this is in athletes preparing to run a marathon so the results may not be directly equivalent to runners training for shorter or longer distances, including the present study where athletes were running a variety of distances. Third, the lack of detail regarding the type of injury is in contrast the present study where there was an effort to categorise injuries. Neither the present study nor the Maughan & Miller (1983) paper have any validation of diagnosis (e.g. checking self-reported injury against hospital records), which would affect the results. Fourth, self-selection bias (i.e. those with history of injury and/or knee OA) may be a significant factor affecting participation. This may affect the survey responses - influencing conclusions drawn - as those who are able to continue running are perhaps more likely to participate in research related to running.

It is suggested that the high incidence of knee injuries amongst runners are related to exceeding the tolerance of tissues (Messier et al, 2008). The most common types of injury reported in the present study were indicative of overuse injuries (e.g. biomechanical, unspecified pain injury), although they

were not formally defined as such. Participants in the current study may have reported altered biomechanics or unspecified pain as an 'injury' although they may have been the symptoms of an another, undefined, underlying joint disorder / injury. Taunton et al (2002) report that PFJ pain was the most reported injury of over 2000 injuries reported by patients at a clinic over a two-year period. The second most common injury was to the iliotibial band, which the authors suggest indicating over-use. The authors suggest a complex relationship between training error, biomechanical malalignment and footwear may all contribute, although further research is warranted to define the effect size for these (section 8.7). Other authors have suggested that the knee may be susceptible to injury due to disrupted timing in the coupled actions of the lower limb joint, which could increase the stresses placed on the knee joint (DeLeo et al, 2004).

It has been reported that overuse injuries in runners occur due to structural overload (van der Worp et al, 2015). Hreljac (2004) reports that overuse injuries occur due to an imbalance between repair and remodelling processes after exceeding running distance or intensity limits. The limits before overload occurs must be complex (and unknown) and unique to each athlete otherwise all runners at the highest levels of exposure would have overuse injuries but the above epidemiological evidence does not show this to be the case. On the other hand, it is also hypothesised that joint loading may also contribute to beneficial joint adaptation. This was tested in an examination of 18 triathletes and 18 controls (matched on body composition, e.g. height, weight and BMI)

who underwent MRI imaging of the knee (Eckstein et al, 2002). This study identified differences between males and females in the two groups, depending on the location of cartilage and the articular surface of interest. The joint surface area was consistently larger in the athletes (ranging from +3.8% in the patellae of females to +16.4% in the tibias of males). Only the increases in joint surface area in males for the patella (+11.9%) and tibia reached statistical significance. There was no consistent change in mean or maximum cartilage thickness, although cartilage volume was increased in the athletes on every knee joint surface. The authors suggest that these changes result from mechanical loading completed by the athletes which optimises load distribution across the joint, preventing focus stresses. Theoretically, this could reduce risk of knee OA although these results would need to be replicated in a larger cohort and different sports to be substantiated. Furthermore, to support the hypothesis, longitudinal data to identify athletes who go on to develop knee OA would be required.

The risk of an injury during running appears to be lower than reported in contact, multidirectional sports, such as soccer (Walden et al, 2011). A study including a large sample of participants (n=15,859) reported the sports-related injuries sustained by athletes (Pons-Villanueva et al, 2010). In this paper, injury was defined as those requiring medical treatment. The adjusted HR for running in males and females was 1.34 (1.18 - 1.52), which is lower than soccer (1.46 (1.25 - 1.70)) and skiing (1.44 (1.27 - 1.64)). The prospective design of the study provides sequencing for cause-effect to be established, although inaccurate

recall of either the injury or how it was sustained cannot be discounted. Poor recall accuracy is also a limitation of the current study (discussed further in section 8.3). It is perhaps most likely that the demands of sports vary and account for a large degree of the variance in injury risk. Multi-directional sports involve sharp, torsional joint stresses (e.g. soccer), jumping sports introduce landing forces (e.g. basketball), contact sports have an unpredictable nature (e.g. rugby), whilst environmental factors can also increase risk (e.g. skiing). For most recreational runners, their activity will avoid these components. A study by Buist et al (2010) identified different risk factors for running injury. In males, for every unit of BMI increase, the HR increased by 1.14 (95% CI, 1.1-1.3), but there was no association between BMI and injury in females. The interaction between BMI and previous injury factors - both influenced by running - could have implications for development of since these are two of the greatest modifiable risk factors for disease (Roos et al, 2005; Losina et al, 2011). Thus, they should remain of interest and be subject to future investigation in populations of athletes.

Due to the cross-sectional nature of these findings, it is not possible to report a cause-effect relationship between running behaviours and risk of injury. Modification of training schedules (e.g. by gradually increasing or decreasing mileage) has not been shown to significantly alter risk of lower-limb injuries in runners (Yeung, Yeung & Gillespie, 2011). In a Cochrane Review, only one paper informing this conclusion was from the general population (Buist, 2008). The results of this randomised controlled trial of novice runners training for a four-

mile event do not suggest that the injury risk per 100 hours exposure is significantly different for two training programs of varying duration and change in running volumes. Although it was hypothesised that increased rest periods would allow the body to adapt and prevent injuries, these findings do not suggest that to be the case, although these results only reflect short-term activity. A trial of longer duration would be necessary for it to have greater external validity to recreational athletes.

Effects of Injury in Runners

Injuries themselves are a significant barrier to participation in sport. They may curtail further participation and reduce or prevent the health benefits being observed (section 2.8). The consequence of joint injury may also lead to increased risk of OA. A meta-analysis that included all knee injuries, regardless of type or definition, identified a four-fold increased risk of knee OA following injury (Muthuri et al, 2011). A sub-group analysis revealed that articles which included a clear definition of injury-type reported a greater risk of OA than those with poorly defined injuries. The authors suggest that specific knee injuries may be more severe than general injuries and therefore recalled with greater accuracy. This observation may be consistent with the methodology in the current study, however interpreting this assumption would be increased by validating the self-report of injury by using medical records.

It is often more significant injuries, for example those to the ACL that appear to increase risk of OA the most (Paschos et al, 2017). The risk of developing

moderate to severe radiographic OA is increased by a factor of 3.84 compared to controls in those with ACL injury (Ajuied et al, 2014). The high number of injuries to these anatomical areas attributed to running is therefore a concern. ACL injury can lead to secondary cartilage loss at the medial and lateral femoral condyles and at the patella, the rate of which accelerates at five to seven years post injury (Potter et al, 2012). In the present study, there were relatively few ligament injuries, although if these results were translated to the wider running population in the UK, the overall impact of ligament injuries could be substantial (Friel & Chu, 2013). Further research into the mechanism of such injuries in runners may influence implementation of successful preventative strategies.

Trends suggest that the number of adolescent lower-limb sports injuries are on the rise (Finch et al, 2015). It can be postulated that injury at a relatively young age and continued sporting activity could have an influence on progression of knee OA in later life. A history of injury is considered one of the greatest risk factors for future injury in runners (van Mechelen, 1992). It may therefore not be the initial injury that directly affects risk of OA. The accumulation of smaller injuries may lead to more severe injuries, resulting in knee OA. Approximately 20-50% of individuals will develop OA following joint trauma. This equates to approximately 12% of all cases (Punzi et al, 2016).

It is unclear how the biomechanical injuries described in the current study may directly influence risk of developing OA. A narrative summary suggests the

need to identify the cause-effect relationship between poor and/or altered biomechanics (e.g. post-injury) and OA (Tiechtahl, Wluka & Cicuttini, 2003). The authors reported the effect of biomechanical factors on joint morphology is unknown. On the other hand, later evidence suggests injuries that result in joint instability have the potential to alter mechanical loading, movement patterns and articular contact patterning (Farrokhi et al, 2013). This study of patients with knee OA (self-reported stable and unstable joints) and patients without knee OA undertaking a gait analysis of downhill treadmill running. The findings show that in the unstable knee, contact point excursions during loading are significantly greater than the stable ($p=0.046$) and control groups ($p=0.016$). How these findings from a relatively small cohort (total 43 participants) conducting a single, treadmill-based activity in a controlled setting translate to running in varied environmental conditions (e.g. uneven terrain) remains unclear and further research is necessary to corroborate these initial findings.

Despite there being a trend for increased prevalence of injury as age rises, this may be due to increased exposure to running accumulated through life leading to more injuries being observed. Kline & Williams (2015) compared the mean kinetic and kinematic forces of younger and older runners. Vertical loading rate and impact peak forces were statistically greater in the older athletes. These results suggest that older runners may have reduced capacity to absorb passive forces during loading. In turn this may expose their lower limb joint surfaces to forces that may result in bone-related injury - although the authors

acknowledge that no threshold for joint loads during running that correspond to injury risk. The direct or indirect consequences of this may lead to increased risk of developing OA in older runners. The external validity of these findings is limited by the small number of participants (n=41) and little detail is provided regarding the training history or injury history of these participants (although it was reported they ran at least six miles per week and at least two days per week and were injury-free for at least six weeks prior to testing).

Notably, there was a trend for runners with a history of injury to have reduced scores obtained by the KOOS. This was particularly noticeable amongst knee cartilage and knee ligament injuries. The importance of these injuries is twofold. First, the immediate effect of injury appears to reduce knee joint health as measured by KOOS. Secondly, these types of injury are significantly and consistently associated with increased risk of knee OA. The importance of further research to identify what effect running has on joint health secondary to such injuries must not be underestimated. The potential mechanisms by which joint loading could affect progression of early OA have been explained in the literature review. It is hypothetically possible that running has an impact on joint health within runners with a history of such significant injuries, but longitudinal data is necessary to identify this association.

In addition, the broader health benefits of running have been identified with the EQ-5D-5L. There appears to be a trend for self-report health status to be lower amongst those running less than previously. It is important to stress that

no cause and effect relationship can be assumed from this data however it is noteworthy to report such findings. This may be an example of what is assumed in other data regarding running – the observation that those who are fit and able to run continue to do so and therefore obtain the greatest health benefit (Chakravarty et al, 2008). A prospective longitudinal study or a randomised controlled trial would be required to establish such a relationship. The former would require a large cohort to be followed over a prolonged period (i.e. more than 20 years to allow the natural course of disease onset and progression) whilst the latter would be difficult to conduct ethically and practically. It is proposed that further research is conducted on large cohorts of recreational athletes ensuring that running exposure is accurately measured contemporaneously.

It is interesting that some of the non-runners reported injuries that occurred during running. Perhaps this is due to cessation of running activity by the time the questionnaire was completed. Alternatively, these injuries may have been sustained during activities that involved running (i.e. other sports) or perhaps involuntary running (i.e. not for pleasure or fitness, such as running for the bus). This observation supports the need for greater longitudinal evidence where running can commence or cease in later life, with the reasons for such change identified.

Running and Knee Pain

Knee pain is a clinically important symptom, particularly if it is associated with PA, such as running. Anterior knee pain is common amongst runners. It is associated with anatomical, kinetic and physiological factors (Duffey et al, 2000). Pain is a complex phenomenon and the underlying cause can be difficult to determine (section 2.3.1.1). It may prevent or reduce the amount of PA completed and this could lead to secondary health issues related to inactivity and/or contribute to an increasingly sedentary lifestyle and obesity. In this study, the prevalence of knee pain was similar between runners and non-runners. Amongst runners, pain was relatively common. Almost a third of runners had a history of knee pain and a similar proportion of non-runners were also afflicted.

A meta-analysis performed by Tesarz et al (2012) identified altered pain perception in athletes compared to normally active individuals. Their findings support the hypothesis that athletes generally have a greater pain tolerance compared to non-athletes. A sub-analysis of endurance athletes reported a moderate effect size and greater homogeneity compared with other athlete groups (e.g. game sports). The controlled nature of the studies involved (i.e. the type of pain stimuli) and the relatively small number of participants involved make the translation of such observations difficult to real-world environments. In addition, the cause-effect relationship between pain tolerance and PA could not be determined. This modified pain perception may

also affect the prevalence of injuries reported in this study due to the choice of definition.

The present study did not identify psychological or social factors that may have influenced pain, but the role of biopsychosocial factors that modulate pain, are worthy of future consideration in runners. The holistic benefits of exercise include reduced stress and anxiety which have been shown to negatively affect pain perception (Callaghan, 2000). Authors speculate that prolonged discomfort from athletic effort during training and competition and nociceptive inputs from injuries trigger brain stem structures that inhibit pain, leading to enhanced pain tolerance and modulation in this population (Geva & Defin, 2013).

In the present study, there was no statistically significant association between history of pain and current running, but there was a trend for those that run the most (runs per week and average volume) to have the lowest prevalence of knee pain. This may indicate that those that are fit and able to run are more likely to be able to participate to the greatest extent or that pain modulation is better regulated in these athletes, but further evidence is required to confirm this hypothesis. Given its subjective nature, if pain perception and tolerance in runners is different to non-runners this would have a profound effect on the prevalence of symptoms reported and may lead to altered rates of OA diagnosis. For example, if pain tolerance is higher in recreational athletes,

although they may have equivalent underlying joint condition, non-athletes may be more proactive in referring themselves for further investigation.

Due to the cross-sectional design of the current study, it is not possible to identify the cause of pain and whether running influenced the onset or severity of pain. Further insight from longitudinal studies involving participants who report subjective pain and running behaviours using valid, contemporaneous measurement tools would identify any causal associations.

The present study reported that the road was the most common surface upon which running was completed. Taunton et al (2003) identified that road was the predominant running surface (69.1%). Further data is needed to establish an effect of surface on running. It is possible that different surfaces convey different risks of injury for example, uneven ground (e.g. trail), may relate more to risk of ankle injury. Hard surfaces, such as the road, may relate more to knee cartilage injury. This is conjecture at this point and would require greater evidence to establish such connections. Running surface preference is unlikely to be completely homogenous and runners may complete running on several surfaces. Further, runners may prefer one surface over another due to perceived risk of injury or pain. The association between the two may not be causal or reverse-causal however further research is required to identify this relationship.

Running and Knee OA

The present study identified the prevalence of knee OA in recreational runners. There were fewer runners reporting knee OA compared to non-runners, but the difference between the two groups did not achieve statistical significance. The cross-sectional design of this study means it cannot provide evidence that either supports or negates the causative role of running in onset or development of OA. The relationship between running and knee OA or other associated symptoms is complex and poorly understood. Several systematic reviews have assessed the literature with no clear consensus (Timmins et al, 2017; Alentorn-Geli et al, 2017; Driban et al, 2017). These reviews are based on few studies of low methodological quality (due to high risk of bias) which involve relatively small numbers of participants. The self-selection of runners that are fit and able to participate in the studies is a limitation that also cannot be discounted from the present study. In contrast to the evidence referenced in these reviews, the current evidence presents a larger cohort of recreational athletes from an international cohort, which improves the external validity of these findings. The reason for previous evidence failing to identify an association are manifold. Broadly, these relate to the variances between studies for measurement of running exposure and the outcomes of interest. This extends to the population of interest (e.g. the age, performance-level, and injury history) and diagnostic criteria, particularly for identifying cases of OA. Greater consistency between studies for defining methods to measure running and consensus for definitions of OA would be beneficial and promote collaboration and facilitate data comparison. The present study attempted to

overcome issues relating to running exposure measurement by using multiple self-report questions to identify running behaviours and several markers of knee joint health.

Since the literature cannot provide a definitive answer, it is likely that many factors remain unidentified or only partly explored. Greater understanding of biomarkers may stimulate future research into the immediate effects of running at different intensities in the healthy and diseased joint. So far, this research is limited to small samples of participants completing laboratory-based running (Hyldahl et al, 2016). Further evidence that reflects real-world running (i.e. greater variances in distance and speed) would be useful to identify the clinical implications of immediate inflammatory markers over time. It is interesting that symptoms do not commonly appear bilaterally in the knees. This may suggest that there is a predisposing factor that influences one knee more than the other if it is assumed that normal forces that occur during running are equally distributed in both limbs. It could be assumed that if running forces were the greatest a risk factor for detrimental joint changes and/or symptoms, then both knees would be affected by symptoms and OA. Instead, it could be local factors in one knee (e.g. injury) that alters the forces across the joint and can influence symptoms onset and/or progression unilaterally.

Authors have described how running could promote joint health since the loads imposed during running stimulate beneficial adaptions to the structures within

and surrounding a joint (Miller et al, 2017). Perhaps it is interesting no running behaviours in the present study were associated with increased risk of OA. It may therefore be that it is other systematic factors that are more influential in runners that increases risk of OA. Further, it may be that it is the risk of injury, rather than the sport itself that raises risk of OA.

An interesting finding of the current study is that when categorised into age groups, there were 39 cases of knee OA in those aged <45. This is notable since the NICE guidelines for diagnosis of knee OA use age (>45) as one of the factors. In the present study, those runners accounted for almost 20% of all cases of knee OA. OA in the younger population has become of increased interest over recent years (Amoako & Pujalte, 2014). Perhaps the prevalence of OA in younger athletes can be explained by the risk of injury, but to confirm this connection, a larger cohort of adolescents would need to be reviewed longitudinally. Prevalence increased as age increased, which is perhaps unsurprising considering the association between age and OA is well established. This cohort included relatively few older athletes (for example there were only 26 aged >75). This may limit the external validity of these findings to the wider population. This age group may become a more important focus of research in the future due to the shift in population demographics (e.g. people are living longer) and therefore health into later life is becoming increasingly important for healthcare systems and society at large.

When categorised by BMI, the lowest prevalence of knee OA was in the 'Underweight' category. Perhaps it would have been expected that the highest prevalence would be in the 'Obese' category, given the strong association between BMI and OA. However, this was not the case in the present study, where the highest prevalence was in the 'Overweight' category. This may be explained by those who are 'Obese' being less likely to run. A larger cohort of 'Overweight' and 'Obese' runners are required to further investigate this link. It would be interesting to explore the association between running and severity of OA to identify whether running could have therapeutic role for those with OA and the underlying mechanisms by which this occurs (i.e. assist weight loss, systemic factors, increased local muscle strength).

A strength of the current research is the large number of runners involved from a variety of running backgrounds (e.g. variable experience and behaviours). The international cohort increases confidence that the results are valid in other western populations. The current study contrasts with other research which has sought to identify factors associated with running injuries, but has not used recreational athletes as subjects, or, has used short-distance track athletes (Kluitenberg et al, 2015). This reduces the external validity of these findings to recreational athletes as elite runners and track athletes are not the same (e.g. training load, running speed, muscular strength and endurance etc) since recreational athletes, by definition, are a heterogeneous group. To strengthen this assumption, further studies should be performed that ensure recruitment occurs within different populations of runners from a variety of backgrounds

(e.g. marathon runners, cross country runners, novice runners), whilst ensuring the sample size is sufficiently large to allow stratification.

Limitations of the current study should be acknowledged. The increasing popularity of wearable technology provide an exciting opportunity to identify behaviour and performance with limited burden on the athlete (Lee, Kim & Welk, 2014). The use of technology enables greater analysis of running behaviour to be identified. Using participants from the present study, it was identified that there is some divergence between self-reported running and running that is contemporaneously recorded (section 4). Accurate reporting of an exposure of interest in epidemiology studies is crucial to ensure that conclusions are accurately interpreted.

The self-report nature of the data may lead to misclassification due to recall bias and inaccuracies. The agreement between self-report OA has been explored relating to diagnosis by a GP (Peat et al, 2005). In this assessment of 45 patients from the UK, GP records and asked patients what they believed the diagnosis was. Agreement between the two was poor (49%; kappa = 0.03; 95% CI 0.32-0.26). Interpretation of the self-report diagnosis of OA must therefore be completed with some caution. Additionally, there may be an assumption that all clinicians diagnose OA in a consistent manner, but this may not have been the case, particularly between different geographies and with clinicians of varying clinical experience. There may be some variation in the diagnostic criteria used to ascertain a diagnosis of OA. Clinicians or participants may not

have adequate anatomical knowledge to divulge whether their knee OA was TFJ or PFJ (or a combination of the two). There were few instances when this distinction was made and therefore an analysis on this basis was not possible, but the ability to do so may have revealed compartmental differences in prevalence amongst runners. No radiographic evidence of OA was available to validate the self-report of knee OA, but this may have been useful.

The choice of definition for cases of knee pain, (i.e. not restricted to a specific period) is likely to have influenced the prevalence reported. Neogi (2013) reports that different pain descriptors in questionnaires can affect the responses given by participants. Unfortunately, there does not appear to be an agreed, valid, standardised question to evaluate pain in knee OA. Bedson & Croft (2008) identified 10 different definitions to identify knee pain and/or other symptoms. These led to variances in the percentage of subjects presenting with radiographic OA in those with knee pain. For example, the prevalence of current pain in those with radiographic knee OA ranged from 59 - 81%, whilst 'ever' pain ranged between 20 - 59%. If there was a restriction to knee pain in the previous month in the current study, this may have skewed the results towards a lower prevalence of knee pain, especially as recruitment largely occurred in environments where active athletes were engaged in running. Athletes with more recent symptoms may have been abstaining from activity at the time of recruitment thus would not be involved. There would therefore be a greater number of pain-free athletes. On the other hand, not limiting the period when pain may have occurred could inflate the prevalence.

Furthermore, the cause of pain is not specified. It is therefore not possible to determine from these results the extent of pain resulting from knee OA (or other factors, such as injury). The fact that the third most reported knee injury was 'unspecified knee pain' could provide some interesting insight if further investigations were performed. It cannot be determined how many of these cases were due to participants failing to recall the diagnosis provided or how many were a failure of the clinician to provide a diagnosis.

Recall accuracy declines as the level of detail requested by researchers increases. In a study of recreational athletes asked to recall injuries over the previous year, 77% could recall the number of injuries and body region but 61% were able to record the number of injuries sustained, body region affected and diagnosis. Twenty-one could not correctly recall the number of injuries sustained (Gabbe et al, 2003). Considering these findings, there is likely to be a significant proportion of misreporting in the present study. If the injury recall time-period had been limited, this may have meant that relevant previous injuries which occurred before the period of interest were not identified. The accuracy of recall may have been increased had a prospective analysis with immediate recall or medical records to validate self-report. These would be labour intensive (for both participant and researcher) and require significant, additional ethical approval.

The sample of non-runners was significantly smaller than the number of runners. It would be advantageous to recruit a control group of non-runners,

however the definition of current runner (running in the previous 12-months) may mean that participants who have previously ran are included as non-runners. This may be more important in older athletes. For example, if an athlete had been a keen recreational athlete until the age of 60 and was recruited at 65, then it could be anticipated that their years of running would have influenced their joints - positively or negatively - after running had ceased. The optimal control group may be individuals that have never run in their life; however, these may be difficult to identify and the definition of what constitutes running would have to be explicitly clear. The effect of this methodological limitation is reported by Alentorn-Geli et al (2017) in their systematic review of literature related to running and risk of knee OA. They conclude that the effects of athletic activity from other sports (e.g. running load, injury) in both runners and non-runners cannot be completely discarded when comparing the two groups. Furthermore, runners may exhibit, or be exposed to, other factors that make them different to non-runners, for example diet and other PA. These undefined confounders could influence risk of knee OA, either directly or indirectly within these populations.

For some of the age-group categories (75-79 and 80-84), there were no non-runners with knee OA which is unlikely to represent the wider population of individuals at that age since prevalence of symptomatic disease is strongly associated with age (Losina et al, 2013). Instead, this is likely due to a small sample size of participants recruited in this age group. Although efforts were made to recruit from all ages, potential participants may not have been as

socially accessible via the methods employed. An alternative recruitment strategy, such as postal-based questionnaires have been successfully employed in older participants for knee OA research (Peat et al, 2006). It has been shown that participants are more likely to participate if they are interested in the topic being researched (Edwards et al, 2002). It is therefore likely to be more difficult to recruit older non-runners who do not have knee OA in a project like this. Incentives may have been useful to gain a higher response rate from this population.

No cause and effect between running and injury or OA can be established due to the nature of the data. Identifying causes in epidemiology is difficult, as presented in a review by Susser (1991). More than one casual mechanism can lead to a given disease, with each mechanism involving several component causes (Rothman & Greenland, 2005). Running is not a necessary and sufficient cause of OA or symptoms in all individuals, otherwise every runner would be afflicted. Instead, it is more likely to assume that running could be a contributory cause (i.e. *x* is neither necessary nor sufficient to cause *y*, but if it is present, an additional factor is present). The interaction of multiple factors does not necessarily mean that they must occur at the same time for a disease to occur. Perhaps the best example of this is previous injury, whereby a serious injury many years before can affect risk of OA in later life. This remains poorly understood in relation to running in later life since longitudinal data is limited. This demonstrates the importance of identifying such factors retrospectively if prospective data is inadequate to capture all other potential contributory

causes (i.e. if data collection does not begin early enough to capture all pre-disease events).

The nine view-points put forward by Bradford-Hill (1965) remain prominent today in discussions regarding association and causation. The implications of these remain key for epidemiological research:

- Strength - the extent of increased risk (which can be strong or slight, but nevertheless meaningful)
- Consistency - repeated observations in other cohorts, in various locations at another time lead to the same observations
- Specificity - the importance of individual or complex multifactorial characteristics
- Temporality - measurement of a factor that pre-dates an outcome of interest
- Biological gradient - the ability to identify dose-response curves (i.e. increased exposure to a certain factor increases incidence of disease)
- Plausibility - a hypothesises according to current knowledge
- Coherence - agreement with biology and natural history of the disease
- Experiment - through removing a factor, is the disease prevented
- Analogy - a strong causal relationship between one factor and a disease may lead to other similar factors and other similar diseases being more accepted with weaker evidence.

Association and causality should not be confused. Association may be due to direct or indirect causation, whilst correlation implies specific types of association but not causation. Thus, interpretation of the findings of the present study must be limited to the evidence it presents. It is also important to acknowledge the effect of confounders, mediators and co-variates that make true association between running and OA difficult to ascertain. Mediation models have a third variable intervening between independent and dependent variable, assuming the independent variable affects the mediator, which then affects the dependent variable (Li, Bienias & Bennett, 2007). For example, competitive recreational running is more likely to contribute to a lower BMI and other healthy lifestyle choices (e.g. dietary factors) which could influence joint health.

There may also be a degree of self-selection bias whereby those runners with injury, pain and/or OA were more inclined to take part in the study since they have a greater interest. On the other hand, those without symptoms that are keen runners may take part as they wish to help contribute towards research that encourages others to take part since they have had benefits from running. It was not possible to compare responders and non-responders to the survey. This is due to the recruitment methods used since it is not possible to identify the number of athletes approached but declined to participate.

8.3 Discussion of Validation Analysis Results

The purpose of this analyses was to report the validity of a running questionnaire using recorded running and/or contemporaneous diaries of running behaviour in recreational athletes. These results provide insight into how 'average' running is estimated by recreational runners and how this may affect epidemiological associations, clinical interactions, as well as the utility of user-owned devices as a gold standard for validation. Employing user-owned devices as a comparator allowed the validity of self-report running data to be assessed in a population in which it would otherwise have been impractical to do so.

Overestimation in self-reported PA and low agreement between subjective and objective measures is not uncommon in the literature. For example, Prince et al (2008) conducted a systematic review of self-report and direct measurement of PA. Sixty percent of the 148 studies included in this review identified self-report PA estimates to be greater than directly measured PA. On one hand, these results are consistent with previous findings. This must be cautiously interpreted however, because other questionnaires use a variety of assessment methods to identify domains of PA. The results of the current study are running specific; thus they may not be directly comparable. Running is the focus of much research relating to health outcomes (Schnohr et al, 2015). These papers are reliant on accurate analysis of running exposure in order to confirm that the conclusions are correct. Over- or under- estimation of self-report could have a critical effect on the conclusions. Standardised

questionnaires that are activity specific could be beneficial where the aim is to understand the health impacts (i.e. benefit/risk) relating to factors specific to a certain activity (e.g. frequency, intensity and/or duration of running) that may not be reflected when overall PA is known. This may enable the development of more personalised guidelines that minimise the risk of harm or injury whilst simultaneously maximising the health benefit. With the increasing rates of chronic disease due to physical inactivity this has never been more important, but an evidence base can only be developed if accurate measurement tools are used.

Validity was assessed in a sample of self-reported running questions within a larger questionnaire incorporating other questions of running that could have been used in this analysis. These questions were chosen because they required participants to complete a table detailing their average running (frequency, duration) over a seven-day period. The format of the question enabled the same seven-day period to be reviewed when assessing the diary. Baseline Questionnaire 1 also included data on running (including number of running sessions per week and average duration).

One trend consistently observed was more active runners (i.e. a higher MET/hrs classification) had higher levels of agreement between their self-report and contemporaneous training diary data. More experienced runners may know more regarding their own running behaviour due to their background in the sport. This may indicate the need for different questions

when assessing more active runners, but this is the subject of further research. This may also have clinical implications as language used when attempting to quantify running behaviour could have a huge effect on the response accuracy. This has been shown in other research studies looking at PA. A review of the extent of agreement identified greatest correlation between questionnaires and other measurement tools when the activity was high intensity (Shephard, 2003). Further research could confirm this finding and whether other running activities (or activities that involve running, i.e. triathlon) present a similar agreement in more active individuals.

The data suggests 'average' running by recreational athletes is most closely associated with recorded running over a 4-week period. Analysis of 12-week diary data revealed complete data, but many participants had no runs recorded during certain weeks. 'Average' running therefore could be derived by recreational runners only considering the weeks that they do run, calculating the value from this, whilst ignoring non-running periods. This could have the effect of artificially inflating the self-report of running. How this affects research or clinical practice is difficult to ascertain and is likely affected by the specific outcome or research question. If a clinician were to ask for 'average' running, the patient may not accurately recall periods of non-running (and may not include runs that were longer than normal) in their calculations. This data suggests 'average' running seems to reflect *usual* patterns rather than an *average* over a specified period of time. This may have implications for research where the dose-response is of interest and the running exposure is

self-reported. Future research in longitudinal cohorts would be useful to confirm this finding as running changes over time and periods of non-running may be more numerous.

From this analysis, many anomalous values could relate to variations in running, issues relating to respondents' reporting of their running and/or those relating to the data rules employed to report running metrics. Reasons why respondents may demonstrate large differences between their diarised runs and their reports of current average running which reflect variations in running include: completing longer runs or tapering running (e.g. preparation for a specific event such as a marathon), recovering from an event or injury, seasonal events (e.g. holidays) or abstaining from running during the diary data collection period but recording usual running pattern in the questionnaire.

The questionnaire consistently refers to 'average' running rather than running over a specified time-period (i.e. last seven days). The reason for this was partly due to the recruitment processes of the study. Much of the cohort was recruited from running events/races, which may have skewed how much running was performed in the preceding week. Further, the runner may have been injured at the time and as a result did not complete any running but would otherwise have been highly active. Thus, these athletes had the opportunity to provide data for what they normally do. Another benefit of not requesting runs over a longer period i.e. over the previous four weeks, is that the degree of burden on the participant to provide large amounts of self-report data may

affect the response rate on the questionnaire and become increasingly inaccurate as the recall time increases.

The divergence described above were most likely to affect run frequency, total distance and duration, but not pace. Pace was affected, however, where the respondent had an unusually long run amongst a steady pattern of shorter runs in their diary data, because the pace would be slower for the former, but the respondent would tend to report their more usual running pattern of much shorter runs on the questionnaire. Pace was also likely to be affected more than other measures where the tendency was for the respondent to 'round-up' running times (to 45 minutes, one hour etc.) or distances (to 10 kilometres, 5 miles etc.) in the questionnaire but had exact times and distances in their diary. There were also a few cases of large discrepancies in running frequency because the respondent appeared to have given a weekly total for distance for their diary, but individual runs on the questionnaire. Such variations may have more significance where intensity is the focus, or where change in fitness levels as indicated by changing pace is of primary interest.

Finally, in terms of data treatment, several outliers occurred when the respondent could only supply a distance but no duration (or vice versa) for some or all runs. When calculating a weekly average for the 4 and 12-week data, a zero was inserted for time and distance in the weeks which did not contain a diarised run. In cases where people ran in some weeks of the diary data collection period but had, for example, missing times for some or all these

runs, but also had weeks where they did not run (and were therefore coded zero for time for that week) their average time over the 4 or 12 weeks would be biased towards zero. There were also a small number of cases where both questionnaire and diary data were accurate and complete but reflected different running amounts which could not be further explained. Therefore, when selecting a running measure for clinical or research purposes, consideration should be given to whether it is important to capture bouts of non-running or whether the nature (pace, total time/distance) of the running if and when it occurs is most important.

The results above assume that all runs were recorded in the running diaries, but it is possible that respondents with discrepant self-report and diary data did run, but for whatever reason they did not measure it. This is a key consideration with these findings, as the assumption is all runs were recorded if a diary was submitted and no other information was provided. The authors did not supply standard tools for participants to provide their diary data (e.g. the same GPS device). This would have been impractical in this research scenario as it would have incurred significant financial costs and the study design required analysis of running already performed. If used in future research, using consistent measurement tools would ensure standardised data against which self-report could be analysed against. In the present study, it was assumed that all tools were equivalent (in terms of accuracy) which may not be the case. There may also have been human errors, incorrect use (i.e. not

starting and stopping them accurately at the start and end of runs) and measurement error (i.e. losing signal during a run, batteries failing mid-run).

To the authors' knowledge, this is the first description of the level of agreement between self-reported running data and contemporaneously collected running diary data in recreational runners. It is perhaps surprising that a greater amount of research has not been conducted in this area. For example, the accuracy of different activity monitors in runners has been explored but such studies are often limited to few well-trained athletes who conduct tests in the laboratory setting with non-commercially available test equipment (John, Tyo & Bassett, 2010). The wider implications of not understanding the accuracy of self-report running can have implications for conclusions drawn in research exploring its effects. This extends beyond knee OA and into other health outcomes (Schnohr et al, 2015; O'Keefe & Lavie, 2012).

A strength of this analysis is that it is running specific and could have further research and clinical applications. This is critical in order to identify the dose-response associations in epidemiological research, where the effects of running are of principle concern (i.e. running and knee OA).

In this study, participants provided retrospective training diary data and therefore it is not possible that they changed their running behaviour specifically because of involvement in the study. Although it is conceivable that participants could have altered their data before providing it to the research

team, it is unlikely. The use of numerous time-points (e.g. seven day, 4-week and 12-week) also enabled the correlational and agreement analysis to examine whether the self-report data better approximated proximal or more extended objective data. Another strength of this study is that it concurs with a potential clinical scenario. If a healthcare professional was looking to identify the cause of a running injury, then they may enquire regarding running behaviour. It is interesting to learn how the phrasing of that question could affect the answer.

However, several limitations of this paper must also be acknowledged. First, the population included in this study were selected on their ability to provide an objective measure of their running history. As such, this sample may be drawn from a more committed subpopulation of recreational athletes and therefore may not be representative of all recreational runners. Indeed, runners who reported they owned an activity device (and therefore formed the population from which the current sample is drawn) ran further (25.3km vs. 17.8km) and more frequently (3.1 vs. 2.9) on average per week than those who did not. Further, the regular use of monitoring devices may enhance accuracy of self-report running.

It is also possible that participants used their diary to input actual responses into the questionnaire artificially generating greater agreement. Measurements provided by the participants were not always complete as some could only provide distance or time, and data treatment rules may have

exacerbated the impact of this on agreement. However, to have removed cases where there was missing data from analyses would have wasted data which was partially complete, and more importantly, have not captured where there was genuinely no running. On the other hand, using data runners collected using devices that they use of their own accord is advantageous since it is perhaps more likely that adherence was upheld whilst also minimising research costs.

8.4 Discussion of Functional Testing Results

An interesting trend from these results are that those with a history of significant injury (knee or attributed to running) perform better at certain tests than those without. The reasons for this can only be speculated upon, but perhaps reflects the population involved in the current study and their interest in running, leading to complete rehabilitation ensuring safe return to activity. Another potential factor that may have influenced this finding is the definition of significant injury which required the participant to receive healthcare attention. On the one hand, one may assume this led to appropriate treatment, but it is also possible that participants in the non-injury group did sustain injuries for which they did not receive treatment, and thus their performance was impaired.

It was notable from these results that test performance did not always decline with age. It perhaps would be expected that this would be the case. Normal ageing processes involve loss of force production and muscle quality in men

and women (Lindle et al, 1997). However, it is important to note that these tests were not solely a test of physiology. There may have been some interpretational differences between younger and older athletes in respect of how they performed the TUG. For example, the test instructions state that the test should be performed at a regular pace. Older participants may have been more motivated to complete it quicker, but it is not possible to substantiate potential differences such as this.

These findings provide an interesting insight into the joint health of runners of different ages by assessing functional capacity through several different tests. Multiple tests provide a variety of challenges to different musculoskeletal and psychological components that may provide an overall impression of functionality. The OARSI tests are designed to provide simple methods for assessing adults aged >40 with a diagnosis of hip and/or knee OA. There is currently no gold standard for performance-based tests of physical function within this group of individuals. A systematic review of measurement properties of hip and knee OA identified a multitude of different tests (26 methods; 13 walking tests, 2 stair-climb tests, 1 chair test and 10 multi-tasks) (Terwee et al, 2006). It was concluded that the lack of consensus in what parameters and activities must be addressed to improve measurement. The OARSI tests are one such proposal, agreed by 138 international researchers and clinicians. The five tests represent performance of sit to stand activity, short-distance walking, stair negotiation, ambulatory transition and long-distance

walking (Dobson et al, 2013). The second set of tests were the TSLH, SEBT and UPDB (Whittaker et al, 2015). In contrast to the OARSI tests, these tests provide a greater single-limb test element rather than combining efforts from both legs. Hop tests have been shown to highlight deficiencies in those with serious joint injuries, such as ACL deficiency or post-reconstruction (Gustavsson et al, 2006).

There is some debate regarding the usefulness of self-report physical function completed with, or in addition to, objective assessment, which could be partly due to subtle differences in the meaning of 'functional limitation/difficulty' posed by the researchers and its interpretation by participants. Furthermore, there may be some discrepancy in tasks that are the basis of assessment. This means that certain activities may or may not be relevant, therefore a better or worse 'performance' may be recorded and disease state may be inappropriately derived. In addition, self-report is preferred because of ease of use and lower burden on participants (Steuljens et al, 2001). Most tools use time or distance to quantify performance. This enables repeated testing to be used to assess change over time.

Most recreational athletes in this sub-analysis did not have OA, but since they were all active runners, the data can still provide objective measures of lower limb functional performance in this population. None of the tests are specific to a joint or one specific component of function (e.g. strength) but some may be more specific to one domain (e.g. balance). Running is a complex activity

involving several of these elements, thus it might be anticipated that runners will perform these tests well. Functional limitations are common in those with OA, but relatively little is known how these change as the disease becomes increasingly chronic. Most of the literature has focused on symptomatic (e.g. pain) or radiographic changes in OA rather than function. A systematic review shows that functional change in those with knee OA does not always lead to deterioration in the short-term (less than three years follow-up) (van Dijk et al, 2006). Further, the results are suggestive that greater muscle strength, better mental health, self-efficiency, social support and more aerobic exercise are protective against decline in function. Since running can positively influence these (as well as play a role in reducing BMI which is a risk factor for functional deterioration), it could be hypothesised that it could have a role in preventing functional decline and pain. Previous research has assessed the lower limb function of elite runners but used self-report questionnaire to do so (Kettunen et al, 2001). Of 71 long distance runners, 7% reported knee disability. This paper does not seek to identify the prevalence of knee disability within the running population, rather the functional performance of runners undertaking a battery of tests. These are not easily comparable to these findings due to the elite standard of the participants involved.

This data does not indicate that running prevents age-related decline in functional capacity, since mean performance declined in all tests with increasing age. That said, on some of the OARSI tests (notably 40mWT and TUG) there was a trend for the difference between runners and normative data

to became greater with increasing age. This may indicate that the beneficial effects of running become more pronounced (e.g. decline occurs at a slower rate) with aging but more evidence is required to substantiate this assertion. Typically, it is reported that physical activity declines with age which can in turn affect the fitness and function of elder individuals. Age-related muscle strength loss has been found to be greater for the lower limbs in comparison to the upper limbs (Landers et al, 2001). Strength training can be used to maintain muscle power in older adults, but the use of isokinetic tests is less practical (e.g. due to costly, specialist equipment) and less functional (e.g. assessment of knee flexion or extension in isolation).

Because of the current study design, it is not possible to attribute a cause and effect relationship between running and test performance. Further, current running may not give an indication of previous running completed. It may be that running behaviour has significantly altered recently with more (or less) being completed previously. To assess this further, assessment of contemporaneous running behaviour over a prolonged period as well as repeated testing would enable a correlation analysis to be completed. A difficulty with research in this area is that a true comparator group would require pre-injury or pre-OA data (depending on the outcome of interest) to enable a true assessment as to the effect of a specified insult to the joint. A more comprehensive and accurate approach would be to create normative values from large populations based on characteristics like gender and age, as well as injury history, joint disease (e.g. OA) and sport specific.

A strength of this study is that it used well-established and widely available testing procedures, developed by expert consensus. The tests are easily replicable and have well defined procedures to enable validation of these findings in larger cohorts. The reliability of these tests has been reported and they have sufficient test-retest accuracy for use in clinical practice (Section 3.5.1.3). The use of OARSI and other (more dynamic) tests provide an array of different challenges to the participants. These tests are designed for those with OA and have been used to report function in those with severe joint injury. Therefore, they are useful to report in cohorts of athletes.

Some limitations of the present study should be acknowledged. First, there is no additional data to corroborate the self-report information that participants supplied (e.g. injury history) and as such this may be liable to inaccuracies and errors. Second, the number of athletes included in the study was limited by geographical proximity to the test centres and therefore the sample size is limited. Thus, there are few participants with injury and a diagnosis of knee. Additional resources (i.e. funds to hire other test locations or more testers) may have enabled participants to attend alternative locations and increased the number of participants. The number of a participants was far below the sample size calculation, although it exceeded the sample size recommended in the literature where the appropriate level of precision and estimates for measurement error was reported for the TUG test (Hopkins, 2000; Walter, Eliasziew & Donner, 1998). Furthermore, there is no control group of non-

runners for direct comparison. Instead, normative data provided in the OARSI test documentation (Dobson et al, 2013). A useful addition to the testing procedures may have been inclusion of a running component since it is running activity that defines this population. The aim of this testing may have been useful to identify running gait patterns, rather than maximal performance. Distance running performance is largely explained by cardiovascular efficiency (Conley & Krahenbuhl, 1980; Noakes, Myburgh & Schall, 1990) thus it is questionable the extent to which identifying this factor would contribute to the outcomes of interest in this research. It is perhaps more important to identify the movement mechanisms used by athletes to run since this may have implications for injury risk. There are several methods for gait analysis including; observation, motion analysis (quantitative description of body section movements without quantifying forces), force-plate analysis (ground reaction forces), dynamic electromyography (muscle activity and timing) and stride analysis (e.g. cadence, step length) (Dugan & Bhat, 2005). Many of these require specialist equipment and can be labour intensive to compute the results. A limitation of observation also often fails to account for changes in running that occur with fatigue and thus do no accurately replicate real-world running. Further, use of a treadmill may induce changes in running gait and thus it would be optimal to observe normal running for everyone - which may not necessarily be the same. This would be time consuming and burdensome for the participant and researcher. It was therefore considered impractical and of limited value to report running gait from a small sample in the current study. This would be useful in future prospective studies where more resources are

available. This could focus on those with and without (but subsequently develop) injuries and OA. The aim of such research would be to identify those at risk and inform preventative strategies to amend suboptimal running techniques.

It would be interesting to explore the findings of the present study alongside radiographic or MRI imaging. The use of MRI has been postulated as a useful tool to identify early and pre-disease (Yusuf et al, 2011). Used in combination, function and imaging could facilitate better outcomes in OA by more comprehensively identifying the effects of the disease allowing optimal interventions to be used throughout the course of the disease. On the other hand, symptoms and functional deficit are likely to be the most important factor to a patient. McAlindon et al (1993) identified that age and pain are greater determinants of functional impairment than radiographic features of disease. A relatively small (n=114) cross-sectional study of participants with severe OA (as shown on radiograph), concluded that knee pain, stiffness and duration of disease may affect the severity of disability in patients with knee OA (Cubukcu, Sarsan & Alkan, 2012).

Further longitudinal data is necessary to confirm these findings. Future research should expand on the use of functional tests as part of a holistic assessment of function within the broader sphere of OA. Along with pain and imaging, function is another critical component of OA that could impact on quality of life. These findings may stimulate further research in other athletic

populations so that there is more comprehensive and specific data to inform clinical decision making in the management of OA - particularly early disease. The inclusion of non-runners and runners that have ceased participation may have provided further valuable insight.

Further research may be required to compare the performance of these tests by runners compared to athletes that complete other sporting activities. Other sports that have different demands (i.e. greater strength requirements, involve jumping), may lead to better performance. This may indicate that sports impart different degrees of functional capacity, and this may extend into later life once activity has ceased. This may in turn affect development of symptomatic OA (or OA that restricts function). A study of elite sportsman (Olympic-standard footballers) identified significantly better performance in tests of knee proprioception, rotational strength and hop for distance in these athletes compared to non-athletes (Muaidi, Nicholson & Refshauge, 2009). It is postulated that long-term training improves proprioception with enhanced mechanisms in central and peripheral neural pathways, augments muscles strength and ultimately improves joint function. Longitudinal data is needed to identify whether sports improve these aspects (and whether different sports convey diverse effects).

8.5 Follow-Up Questionnaire Results Discussion

The data presented above relates to data collected at a second time-point and refers to running and symptoms during the previous 12 months. The data

suggests that runners generally complete a similar amount of running compared to 12 months ago.

Most runners reported either similar or better knee joint health markers as indicated by the KOOS. The KOOS is widely applied in research and clinical practice (Roos & Lohmander, 2003). It is a comprehensive assessment, covering five separate domains, and can be completed independently online due to its user-friendly nature. For this research it was chosen since it covers both injury and OA - two key outcomes in this population. It is reported to be amongst the best knee assessment instruments regarding reliability, content validity and construct validity (Garratt, Brealey & Gillespie, 2004). The test-retest reliability and internal consistency of the KOOS has been identified by Collins et al, (2011). In patients with knee injury, the ICC and Cronbachs alpha were shown to vary slightly between the five domains (table 76)

Domain	ICC	Cronbach's alpha
Pain	0.85 - 0.95	0.84 - 0.91
Symptoms	0.75 - 0.91	0.25 - 0.75
ADL	0.75 - 0.91	0.94 - 0.96
Sport / Recreation	0.61 - 0.89	0.85 - 0.89
Quality of Life	0.83 - 0.95	0.64 - 0.90

Table 76: Test reliability of KOOS

This is critical since the measurement precision is inversely related to the measurement error. For this research, where some participants may have had bilateral symptoms (or none or very minor symptoms in the absence of a history of injury or surgery), the KOOS was adapted to enable responses for both knees. As far as the author is aware, the KOOS has not been widely used before in large cohorts (the majority of whom are absent of symptoms) for longitudinal data collection. Modification of the questionnaire was limited to the expansion enabling responses for both knees. The effect of this remains subject to future research as this may provide useful insight into currently asymptomatic patients in research where symptoms could develop in either limb. Further, use of the KOOS to identify symptomatic changes in the pre-OA state or early disease state require greater exploration. For longitudinal purposes in such participants, it is necessary to identify the optimal frequency of its use to provide clinically relevant findings that can influence treatment.

It is interesting to note the findings that those that reported they are running a lot less than a year ago generally reported the greatest negative shift in KOOS scores. This is limited by the duration of follow-up and it would be of benefit to note whether a subsequent increase in running reverses the KOOS values obtained. The reasons for running less have not been analysed but it may be postulated that injury is perhaps the most common physical limitation to running that would explain both a reduction in joint health and the amount of running performed. Data from the current study shows that the knee is the joint most injured in runners. Perhaps the KOOS data is best used to strengthen

the implementation of further research to identify injury reduction schemes for runners, based on the positive impact of injury reduction schemes implemented in other sports (Bahr & Krosshaug, 2005).

The strong association between risk of knee pain and injury in this study was a key finding. However, there may be an explanation for this in the underlying methods of the study. For example, a significant injury would be associated with pain at the time of its occurrence. It could be that both measurement tools are in fact assessing one event. This could have artificially inflated the association. A useful tool to differentiate between background pain and pain resulting from the injury would have been useful, although for participants to separate the two may have been difficult.

There are relatively few longitudinal prospective studies that explores the effects of running. This is perhaps surprising given the popularity of running and the burden of OA. One of the papers which reports data over several years (mean 11.7), Chakravarty et al (2008) reported that there was no difference in prevalence or severity of radiographic knee OA in runners and non-runners. This study did not have adequate follow-up nor resources to contemplate analysis of x-ray data. It is unlikely that within a 12-month period that there would be any significant alterations visible or quantifiable. The data presented here was collated at a minimum of 7 months after completing the first questionnaire. The potential range of follow-up for some participants may not have been a full year as a result of practical limitations within this study.

Therefore, the data presented focuses on the KOOS domains which, as discussed above, can be used over relatively short time periods. Data here is reported bilaterally, rather than for one knee since symptoms may be present or absent (to varying degrees) in both limbs. Further, it was considered that injury to either leg may impact on the health of the contralateral limb and therefore both were included separately.

8.6 Study Strengths and Limitations

Several strengths and limitations of the overall study should be outlined and acknowledged, in addition to those outlined in the relevant sections above. This evaluation is an important part of the research process and will support interpretation of the findings. The strengths and limitations outlined in the following sections relate to the overall study design and are pertinent to multiple results sections. This aspect of the discussion must be considered with regards to the conclusions drawn, including how the factors can affect the internal and external validity of the findings. Ultimately, this can aid future research and how it is conducted.

8.6.1 Study Strengths

Ideally, a study of recreational running would include all runners since this would ensure that the results are truly applicable to that population by including all the different characteristics of that group. However, this would be logistically problematic, impossible ethically and prohibitively expensive to

conduct. Instead, a sample of all runners was used in this research and the extent to which these results can be applied to other running populations is limited. To ensure that the results can be extrapolated to the wider population of recreational runners, it was important to include as many runners as possible. A large sample means that the individual differences in demographics, running behaviours and outcomes observed in the study population more accurately represent all recreational runners. This 'external validity' is important. External validity assesses which populations the results can be generalised to. The inclusion criteria were intentionally open to enable as many runners as possible to participate. These are reflected in the demographics (e.g. wide age-range; 18-81) and the running behaviour (e.g. broad current average weekly running distance). In contrast to the present studies, previous research has limited the study of population to specific runners, for example cohorts based on age, performance level or minimum amount of running. Certain analyses in the present study have been conducted using specific sub-groups on similar basis (e.g. age groups, running behaviours), but the overall cohort was not limited to these from the outset.

Studies that recruit participants based on predetermined characteristics have benefits and drawbacks (e.g. Chakravatry et al, (2007) only reporting findings on runners aged over 50) - but their external validity is determined by the study question posed and how the results are interpreted. One potential benefit of identifying only a certain group of athletes is that it could aid recruitment efforts by focussing efforts and resources into one specific area, club or

organisation. A limitation of using runners that can only run to a certain standard (for example, complete a defined distance within a specified time, ability to run a defined distance or a minimum number of runs per week) is that it fails to encapsulate the runners within a recreational setting. Recruitment of runners based on high running performance ability reduces the heterogeneity of the cohort. It limits the ability to confidently apply the findings to all runners since most runners are not professional or would be considered high performing. Many may not be interested in performance improvements and simply run for enjoyment. Running performance can be limited by many factors, including genetics, previous injury or other lifestyle factors such as participation in other sports limiting training time. On the one hand, restricting age of participants limits the cohort to those that are known to be most susceptible since prevalence of OA and pain increase with age. Further, diagnoses of OA often require age to be taken into consideration (NICE, 2014). That said, there are limitations of this approach in both longitudinal cohorts and cross-sectional data. It does not allow the prevalence or incidence of OA to be identified in those that are younger. It makes identification of risk factors in earlier life more difficult since no contemporaneous data is available.

For the current study, limiting recruitment to a specific section of the running community may have been helpful as most of the recruitment was completed by one individual with limited resources at their disposal. Greater focus may have improved the efficiency of efforts. However, it was felt that with opportune planning and support from influential organisations (e.g. parkrun)

that a sufficiently sample of diverse runners could be obtained. The population in the current study is diverse and the amount of running they do is highly variable. It could be argued that by recruiting through running events and clubs that this is limiting recruitment to those that feel they are physically able and confident enough to take part. There may be runners that do not participate in any events and therefore were not approached to take part. These runners would be problematic to recruit since they would need to be approached via other - potentially time-consuming - means. It is impossible to identify the number of runners that do not take part in any events nor can the extent to which their non-involvement influenced the outcomes obtained. That said, the author is confident that the cohort obtained is a fair reflection of recreational runners.

The current study represents one of the largest samples of runners ever assessed in relation to knee joint health (particularly OA). The cohort is also larger than other studies that have looked at risk of OA in other specific groups of athletes (e.g. footballers), although these have been ex-professionals rather than the general population (Fernandes et al, 2017).

This study used several markers of knee joint health. Briefly, these included;

Self-reported:

- History of injury
- Knee pain
- Other symptoms (e.g. stiffness, crepitus, reduced ROM)

- Clinical measures (e.g. KOOS)

Functional, physical tests:

- Simple, common tasks (e.g. OARSI)

Joint health is a multi-component concept and it is important to differentiate between these dimensions. This stipulates the need for several assessment tools as there is no single method that could capture all aspects. The use of the KOOS enabled multiple components of knee joint health to be simultaneously assessed (Roos & Lohmander, 2003). Additional symptoms are important to recognise as these may precede pain in early OA and could allow prediction of symptom progression to be recognised. They can also be analysed in combination depending on the specific outcomes of interest. The use of several different functional tests has already been described in detail (section 3.5.1.3), although each is biased towards a specific component of overall function.

The questionnaire was designed to capture running behaviour as thoroughly as possible. This meant that current and historical running was identified. There are few examples from previous research that could inform the current study because of differences in study design. Many studies do not report the exact questions used to ascertain running (section 2.9.2). In the present study, a selection of responses to the running questions were validated using contemporaneous running data from a variety of sources. This strengthens the interpretation of the conclusions drawn.

Despite a focus towards running, other factors were also captured in the questionnaire, such as other constituents of overall PA (e.g. occupational PA). These could affect outcomes of interest and were therefore necessary to report. This study identified running conducted by runners that was freely conducted according to the individual. An alternative study designs for identifying running would be to prescribe running, but this would be challenging to enforce and ethically difficult.

8.6.2 Study Limitations

Due to the logistical challenges of distributing and financial costs of printing paper copies of the questionnaire, the principle method of completion was online. This had ramifications for the composition of the questionnaire including the absence of illustrations that may have enabled further scrutiny of knee/body pain (e.g. some did not load when using slower internet connections, thus it was removed from the final version). A mannequin for identifying the specific location of body pain and an outline of knee anatomy to identify the location of joint specific pain (i.e. medial and lateral TFJ, PTFJ) may have been more user-friendly, facilitated quicker completion and provided additional pain detail.

It is possible that an online questionnaire had both a negative and positive effect on recruitment. The expectation was that most people have internet access and therefore could use the online interface. It is possible that some

individuals - perhaps older or more economically deprived - do not own a computer or other device that would allow access. The alternative was to provide printed copies of the questionnaire, along with a pre-paid envelope for return. This comes at significant financial cost and additional logistical challenges for both the researcher (e.g. transportation) and participant (e.g. posting the return). On the other hand, handing out questionnaires may have encouraged participation by facilitating completion and removing the need to login online, particularly if certain runners were not computer literate.

Recruitment of participants at events was undertaken by one individual. Therefore, it is possible that more additional personnel supporting recruitment would have aided the sample size further. This could also have altered the demographics of the sample recruited. For example, at events where there were many runners, the fastest and slowest runners were the most likely to be provided with research recruitment information since there were fewer runners at these points relative to the periods around the average finishing time when most runners finished in a short period. As the final runners completed each event, there was longer between the finishers which also facilitated longer explanation of the research to those that were interested. This may lead to recruitment bias towards higher performing runners (the fastest runners) and less able or more novice runners (the slowest runners). The true effect of this is unknown but it may have ramifications for some of the analyses performed. For example, it could skew the data to include a

disproportionate number of older runners with a greater number of injuries which were contributory factors towards them achieving a slower time.

Continuation of running is reliant upon the motivation and physical ability to do so. If either is compromised, then running could cease. The effect of self-selection bias is that it may underestimate the true prevalence of a condition within a specific population. Self-selection bias in researching exploring an association between running and OA may represent 'survival of the fittest' (Engebretsen, 2018). In other words, those that can continue are included in research, whereas those with symptoms may be inadvertently excluded at inception or drop out since they no longer run.

There was attrition in sample size between the baseline and follow-up data collection. In part, this was due to participants not providing consent for further contact and a focus on data collection in the UK. It is speculated that other participants lost interest or suffered from questionnaire fatigue. Furthermore, there may have been some logistical errors that prevented further communications between researchers and participants. For example, participants may have incorrectly entered their contact details (e.g. email address) thus were not contactable again. It is also possible that participants changed their email address, perhaps through a job change, which meant that correspondence was not received. There could also be other factors that prevented further involvement, such as severe disease or death, but these are impossible to verify.

Attrition can affect the internal and external validity of results in longitudinal studies. Limitations of attrition can include introduction of bias and reduce the generalisability of results (Barry, 2005). This emanates from the characteristics in the follow-up group not being consistent with the original sample. For example, those with knee pain or knee OA at baseline may have been more likely to continue participation in the study. Ideally, all participants would have been contactable at follow-up and have returned the questionnaire. Attrition limits the amount of data available for analyses, as those who cease participation do not provide additional responses (Gustavson et al, 2012). In the current study, all available data was included in all analyses to avoid dismissing data that had been collected.

It is possible that other relevant factors have not, or could not, be identified in the present study. These may include, but not limited to:

1. Joint hypermobility

Static and dynamic joint stability are important for normal knee mechanics. These are maintained by anatomical structures (e.g. ligaments), proprioceptive input and muscular activity (reflex and centrally driven). Postulated as a possible risk factor for OA, hypermobility may impact on joint function and health, and potentially impact on risk of injury and subsequent OA. Hypermobility is characterised by joint laxity in an otherwise normal subject (Grahame, 1990). Excess movement could directly relate to increased risk of

developing OA or indirectly (for example, contributing to increased risk of joint injury). Proprioception can be adversely affected by low levels of activity, joint instability, reduced muscle strength and decreased endurance. In turn, reduced proprioception could elevate risk of microtrauma to the joint, but further evidence for this is needed (Sharma & Pai, 1997). Laxity itself can be influenced by injury, genetic factors, gender, or due to the normal ageing process, and may contribute to subsequent disease progression by affecting joint distribution across the joint surfaces (Sharma et al, 1999). There is therefore potential for running to affect both hypermobility and underlying components of hypermobility. Whether or not running affects joint hypermobility - perhaps by strengthening the contractile tissues or the passive structures that support the joints - remains to be discovered.

2. Diet

Runners may have a keen interest in diet, particularly if it impacts on performance. PA (calorie expenditure) is one of the greatest contributing factors towards body weight maintenance/change. Another is calorie intake, but other components of diet may influence joint health. Obesity is one of the main factors for onset and progression of knee OA (Berenbaum, Eymard, Houard, 2013). Energy balance (the difference between intake and expenditure) will be a major determinant of whether body weight increases or decreases. The mechanisms by which obesity raises risk of OA were discussed previously. It is likely that running will contribute towards greater calorie expenditure and therefore lower risk of OA. There is a recommendation for

exercise and weight reduction in OA management but their role in preventing OA onset is less well defined (Bliddal, Leeds & Christensen, 2014).

Furthermore, research is needed to review whether dietary composition affects risk of OA independent of weight status. There is a hypothetical link between dietary fat intake and OA, since OA has been described as a metabolic syndrome, characterised by dyslipidaemia. A key factor worthy of investigation is the increased intake of dietary saturated fatty acids. Lipids are stored in the matrix and chondrocytes of cartilage and could contribute towards inflammation, cartilage degradation and poor chondrocyte structure (Masuko et al, 2009). Fatty acids and cholesterol are common lipids associated with cartilage physiology (Gkretsi et al, 2011). Dietary fatty acids could play a role in modulating disease, but this should be explored further as a potential intervention to prevent disease onset and progression.

3. Psychological Effects of Running

The psychological profiles of runners and non-runners may differ. This may affect the extent to which subjective symptoms (e.g. pain) are recognised and influence how likely they are to seek healthcare assessment (e.g. Biopsychosocial model, section 2.3.1.1). This could impact injury management, diagnosis of OA and running status. Novice runners and more experienced runners may also experience pain differently. No cause-effect relationship between running and symptom subjectivity has been established but it is a possibility. It is possible that the EQ-5D-5L data relating to anxiety may require

further examination in larger populations of non-runners since these could in fact have an important role in perception of injury and levels of PA performed. It may also be worth exploring whether runners are different from other endurance athletes.

4. Genetics / Epigenetics

The genetic component of risk for OA has been explained previously. The genetics that raise predisposition to injury are also coming under greater scrutiny. Acute changes in the genetic markers that signify underlying joint condition have been identified and explored in healthy runners undertaking running. Limited to a small cohort, early results suggest that running alters the chemical composition within the knee, specifically of inflammation and cartilage turnover (Hyldahl et al, 2016). Significant further research is required to review these findings amongst a greater cohort outside the laboratory setting over various intensities of running.

5. Running Attire

Running surface (e.g. road, trail) was identified in this study as this is the interface between the ground and the body and therefore could influence the magnitude of forces involved. This is difficult to quantify accurately in the real-world setting. However, the interface with the floor, footwear, can be more closely controlled and a potential source of assessment. Ground reaction forces can be affected by running footwear (Logan et al, 2010). Thus, if modulating

load is found to be beneficial for symptoms / risk of OA, it could be worth pursuing with additional randomised trials.

6. The Effects of Running on Other Joints

Some risk factors for OA are joint specific, but those that affect the knee may not impact other joints in the same manner or to the same extent. A limitation of this study is that it does not examine the effect of running on other joints. It would be interesting to identify the long-term effects of running on the other load bearing joints, such as the hips, ankles and lumbo-pelvic complex. Current evidence suggests that patients with hip OA may be able to continue running, but as with the knee, further research is needed to identify sport-specific risk factors (Silverling et al, 2012).

8.7 Future Research Directions

Previous research has identified both a positive and negative impact of running on the lower limb joints and hypotheses can explain both. Despite the present study providing further insight, the need for further research remains. The following section outlines how the present study informs future research designs and areas that require more detailed exploration.

The ethical implications of implementing the gold standard of research, a randomised controlled trial, prevent it from being a viable option. Prescribing running and ensuring adherence would be difficult logistically and it is likely that adherence would be low within a substantial proportion of the population.

This would be especially relevant if participants were required to continue running if symptoms or injury (whether related to OA, other health conditions or activities) were to develop. The indications for future research are partly described in the limitations above but further evidence is required to ensure findings are robust and clinically relevant. In the following sections, the key components for future studies are identified.

Long-term follow up is necessary to identify onset and progression of OA. Hypothesised associations between an exposure and an outcome can be more robustly reported if there are trends over time. Cross-sectional data on the other hand does not provide a causal inference but can generate hypotheses for future research.

Longitudinal data exploring running and knee OA should meet several criteria:

1. Adequate duration

   Since OA is a condition that may develop gradually over prolonged period, it is necessary that the period of observation is enough to ensure that the condition can be observed pre-disease and once it has begun to progress. It may mean that a period more than several decades is necessary so that exposures and outcomes can be tracked from an early age into later life.

2. Representative population of runners

   A community-based observational study must include runners from all backgrounds, i.e. varying doses of running. The individual variances, not

only in running but other lifestyle factors that could act as confounders in the onset or progression of OA, such as BMI and injury. Recreational runners are highly diverse and likely do not complete the same amount of running one week to the next, and behaviour is inclined to change considerably over time.

3. Running behaviour assessment

   Current and previous running are important to know in the context of future running behaviour. Trends of running (i.e. change in volume, alteration in performance, starting or stopping running) could all influence joint health. It is therefore important that the ability to identify any alterations is maintained throughout the period of interest.

4. Identification of confounders

   Previous research has repeatedly shown the extensive health benefits that running provides. In addition, runners are more likely to live a healthy lifestyle, for example, less alcohol consumption, fewer smokers. It may therefore be a complex mechanism by which running influences risk of knee OA and running itself is only a contributor.

8.7.1 Themes for Future Research

There are several areas that researchers may wish to focus on, in pre- and existing OA, relating to running. Some of these are outlined below.

Running Throughout Life

The effect of running at various stages of life is important to explore further. It is worth investigating whether an amount of running performed in early, mid, or later life has equivalence or whether there is a period when running is most beneficial/risky.

In the current study, running duration was defined as the number of years that an athlete has been running. This is an estimation since no definitive start date can normally be identified. It could be that some runners run for several years before stopping and then restarting, and therefore total running is overestimated.

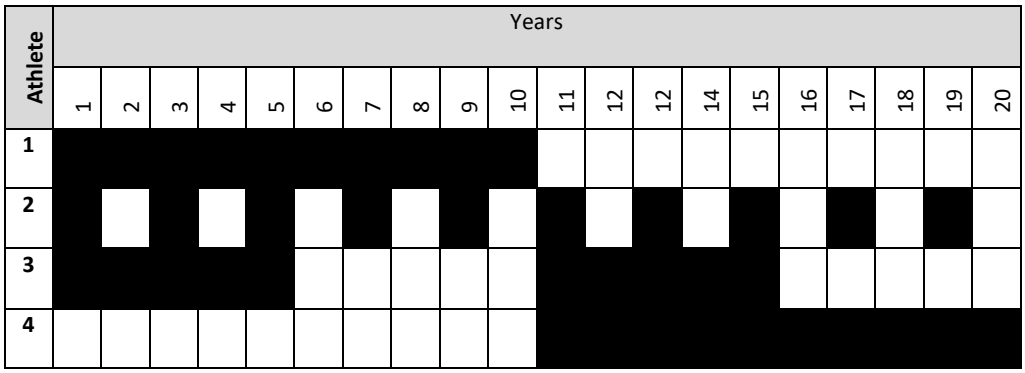


Figure 95: Hypothetical running distribution over 20-year period

There was also no minimum number of runs necessary to define continuous running throughout a specified period. The potential effect of this is shown in figure 95. Each of the four hypothetical athletes in the diagram runs for 10 years throughout a 20-year period. If each were to run the same amount during each year, the running is equivalent, but the effects may be different because of the distribution. It is also possible that running for a comparable duration at

various times in life has some effect. Running when the cartilage is maturing (predominantly teenage years) may promote its structural and functional health in later life by optimising development. In later life, instead of further cartilage development, running may ensure that cartilage quality is maintained and prevents deterioration.

This relates to the prevention and management of OA and injury. Encouraging running in later life could be associated with greater risk of injury if individuals are not accustomed to PA. This in turn may lead to risk of knee pain and raise susceptibility to symptomatic OA.

Injury Prevention

The need to identify ways to promote safe running that prevents, or reduces incidence of, injury amongst recreational runners is a significant challenge. Injury reduction strategies have been used in other sports, e.g. football, with some successes. A similar strategy may be of use in running, but a more detailed analysis of running injuries and their risk factors may be useful. For example, an understanding of the running load immediately preceding injury may reveal interesting insight and form guidance for runners.

Running and Pain Perception

Evidence suggests that controlled pain stimuli are reported differently in athletes and non-athletes (Tesarz et al, 2012). Evidence that could identify the contribution of biopsychosocial factors in runners and non-runners would

assist in the management of those at risk of, or with, established knee OA. It has been observed that athletes who are able to ignore pain are more likely to continue their participation despite the pain (Deroche et al, 2011). If this were the case amongst the athletes in the current cohort, prevalence of pain may be under-reported. Further longitudinal data from athlete diaries may aid understanding between the relationship between pain coping, pain behaviour and running.

Clinical Interventions

The health benefits of running are numerous and broad. Therefore, it is important that clinical professionals support those with OA to remain active. It is key to identify the effect of different interventions to manage symptoms in runners with OA of varying severity. Running may have a clinical role in both the detection and care of those with OA. This may be various guises:

Running as a Barometer of Joint Health

There is a growing emphasis on early intervention since this is when it may be possible to have the greatest impact and even reverse structural and symptomatic changes. The ability to intervene early is dependent upon sensitive tools that can identify minor but clinically significant changes in symptoms that precede more significant disease. The opportunity to do this in runners may be possible using running itself as a barometer of joint health as it could be one of the most demanding activities completed. Longitudinal

analysis of detailed running behaviour and symptoms post-running could enable symptoms to be identified pre-disease.

Running as a Therapeutic Adjunct in OA

Evidence that PA does not worsen knee pain is important to emphasise (Esser & Bailey, 2011). Exercise, either muscular strengthening or aerobic activities, benefit those with OA. The optimal dose of either is unclear, but it is known that focus on one rather than a combination of both is best. Running therefore has the potential to provide a straightforward way of providing a 'dose' of exercise that can be prescribed (Urquhart et al, 2011). It requires minimal equipment or skill and can be performed in publicly accessible environments.

Running as a Tool for Weight Loss

One of the principle motivations for running is to assist weight loss. Since BMI and obesity are strongly associated with knee OA, it is reasonable to assume that the net effect of running in this instance may reduce risk of OA. That said, it is unclear what short-term effects running has on the knee joints in obese individuals, and whether there is an increase in pain or other symptoms that may prevent further participation. Due to the increased force that the knee must functionally support during running with excess body weight, it is also worth investigating individuals were run but are unable to reduce body weight to a sufficient level, perhaps due to other lifestyle factors, such as diet. Previous studies have shown that in isolation, diet or exercise can reduce symptoms and improve function, but the greatest benefit occurs when they occur together

(Messier et al, 2013). This evidence is restricted to those seeking to reduce body weight. A proportion of individuals run to aid weight loss, but this is not the case in every instance.

Running Mechanics

The methods of the current study meant that it was not possible to assess running gait. Instead, it was limited to quantifying the amount of running performed. It may be that it is not just running behaviour patterns (i.e. the amount and/or speed of running) that affects joint health, but how. Despite appearing a relatively simple task, running requires complex co-ordination of the entire musculoskeletal system to be performed efficiently. If there is a deficiency at one point (e.g. muscular weakness, congenital abnormality) then a compensation may occur elsewhere. This could raise susceptibility to injury or increase forces that affect risk of knee OA. This may also be the case, even in the absence of injury or other factors. Running may habitually be completed with a gait pattern that detrimentally affects joint forces. For instance, the effect of foot-strike pattern, stride length and location of centre of mass throughout the step cycle can affect how forces act across the lower limb joints (Hreljac & Ferber, 2006).

The analysis of gait is difficult when it does not occur within a laboratory. Further, it could be expected that running mechanics alter with fatigue and therefore such an observation may take a long time to be observed, making research such as this difficult. Changes in running over time, or faulty

mechanics to begin with may result in altered forces through the joints, but the ultimate effect of this in relation to knee OA remains unclear. Muscular dysfunction is proposed as a contributory factor towards development of OA (Shrier, 2004). Muscles are not entirely responsible for controlling load across the joint during loading activities. This means that when damage has occurred to other load-bearing structures (e.g. menisci), joints may be more susceptible to further micro-damage. This may be compounded by the short-term effects of running where compression equivalent to 7.2x body weight was calculated in healthy individuals. A 30-minute run resulted in deformation of the femoral and tibial articular cartilage volume, although this was compartment specific and the long-term implications of this in relation to injury and OA are not known (Boocock et al, 2009). Nevertheless, maximising muscular strength therefore becomes a key clinical outcome after injury. Some authors suggest the association between injury and re-injury is due to incomplete rehabilitation (Taunton et al, 2003).

The high prevalence of injuries reported in the current study may have direct and indirect consequences for knee OA. Evidence from a small cohort of athletes suggests that loading variables (rate and magnitude of impact) differ between injured and non-injured runners, whilst there were also non-statistically significant trends for differences in running biomechanics (Hreljac, Marshall & Hume, 2000). Injured runners were defined as those with at least one overuse injury attributed to running and had been running regularly and pain free for more than three months before the study. The prevalence of

injury in the present cohort suggests that overuse injuries are common. Furthermore, differences between younger (mean age 29) and older runners (mean age 60) in respect of reduced muscular force production, reduced joint flexibility and altered running biomechanics. There is also increased knee vertical loading rates (p 0.03). Although several individual outcomes were statistically significant, many were not, indicating age-related biomechanical changes are clearly complex. Further research will be needed to identify the clinical significance of these and how they may be altered to prevent injury and optimise loading to protect the joints.

Footwear

To date, there is limited to evidence to support the role of impact forces (peak and/or vertical) being associated with increased risk of injury / knee OA (Miller, 2017). If this were the case, faster runners would have more injuries related to impact but there is no evidence to suggest that this is the case (Nigg et al, 2015).

Another systematic review described evidence looking at shod and unshod running - a growing phenomenon amongst recreational athletes and subject to considerable research interest recently. It is postulated that barefoot running reduces injury risk (Hashish et al, 2016). The link between running shoes and running biomechanics has been described by Nigg et al (2015). The authors propose the concept of 'preferred movement pattern' to describe the way the skeletal system of individuals move during running. According to this

hypothesis, the muscles act to ensure that the bones move according to this path. The authors go on to describe that a 'good' running shoe is one that facilitates this movement pattern with minimal demands on muscle activity. Mundermann, Stefanyshyn & Nigg (2001) identified that increased footwear comfort reduces the incidence of pain and foot injury because of running.

Orthotics and Insoles

Insoles may be used by athletes in their shoes to aid comfort or performance when running. These differ from prescribed insoles but there could be some benefit from others that are used. The aim of providing Insole use as an adjunct therapy in OA management is to provide shock absorption or unload the TFJ (Rannou & Poiraudeau, 2010). Guidelines provide mixed recommendations for insole use in knee OA. ACR recommend both medial and lateral wedges (Hochberg et al, 2012), EULAR do not recommend use of lateral inserts (Fernandes et al, 2013), whilst OARSI recommend the consideration of shock-absorbing or unloading insoles (McAlindon et al, 2014). A Cochrane Review reported that there was low-quality evidence for reduced pain of using lateral wedges compared to no use, but a lack of evidence for other outcomes (e.g. function) (Duivenvoorden et al, 2015). There was no optimal treatment choice regarding orthoses. The need for more studies including more participants with greater periods of follow-up duration and an assessment of potential adverse outcomes are necessary. Importantly, these must be extended to include insoles used during running.

Joint Supports

Many runners are seen wearing joint supports that allegedly help them participate in activities such as running easier, perhaps following injury or through fear of an injury. It is argued that functional braces could improve proprioceptive feedback around the joint and improve stability and confidence in non-injured athletes (Rishiraj et al, 2011). Evidence as to whether an external support can provide relief from symptoms or provide additional benefit during activity is inconclusive for patellofemoral pain syndrome (Swart et al, 2012). A Cochrane Review identified that pain, stiffness and physical function improve when a knee brace is used (Brouwer et al, 2005). How these benefits translate to highly active individuals, i.e. those that wish to continue running, remains to be determined.

Other Sources of Running

Running is a key component of many other sports, even if it does not directly relate to performance of that activity (e.g. football, rugby, netball). In these examples, the demands of running are very different to road running. A greater proportion is multidirectional and can include many more accelerations and decelerations interspersed by periods of recovery/walking. Previous research has shown that participation in some sports raises risk of OA and is likely linked to the high incidence of joint injuries in these sports. The contribution of running in these sports (especially in the absence of previous injury) to the heightened risk of OA is poorly defined. It would be difficult to assess the total amount of running performed in other sports, but highly active individuals may

complete multiple sports and therefore the total amount of running may be underestimated if just running alone is assessed. This could be positive or negative. Alternative running activities may aid joint health by maintaining (or enhancing) cartilage structure by applying adequate forces through a greater proportion of the entire joint, including the PFJ. Alternatively, rotational forces at the knee may cause micro-trauma to the cartilage and thus raise the risk of accumulative damage over time. These are merely hypotheses and the overall effect is not yet known - but the importance of measuring running from all activities is clear.

The Broader Context

It would be remiss to only consider running and its effects in relation to the knee joint in future research. The wider health risks and benefits of participation require some acknowledgement. PA, from any source, has numerous physical effects on multiple bodily systems. A holistic view of these responses to running are required for a more comprehensive understanding. It is beyond the scope of this paper to discuss these in detail, but a brief overview of two initial areas are described below:

1. Running and General Health

   Research has unequivocally shown that PA is a critical component of a healthy lifestyle. Running is just one of many methods of by which recommended levels of PA can be achieved for the health benefits to be realised. The risk-benefit of running for knee OA must be identified in the

context of overall health. Promoting safe running will have benefits not just for the knee but general wellbeing. Evidence has shown that runners have a 30% reduced risk of all-cause mortality (Lee et al, 2014). Specific health benefits have been observed regarding running and chronic disease prevention, including coronary heart disease, stroke, hypertension, diabetes and high cholesterol (Chomistek et al, 2012). That said, the specific risk reduction for each disease and the dose response may not correlate precisely to the effects of different running behaviours for the knees. Clinical guidance for running should therefore include a balanced approach and an appreciation of broader consequences.

2. OA and Co-morbidities

Evidence shows that individuals with OA could be likely to have multiple health problems. This may occur because of common pathways for development or the presence of one elevating vulnerability to another. Prevalence of high morbidity count (six or more conditions other than OA) is greater in those with OA (31%) than those without (21%) (Kadam, Jordan & Croft, 2004). In this case-control study of over 11,000 patients aged over 50 with OA, high morbidity was associated with being female, older age and of lower socioeconomic status, but these do not explain the difference between patients with OA and those without. It must be explored further as to whether there are true pathological relationships between them and OA or if the associations are down to bias or confounding in research. There may be certain conditions that are relevant to the knee and thus of greater

concern. If indeed there is a clinical relationship between certain diseases, running could have a broader benefit e.g. preventing their onset or limiting their severity. One further consideration is whether comorbidities vary by the joint affected by OA.

Collaboration across research groups to look at the varied outcomes of interest would be improved by consensus on the definition of what constitutes a runner, particularly in recreational cohorts. This could be taken further, with distinct types of runner based on running behaviours and other demographics to allow ease of stratification and data sharing.

Dissemination of Evidence

Current clinical management of OA is not optimal. Practitioners fail to use the available evidence and guideline adherence is poor. It is well-established that the use of contemporaneous evidence in clinical practice is severely restricted and can take a long time to implement on a widespread scale. Another factor that contributes to management failures is the trivialisation of the condition (Egerton et al, 2016). Factors that affect clinical translation must be reflected in research and how it is undertaken and disseminated. Research must be planned cognisant of the practitioners and service-users that will ultimately rely on the available evidence to ensure that outcomes are enhanced. Engagement with multiple stakeholders is a critical phase of disseminating evidence and best practice. This is not limited to clinical professionals but extended to include other influential bodies and organisations such as the

wider media, running clubs and organisations, policy makers and research funders. It is essential that the best methods to share knowledge are used to dispel misconceptions around running and OA and ensure that those that wish to be active are provided with balanced evidence relating to the health benefits and risks.

8.8 Conclusion

In summary, this research aimed to investigate the association between recreational running and knee symptoms (e.g. pain), OA and function. This research has provided new insight into measurement techniques for assessing running behaviour in recreational athletes. The findings of the validation study suggest that runners over-estimate when self-reporting running activity. Such a finding is useful when assessing the current body of evidence and future work in this area. The findings presented here do not suggest that running has a detrimental effect on joint health, but due to the study design, no causation can be interpreted. Further longitudinal data, over a prolonged period is necessary to ensure that recreational athletes can continue to enjoy their chosen pastime safely.

9 References

Ackerman IN, Bucknill A, Page RS, et al (2015) The substantial personal burden experienced by younger people with hip or knee osteoarthritis. Osteoarthritis Cartilage 23 (8) pp 1276 – 1284

Ainsworth B, Cahalin L, Buman M, et al (2015) The current state of physical activity assessment tools. Prog Cardiovasc Dis 57 (4) pp 387 – 395

Ajuied A, Wong F, Smith C, et al (2014) Anterior cruciate ligament injury and radiologic progression of knee osteoarthritis: a systematic review and meta-analysis. Am J Sports Med 42 (9) pp 2242 – 2252

Alentorn-Geli E, Samuelsson K, Masahl V (2017) The Association of Recreational and Competitive Running With Hip and Knee Osteoarthritis: A Systematic Review and Meta-analysis. J Orthop Sports Phys Ther 47 (6) pp 373 – 390

Allen AA, Caldwell GL, Fu FH (1995) Anatomy and biomechanics of the meniscus. Operative Techniques in Orthopaedics 15 (1) pp 2 – 9

Allen KD, Golightly YM (2015) Epidemiology of osteoarthritis: state of the evidence Curr Opin Rheumatol 27(3) pp. 276 – 283

Allen KD, Helmcij CG, Schwartz, et al (2009) Racial Differences in Self-Reported Pain and Function among Individuals with Radiographic Hip and Knee Osteoarthritis: The Johnston County Osteoarthritis Project Osteoarthritis Cartilage 17 (9) pp 1132 – 1136

Allen KD, Oddone EZ, Coffman CJ, et al (2010) Racial differences in osteoarthritis pain and function: potential explanatory factors Osteoarthritis Cartilage 18 (2) pp 160-167

Allender S, Cowburn G, Foster C (2006) Understanding participation in sport and physical activity among children and adults: a review of qualitative studies. Health Educ Res 21 (6) pp 826 – 835

Allender S, Foster C, Scarborough P et al (2007) The burden of physical activity-related ill health in the UK J Epidemiol Community Health 61 (4) pp 344 – 348

Almedia MO, Davis IS, Lopes AD (2005) Biomechanical Differences of Foot-Strike Patterns During Running: A Systematic Review With Meta-analysis. J Orthop Sports Phys Ther 45 (10) pp 738 - 755

Altman R, Asch E, Bloch D et al (1986) Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of

the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 29 (8) pp 1039 – 1049

Altman RD, Gold GE (2007) Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis Cartilage 15 Suppl A pp A1-56

Amoako AO, Pujalte GG (2014) Osteoarthritis in young, active, and athletic individuals. Clin Med Insights Arthritis Musculoskelet Disord 7 pp 27 – 32

Andersen LB (2015) Light and moderate joggers do not have lower mortality rates than strenuous joggers Journal of the American College of Cardiology 65 (24) pp 2670 – 2671

Andriacchi TP, Mündermann A (2006) The role of ambulatory mechanics in the initiation and progression of knee osteoarthritis. Curr Opin Rheumatol 18 (5) pp 514 – 518

Apold H, Meyer H, Nordsletten L et al (2014) Risk factors for knee replacement due to primary osteoarthritis, a population based, prospective cohort study of 315,495 individuals BMC Musculoskeletal Disorders 15 pp 217

Archer CW, Francis-West P (2003) The chondrocyte. Int J Biochem Cell Biol 35 (4) pp 401 – 404

Ardern CL, Khan KM (2016) The old knee in the young athlete: knowns and unknowns in the return to play conversation. Br J Sports Med 50 (9) pp 505 – 506

Arokoski JPA, J. S. Jurvelin JS, Väätäinen U, et al (2000) Normal and pathological adaptations of articular cartilage to joint loading Scand J Med Sci Sports 10 pp 186 – 198

Aspden RM (2011) Obesity punches above its weight in osteoarthritis. Nat Rev Rheumatol 7 pp 65 - 68

Ateef M, Kulandaivelan S, Tahseen S (2016) Test-retest reliability and correlates of 6-minute walk test in patients with primary osteoarthritis of knees Indian Journal of Rheumatology 11 (4) pp 192 – 196

Attur M, Krasnokutsky-Samuels S, Samuels J (2013) Prognostic biomarkers in osteoarthritis Curr Opin Rheumatol 25 (1) pp 136 – 144

Baarveld F, Visser CAN, Kollen B, et al (2010) Sports-related injuries in primary health care Fam Pract 28 (1) pp 29 – 33

Bahr (2009) No injuries, but plenty of pain? On the methodology for recording overuse symptoms in sports. Br J Sports Med 43 (13) pp 966 – 972

Bahr R, Krosshaug T (2005) Understanding injury mechanisms: a key component of preventing injuries in sport Br J Sports Med 39 pp 324 – 329

Baker P, Reading I, Cooper C, et al (2003) Knee disorders in the general population and their relation to occupation Occupational and Environmental Medicine 60 pp 794 – 797

Baker-LePain JC, Lane NE (2012) Role of bone architecture and anatomy in osteoarthritis. Bone 51 (2) pp 197 - 203

Baratz ME, Fu FH, Mengato R (1986) Meniscal tears: the effect of meniscectomy and of repair on intraarticular contact areas and stress in the human knee. A preliminary report. Am J Sports Med 14 (4) pp 270 – 275

Barton B, Peat J (2014) Medical Statisitcs: A guide to SPSS, data analysis and critical appraisal Second edition; BMJ Books, Chichester, UK

Bauman AE, Reis RS, Sallis JF, et al (2012) Correlates of physical activity: why are some people physically active and others not? Lancet 380 (9838) pp 258 – 271

Bauman AE, Sallis JF, Dzewaltowski DA, et al (2002) Toward a better understanding of the influences on physical activity: the role of determinants, correlates, causal variables, mediators, moderators, and confounders. Am J Prev Med 23(2 Suppl) pp 5 - 14.

Bedson J, Croft PR (2008) The discordance between clinical and radiographic knee osteoarthritis: A systematic search and summary of the literature BMC Musculoskeletal Disorders 9 pp 116

Belo JN, Berger MY, Reijan M, et al (2007) Prognostic Factors of Progression of Osteoarthritis of the Knee: A Systematic Review of Observational Studies Arthritis Care & Research 57 (1) pp 13 – 16

Bennell KL, Crossley K (1996) Musculoskeletal injuries in track and field: incidence, distribution and risk factors. Aust J Sci Med Sport 28 (3) pp 69 – 75

Bennell KL, Hinman RS (2011) A review of the clinical evidence for exercise in osteoarthritis of the hip and knee. J Sci Med Sport 14 (1) pp 4-9

Bennell KL, Hinman RS, Metcalf BR, et al (2003) Relationship of knee joint proprioception to pain and disability in individuals with knee osteoarthritis. J Orthop Res 21 (5) pp 792 - 797

Bennell Kl, Hunt MA, Wrigley TV (2008) Role of muscle in the genesis and management of knee osteoarthritis. Rheum Dis Clin North Am 34 (3) pp 731 – 754

Bennell KL, Hunt MA, Wrigley TV, et al (2010) Hip strengthening reduces symptoms but not knee load in people with medial knee osteoarthritis and varus malalignment: a randomised controlled trial. Osteoarthritis Cartilage 18 (5) pp 621 – 628

Berenbaum F (2013) Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthritis Cartilage 21 (1) pp 16 – 21

Berenbaum F, Eymard F, Houard X (2013) Osteoarthritis, inflammation and obesity. Curr Opin Rheumatol 25 (1) pp 114 – 118

Berra K, Rippe J, Manson JE (2015) Making Physical Activity Counseling a Priority in Clinical Practice: The Time for Action Is Now. JAMA 314 (24) pp 2617 – 2618

Bhattacharyya T, Gale D, Dewire P, et al (2003) The clinical importance of meniscal tears demonstrated by magnetic resonance imaging in osteoarthritis of the knee. J Bone Joint Surg Am (1) pp 4 – 9

Bijlsma JW, Berenbaum F, Floris PJ, et al (2011) Osteoarthritis: an update with relevance for clinical practice. Lancet 18 (377) pp 2115 – 2126

Bijlsma JW, Berenbaum F, Lafeber FPJG (2011) Osteoarthritis: an update with relevance for clinical practice Lancet 377 pp 2115 - 2126

Bindawas SM, Vennu V, Al Snih S (2015) Differences in health-related quality of life among subjects with frequent bilateral or unilateral knee pain: data from the Osteoarthritis Initiative study. J Orthop Sports Phys Ther 45 (2) pp 128 – 136

Blagojevic M, Jinks C, Jeffery A (2010) Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. Osteoarthritis Cartilage 18 (1) pp 24-33

Bland M (2015) An introduction to medical statistics 4th edition; Oxford University Press, Oxford, UK

Bland JM, Altman DG (1986) Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1 (8476) pp 307 – 310

Bley AS, Correa JCF, Dos Reis AC, et al (2014). Propulsion phase of the single leg triple hop test in women with patellofemoral pain syndrome: a biomechanical study. PloS one 9(5).

Bliddal H, Leeds AR, Christensen R (2014) Osteoarthritis, obesity and weight loss: evidence, hypotheses and horizons – a scoping review Obes Rev 15 (7) pp 578 - 586.

Bohannon RW (2006) Reference values for the timed up and go test: a descriptive meta-analysis. Journal of geriatric physical therapy 29 (2) pp 64-68

Bolay H, Moskowitz MA (2002) Mechanisms of pain modulation in chronic syndromes. Neurology 10 59 (5 Suppl 2) pp S2-7

Bonewald LF, Johnson ML (2008) Osteocytes, mechanosensing and Wnt signalling Bone 42 (4) pp 606 – 615
Bonfield M, Fearnisde L, Cramp F (2018) A personal experience of performing a systematic literature review J Allied Health 47 (3) pp 167 – 171

Bonnet CS, Walsh DA (2005) Osteoarthritis, angiogenesis and inflammation. Rheumatology 44 (1) pp 7 – 16

Booker CL, Harding S, Benzeval M (2011) A systematic review of the effect of retention methods in population-based cohort studies BMC Public 249

Bourne RB, Chesworth BM, Davis AM, et al (2010) Patient satisfaction after total knee arthroplasty: who is satisfied and who is not? Clin Orthop Relat Res 468 (1) pp 57 – 63

Bowling A (2005) Mode of questionnaire administration can have serious effects on data quality. J Public Health 27 (3) pp 281 – 291

Brachman A, Kamieniarz A, Michalska J et al (2017) Balance training programs in athletes–A systematic review. Journal of human kinetics 58 (1) pp.45-64.

Bradford Hill A (1965) The Environment and Disease: Association or Causation? Proc R Soc Med 1965 58 (5) pp 295 – 300

Brandt KD (1999) Osteophytes in osteoarthritis. Clinical aspects. Osteoarthritis Cartilage 7(3) pp 334 – 335

Breivik H, Eisenberg E, O'Brien T (2013) The individual and societal burden of chronic pain in Europe: the case for strategic prioritisation and action to improve knowledge and availability of appropriate care BMC Public Health 13 pp 1229

Brody LT (2015) Knee osteoarthritis: Clinical connections to articular cartilage structure and function Phys Ther Sport 16 (4) pp 301 – 316

Brouwer RW, Jakma TS, Verhagen AP (2005) Braces and orthoses for treating osteoarthritis of the knee. Cochrane Database Syst Rev 25 (1) CD004020

Bruce B, Fries JF, Lubeck DP (2005) Aerobic exercise and its impact on musculoskeletal pain in older adults: a 14 year prospective, longitudinal study Arthritis Research & Therapy 7 (6) pp 1263 – 1270

Brughelli M, Cronin J, Chaouachi A (2011) Effects of running velocity on running kinetics and kinematics. J Strength Cond Res 25 (4) pp 933 - 939

Buist I, Bredeweg SW, Van Mechelen W, et al (2008) No effect of a graded training program on the number of running-related injuries in novice runners: a randomized controlled trial. The American Journal of Sports Medicine, *36* (1) pp 33 - 39

Buist I, Bredeweg SW, Lemmink KA, et al (2010) Predictors of running-related injuries in novice runners enrolled in a systematic training program: a prospective cohort study. Am J Sports Med 38 (2) pp 273 – 280

Burr DB, Gallant MA (2012) Bone remodelling in osteoarthritis. Nat Rev Rheumatol 8 (11) pp 665 – 673

Butte NF, Ekelund U, Westerterp KR (2012) Assessing physical activity using wearable monitors: measures of physical activity. Med Sci Sports Exerc 44 (1 Suppl 1) pp 5-12

Callaghan P (2004) Exercise: a neglected intervention in meantal health care? J Psychiatr Ment Health Nurs 11 (4) pp 476 - 483

Campbell AB, Pineda M, Harris JD (2016) Return to Sport After Articular Cartilage Repair in Athletes' Knees: A Systematic Review Arthroscopy 32 (4) pp 651 – 668

Caspersen CJ, Powell KE, Christenson GM (1985) Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep 100 (2) pp 126 – 131

Castañeda S, Roman-Blas JA, Largo R et al (2014) Osteoarthritis: a progressive disease with changing phenotypes Rheumatology 53 (1) p 1 – 3

Chaganti RK, Lane NE (2011) Risk factors for incident osteoarthritis of the hip and knee Curr Rev Musculoskelet Med 4 (3) pp 99 – 104

Chakravarty EF, Hubart HB, Lingala VB, et al (2008) Long distance running and knee osteoarthritis. A prospective study. Am J Prev Med 35 (2) pp 133 – 138

Chan WP, Lang P, Stevens MP (1991) Osteoarthritis of the knee: comparison of radiography, CT, and MR imaging to assess extent and severity. AJR Am J Roentgenol 157 (4) pp 799 – 806

Chappell JD, Yu B, Kirkendall DT, et al (2002) A comparison of knee kinetics between male and female recreational athletes in stop-jump tasks. Am J Sports Med 30 (2) pp 261 – 267

Chen A, Gupte C, Akhtar K, et al (2012) The Global Economic Cost of Osteoarthritis: How the UK Compares Arthritis 2012 p 1 - 6

Chomistek AK, Cook NR, Flint AJ, et al (2012) Vigorous-intensity leisure-time physical activity and risk of major chronic disease in men Med Sci Sports Exerc 44 (10) pp 1898 – 1905

Cibere J (2006) Do we need radiographs to diagnose osteoarthritis? Best Pract Res Clin Rheumatol 20 (1) pp 27 – 38

Cibere J, Zhang H, Thorne A et al (2010) Association of clinical findings with pre-radiographic and radiographic knee osteoarthritis in a population-based study. Arthritis Care Res 62 (12) pp 1691 – 1698

Clagg S, Paterno MV, Hewett TE, et al (2015) Performance on the modified star excursion balance test at the time of return to sport following anterior cruciate ligament reconstruction. J Orthop Sports Phys Ther 45 (6) pp 444 – 452

Cleas S, Hermie L, Verdonk R (2012) Is osteoarthritis an inevitable consequence of anterior cruciate ligament reconstruction? A meta-analysis. Knee Surg Sports Traumatol Arthrosc 21(9) pp 1967 – 1976

Collins NJ, Misra D, Felson DT, et al (2011) Measures of knee function: International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, Knee Injury and Osteoarthritis Outcome Score (KOOS), Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form (KOOS-PS), Knee Outcome Survey Activities of Daily Living Scale (KOS-ADL), Lysholm Knee Scoring Scale, Oxford Knee Score (OKS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Activity Rating Scale (ARS), and Tegner Activity Score (TAS). Arthritis Care Res 63 Suppl 11 pp S208 – 228

Conaghan PG (2002) Update on osteoarthritis part 1: current concepts and the relation to exercise Br J Sports Med 36 pp 330 – 333

Conaghan P (2006) Is MRI useful in osteoarthritis? Best Pract Res Clin Rheumatol 20 (1) pp 57 – 68

Conley DL, Krahenbuhl GS (1980) Running economy and distance running performance of highly trained athletes. Med Sci Sports Exerc 12 (5) pp 357 – 360

Cooper C, Snow S, McAlindon TE et al (2000) Risk factors for the incidence and progression of radiographic knee osteoarthritis. Arthritis Rheum 43 (5) pp 995 – 1000

Craig CL, Marshall AL, Sjostrom M, et al (2003) International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 35 (8) pp 1381 – 1395

Creamer P, Lethbridge-Cejku M, Hochberg MC (1998) Where does it hurt? Pain localization in osteoarthritis of the knee. Osteoarthritis Cartilage 6 (5) pp 318 – 323

Crema MD, Guermazi A, Sayre EC et al (2011) The association of magnetic resonance imaging (MRI)-detected structural pathology of the knee with crepitus in a population-based cohort with knee pain: the MoDEKO study. Osteoarthritis Cartilage 19 (12) pp 1429 – 1432

Cross M, Smith E, Hoy D, et al (2014) The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis 73 (7) pp 1323 – 1330

Crossley KM (2014) Is patellofemoral osteoarthritis a common sequela of patellofemoral pain? Br J Sports Med 48 (6) pp 409 – 410

Cruz-Almeida Y, Sibille KT, Goodin BR, et al (2014) Racial and ethnic differences in older adults with knee osteoarthritis. Arthritis Rheumatol 66 (7) pp 1800 – 1810

Csuka M, McCarty DJ (1985) Simple method for measurement of lower extremity muscle strength Am J Med 78 (1) pp 77-81

Cubukcu D, Sarsan A, Alkan H (2012) Relationships between Pain, Function and Radiographic Findings in Osteoarthritis of the Knee: A Cross-Sectional Study. Arthritis 2012 pp 1 – 5

Culliford DJ, Maskell J, Beard DJ, et al (2010) Temporal trends in hip and knee replacement in the United Kingdom: 1991 to 2006. J Bone Joint Surg Br 92 (1) pp 130 – 135

Culliford D, Maskell J, Judge A, et al (2015) Future projections of total hip and knee arthroplasty in the UK: results from the UK Clinical Practice Research Datalink. Osteoarthritis Cartilage 23 (4) pp 594 – 600

Culvenor AG, Cook JG, Collins NJ, et al (2013) Is patellofemoral joint osteoarthritis an under-recognised outcome of anterior cruciate ligament reconstruction? A narrative literature review. Br J Sports Med 47 (2) pp 66-70

Culvenor AG, Engen CN, Oiestad BE, et al (2015) Defining the presence of radiographic knee osteoarthritis: a comparison between the Kellgren and Lawrence system and OARSI atlas criteria. Knee Surgery, Sports Traumatology Arthroscopy *23* (12) pp 3532 – 3539

D'Agostino MA, Conaghan P, Le Bars M, et al (2005) EULAR report on the use of ultrasonography in painful knee osteoarthritis. Part 1: prevalence of inflammation in osteoarthritis. Ann Rheum Dis 64 (12) pp 1703 - 1709

Davies AP, Vince AS, Shepstone L, et al (2002) The Radiologic Prevalence of Patellofemoral Osteoarthritis. Clinical Orthopaedics and Related Research 402 pp 206 – 212

Day N, Oakes S, Luben R, et al (1999) EPIC-Norfolk: study design and characteristics of the cohort. European Prospective Investigation of Cancer. British Journal Of Cancer 80 (Suppl) pp 195 - 203

DeLeo, AT, Dierks TA, Ferber R, et al (2004) Lower extremity joint coupling during running: a current update. Clinical Biomechanics 19 (10) pp 983 - 991

Deroche T, Woodman T, Stephan Y, et al (2011) Athletes inclination to play through pain: a coping perspective Anxiety Stress Coping 24 (5) pp 579 – 587

Devlin NJ, Krabbe PFM (2013)The development of new research methods for the valuation of EQ-5D-5L Eur J Health Econ 14(Suppl 1) pp 1–3

Dieppe PA, Lohmander LS (2005) Pathogenesis and management of pain in osteoarthritis. Lancet 365 (9463) pp 965 – 973

DiMicco MA, Kisiday JD, Gong H, et al (2007) Structure of pericellular matrix around agarose-embedded chondrocytes Osteoarthritis Cartilage 15 (10) pp 1207-1121

Dixon SJ, Hinman RS, Creaby MW et al (2010) Knee joint stiffness during walking in knee osteoarthritis Arthritis Care & Research 62 (1) pp 38 – 44

Dobson F, Hinman RS, Hall M, et al (2012) Measurement properties of performance-based measures to assess physical function in hip and knee osteoarthritis: a systematic review. Osteoarthritis Cartilage 20 (12) pp 1548 - 1562

Dobson F, Hinman RS, Roos EM, et al (2013) OARSI recommended performance-based tests to assess physical function in people diagnosed with hip or knee osteoarthritis. Osteoarthritis Cartilage 21 (8) pp 1042 – 1052

Driban JB, Hootman JM, Sitler MR JM (2017) Is Participation in Certain Sports Associated With Knee Osteoarthritis? A Systematic Review Journal of Athletic Training 50 (2) pp 497 – 506

Driban JB, Stout AC, Lo GH et al (2016) Best performing definition of accelerated knee osteoarthritis: data from the Osteoarthritis Initiative Ther Adv Musculoskelet Dis 8 (5) pp 165 – 171

Duffey MJ, Martin DF, Cannon DW, et al (2000) Etiologic factors associated with anterior knee pain in distance runners. Med Sci Sports Exerc 32 (11) pp 1825 - 183

Dugan SA, Bhat KP (2005) Biomechanics and analysis of running gait. Phys Med Rehabil Clin N Am 16 (3) pp 603 – 621

Duivenvoorden T, Brouwer RW, van Raaij TM, et al (2015) Braces and orthoses for treating osteoarthritis of the knee. Cochrane Database Syst Rev 16 (3):CD004020

Duncan RC, Hay EM, Saklatvala J et al (2006) Prevalence of radiographic osteoarthritis--it all depends on your point of view. Rheumatology 45 (6) pp 757 – 760

Eckstein F, Faber S, Muhlbauer R, et al (2002) Functional adaptation of human joints to mechanical stimuli Osteoarthritis Cartilage 10 pp 44 – 50

Edwards P, Roberts I, Clarke M, et al (2002) Increasing response rates to postal questionnaires: a systematic review BMJ 324 (7347) pp 1183

Egerton T, Diamond LE, Buchbinder R, et al (2016) A systematic review and evidence synthesis of qualitative studies to identify primary care clinicians' barriers and enablers to the management of osteoarthritis. Osteoarthritis Cartilage 25 (5) pp 625 - 638

Eijsvogels TM, Thompson PD (2015) Exercise Is Medicine: At Any Dose? JAMA 314 (18) pp 1915 – 1916

Emery CA, Cassidy JD, Klassen TP (2005) Effectiveness of a home-based balance-training program in reducing sports-related injuries among healthy adolescents: a cluster randomized controlled trial. CMAJ 172 (6) pp 749 - 754.

Engebretsen L (2018) Decreased Osteoarthritis Risk in Experienced Marathon Runners: Commentary on an article by Danielle Y. Ponzio, MD, et al.: “Low

Prevalence of Hip and Knee Arthritis in Active Marathon Runners" The journal of bone and joint surgery 100 (2) p 12

Englund M, Guermazi A, Gale D, et al (2008) Incidental meniscal findings on knee MRI in middle-aged and elderly persons. N Engl J Med 359 (11) pp 1108 – 1115

Englund M, Lohmander LS (2006) Menisectomy and osteoarthritis: what is the cause and what is the effect? Future Rheumatol 1 (2) pp 207 - 215

Espana-Romero V, Golubic R, Martin KR, et al (2014) Comparison of the EPIC Physical Activity Questionnaire with Combined Heart Rate and Movement Sensing in a Nationally Representative Sample of Older British Adults PLoS One 9 (2) e87085

Esser S, Bailey A (2011) Effects of exercise and physical activity on knee osteoarthritis Curr Pain Headache Rep 15 (6) pp 423 - 430

Everhart JS, Sojka JH, Kaeding CC, et al (2017) The ACL injury response: A collagen-based analysis Knee 24 (3) pp 601 - 607

Eyre D (2002) Collagen of articular cartilage Arthritis Res 4 (1) pp 30 -35

Eyre DR (2004) Collagens and cartilage matrix homeostasis. Clin Orthop Relat Res (427 Suppl) pp S118 – 122

Eze-Nliam, Cain K, Bond K, et al (2012) Discrepancies between the medical record and the reports of patients with acute coronary syndrome regarding important aspects of the medical history BMC Health Services Research 12 p 78

Faber SC, Eckstein F, Lukasz S, et al (2001) Gender differences in knee joint cartilage thickness, volume and articular surface areas: assessment with quantitative three-dimensional MR imaging. Skeletal Radiol 30 (3) pp 144 – 150

Farrokhi S, O'Connel M, Gil A, et al (2013) Alterations in sagittal-plane knee joint kinematics and kinetics during gait in knee osteoarthritis patients with complaints of instability Osteoarthritis & Cartilage 21 (suppl) S 88

Favero M, Ramonda R, Goldring MB et al (2015) Early knee osteoarthritis RMD Open (Suppl 1) pp 62

Felson DT (2005) The sources of pain in knee osteoarthritis. Curr Opin Rheumatol 17 (5) pp 624 – 628

Felson DT (2009) Developments in the clinical understanding of osteoarthritis. Arthritis Res Ther 11 (1) pp 203

Felson DT (2010) Identifying Different Osteoarthritis Phenotypes through Epidemiology Osteoarthritis Cartilage 18 (5) pp 601 - 604

Felson DT (2013) Osteoarthritis as a disease of mechanics Osteoarthritis Cartilage 21 (1) pp 10 - 15

Felson DT, Chaisson CE (1997) Understanding the relationship between body weight and osteoarthritis Baillieres Clin Rhematol 11 (4) pp 671 -681

Felson DT, Gale DR, Gale ME et al (2005) Osteophytes and progression of knee osteoarthritis Rheumatology 44 (1) pp 100 – 104

Felson DT, Naimark A, Anderson J (1987) The prevalence of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. Arthritis Rheum 30 (8) pp 914 – 918

Felson DT, Niu J, Clancy M, et al (2007) Effect of recreational physical activities on the development of knee osteoarthritis in older adults of different weights: the Framingham Study. Arthritis Rheum. 57 (1) pp 6 - 12

Felson DT, Zhang Y (1998) An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. Arthritis Rheum 41(8) pp 1343 – 55

Ferber R, Davis IM, Williams DS (2003) Gender differences in lower extremity mechanics during running. Clin Biomech 18 (4) pp 350 - 357.

Ferket BS, Feldman Z, Zhou J, et al (2017) Impact of total knee replacement practice: cost effectiveness analysis of data from the Osteoarthritis Initiative. BMJ 356 p 356

Fernandes L, Hagen KB, Bijlsma JW, et al (2013) EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. Ann Rheum Dis 72 (7) pp 1125 1135

Fernandes GS, Parekh SM, Moses J, et al (2017) Prevalence of knee pain, radiographic osteoarthritis and arthroplasty in retired professional footballers compared with men in the general population: a cross-sectional study Br J Sports Med 52 pp 678 - 683

Fernandes GS, Valdes AM (2015) Cardiovascular disease and osteoarthritis: common pathways and patient outcomes European Journal of Clinical Investigation 45 (4) pp 405 – 414

Fernández-Moreno M, Ignacio Rego I, Vanessa Carreira-Garcia V, et al (2008) Genetics in Osteoarthritis Curr Genomics 9 (8) pp 542 - 547

Fewtrell MS, Kennedy K, Singhal A, et al (2008) How much loss to follow-up is acceptable in long-term randomised trials and prospective studies? Arch Dis Child 93 (6) pp 458 - 461

Finch CF, Kemp JL, Clapperton AJ (2015) The incidence and burden of hospital-treated sports-related injury in people aged 15 years in Victoria, Australia, 2004-2010: a future epidemic of osteoarthritis? Osteoarthritis Cartilage 23 pp 1138 – 1143

Finch CF, Orchard JW, Twomey DM, et al (2014) Coding OSICS sports injury diagnoses in epidemiological studies: does the background of the coder matter? Br J Sports Med 48 (7) pp 552 – 556

Finkelstein EA, Khavjou OA, Thompson H, et al (2012) Obesity and severe obesity forecasts through 2030. Am J Prev Med 42 (6) pp 563 – 570

Fitzgerald GK, Lephart SM, Hwang JH, et al (2001) Hop tests as predictors of dynamic knee stability. Journal of Orthopaedic & Sports Physical Therapy 31(10) pp 588-597

Flandry F, Hommel G (2011) Normal anatomy and biomechanics of the knee Sports Med Arthrosc Rev 19 (2) pp 92 -92

Focht BC, Rejeski J, Ambsosius WT, et al (2005) Exercise, self-efficacy and mobility performance in overweight and obese older adults with knee osteoarthritis Arthritis Care & Research 53 (5) pp 659 - 665

Fowler-Brown A, Kim DH, Shi L, et al (2015) The mediating effect of leptin on the relationship between body weight and knee osteoarthritis in older adults. Arthritis Rheumatol 67 (1) pp 169-75

Fox AJS, Bedi A, Rodeo SA (2012) The Basic Science of Human Knee Menisci: Structure, Composition, and Function Sports Health 4 (4) pp 340 – 351

Fransen M, McConnell S (2008) Exercise for osteoarthritis of the knee Cochrane Database Syst Rev 8 (4)

Frost HM (1994) Wolff's Law and bone's structural adaptations to mechanical usage: an overview for clinicians Angle Orthod 64 (3) pp 175 – 188.

Gabbe BJ, Finch CF, Bennell KL, et al (2003) How valid is a self reported 12 month sports injury history? Br J Sports Med 37 (6) pp 545 - 547

Gabbett TJ (2016) The training-injury prevention paradox: should athletes be training smarter and harder? Br J Sports Med 50 (5) pp 273 -280

Garratt AM, Brealey S, Gillespie WJ, et al (2014) Patient-assessed health instruments for the knee: a structured review. Rheumatology 43 (11) pp 1414 – 1423

Garrett WE, Speer KP, Kirkendall DT (200) Principles and Practice of Sports Orthopaedic Medicine Lippincott, Williams and Wilkins; Philadelphia, USA

George DR, Rovniak LS, Kraschnewski JL (2013) Dangers and opportunities for social media in medicine Clin Obstet Gynecol 56 (3) pp 453 – 462

Geva N, Defrin R (2013) Enhanced pain modulation among triathletes: a possible explanation for their exception capabilities Pain 154 (11) pp 2317 - 2323

Giavarina D (2015) Understanding Bland Altman analysis Biochem Med 25 (2) pp 141 - 151

Gkretsi V, Simopoulou T, Tsezou A (2011) Lipid metabolism and osteoarthritis: lessons from atherosclerosis. Prog Lipid Res 50 (2) pp 133 – 140

Glasgow P, Phillips N, Bleakley C (2015) Optimal loading: key variables and mechanisms. Br J Sports Med 49 (5) pp 278 -279

Glass N, Segal NA, Sluka KA, et al (2014) Examining Sex Differences in Knee Pain: The Multicenter Osteoarthritis Study Osteoarthritis Cartilage 22 (8) pp 1100 - 1106

Glyn-Jones S, Palmer AJ, Agriocola R et al. (2015) Osteoarthritis Lancet 386(9991) pp 376 – 387

Gogia PP, Braatz JH (1986) Validity and reliability of leg length measurements. J Orthop Sports Phys Ther 8(4) pp 185 - 188

Goldring MB, Goldring SR (2007) Osteoarthritis J Cell Physiol 213 (3) pp 626 - 634

Goldring MB, Goldring SR (2010) Articular cartilage and subchondral bone in the pathogenesis of osteoarthritis Ann N Y Acad Sci 1192 pp 230 – 237

Grahame R (1990) 'The hypermobility syndrome'. Ann Rheum Dis 49 (3) pp 199 – 200

Greenland S, Pearl J, Robins JM (1999) Causal diagrams for epidemiologic research. Epidemiology 10 (1) pp 37 - 48.

Gregor MF, Hotamisligil GS (2011) Inflammatory mechanisms in obesity. Annu Rev Immunol 29 pp 415 – 445

Grelsamer RP, Klein JR (1998) The biomechanics of the patellofemoral joint. J Orthop Sports Phys Ther 28 (5) pp 286 – 298

Gribble PA, Hertel J (2003) Considerations for Normalizing Measures of the Star Excursion Balance Test Measurement in Physical Education and Exercise Science 7 (2) pp 89 - 100

Gribble PA, Hertel J, Plisky P (2012) Using the Star Excursion Balance Test to assess dynamic postural-control deficits and outcomes in lower extremity injury: a literature and systematic review. J Athl Train 47 (3) pp 339 – 357

Gross DK, Hillstrom HJ (2008) Noninvasive devices targeting the mechanics of osteoarthritis Rheumatic Disease Clinics 34 (3) pp 755 - 776

Guilak F (2012) Biomechanical factors in osteoarthritis Best Pract Res Clin Rhematol 25 (6) pp 815 – 823

Guilak F, Fermor B, Keefe FJ, et al (2004) The role of biomechanics and inflammation in cartilage injury and repair. Clin Orthop Relat Res. (423) pp 17 – 26

Gustavson K, von Soest T, Karevold E, et al (2012) Attrition and generalizability in longitudinal studies: findings from a 15-year population based study and a Monte Carlo simulation study BMC Public Health 12 p 918

Gustavsson A, Neeter C, Thomee P, et al (2006) A test battery for evaluating hop performance in patients with an ACL injury and patients who have undergone ACL reconstruction Knee Surg Sports Traumatol Arthrosc 14 (8) pp 778-788

Guyatt GH, Pugsley SO, Sullivan MJ, et al (1984) Effect of encouragement on walking test performance Thorax 39 (11) pp 818 - 822

Haitz K, Schultz R, Hodgins M, et al (2014) Test-Retest and Interrater Reliability of the Functional Lower Extremity Evaluation Journal Of Orthopaedic & Sports Physical Therapy 44 (12) pp 947 – 954

Hame SL, Alexander RA (2013) Knee osteoarthritis in women Curr Rev Musculoskelet Med 6 (2) 182 – 187

Hamilton RT, Schultz SJ, Schmitza RJ, et al (2008) Triple-Hop Distance as a Valid Predictor of Lower Limb Strength and Power Journal of Athletic Training 43 (2) pp 144 – 151

Hashish R, Samarawickrame SD, Baker L, et al (2016) The Influence of a Bout of Exertion on Novice Barefoot Running Dynamics. J Sports Sci Med 15 (2) pp 327 - 334

Haskell WL, Lee IM, Pate RR (2007) Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc 39 (8) pp 1423 – 1434

Hatfield GL, Morrison A, Wenman M etal (2016) Clinical tests of standing balance in the knee osteoarthritis population: systematic review and meta-analysis. Physical therapy 96 (3), pp.324-337.

Henriksen M, Creaby MW, Lund H (2014) Is there a causal link between knee loading and knee osteoarthritis progression? A systematic review and meta-analysis of cohort studies and randomised trials BMJ Open 4 (7)

Herdman M, Gudex C, Lloyd A, et al (2011) Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 20 (10) pp 1727 – 1736

Herman T, Giladi N, Hausdorff JM (2011) Properties of the timed up and go test: more than meets the eye Gerontology 57 (3) pp 203 - 210

Hernan MA, Hernandez-Diaz S, Robins JM (2004) A structural approach to selection bias. Epidemiology 15(5) pp 615 - 625

Hill J, Bullock I, Anderson P (2011) A summary of the methods that the

Hinman RS, Crossley KM (2007) Patellofemoral joint osteoarthritis: an important subgroup of knee osteoarthritis. Rheumatology 46 (7) pp 1057 – 1062

Hochberg MC, Altman RD, April KT (2012) American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res 64 (4) pp 465 - 474

Hochman JR, Gagliese L, Davis AM et al (2011) Neuropathic pain symptoms in a community knee OA cohort. Osteoarthritis Cartilage 19 (6) pp 647 – 654

Holla JF, Steultjens MP, van der Leeden M et al (2011) Determinants of range of joint motion in patients with early symptomatic osteoarthritis of the hip and/or knee: an exploratory study in the CHECK cohort. Osteoarthritis Cartilage 19 (4) pp 411 – 419

Hootman JM, Helmick CG, Barbour KE, et al (2016) Updated Projected Prevalence of Self-Reported Doctor-Diagnosed Arthritis and Arthritis-Attributable Activity Limitation Among US Adults, 2015-2040. Arthritis Rheumatol 68 (7) pp 1582 - 1587

Hootman JM, Macera CA, Helmick CG, et al (2003) Influence of physical activity-related joint stress on the risk of self-reported hip/knee osteoarthritis: a new method to quantify physical activity. Prev Med 36(5) pp 636 – 644

Hopkins WG (2000) Measures of reliability in sports medicine and science Sports Med 30 (1) pp 1- 15

Hreljac A, Marshall RN, Hume PA (2000) Evaluation of lower extremity overuse injury potential in runners Med Sci Sports Exerc 32 (9) pp 1635 – 1641

Hreljac A (2004) Impact and overuse injuries in runners Med Sci Sports Exerc 36 (5) pp 845 - 849

Hulteen RM, Smith JJ, Morgan PJ et al (2017) Global participation in sport and leisure-time physical activities: A systematic review and meta-analysis. Prev Med 95 pp 14-25

Hunter DJ, Arden N, Conaghan PG et al (2011) Definition of osteoarthritis on MRI: results of a Delphi exercise Osteoarthritis Cartilage 19 (8) pp 963 - 969

Hunter DJ, Felson DT (2006) Osteoarthritis BMJ 332 pp 639 – 642

Hunter DJ, McDougall JJ, Keefe FJ (2008) The symptoms of OA and the genesis of pain Rheum Dis Clin North Am 34 (3) pp 623 – 643

Hunter DJ, Riordan EA (2014) The impact of arthritis on pain and quality of life: an Australian survey. Int J Rheum Dis 17 (2) pp 149 – 155

Hunter DJ, Schofield D, Callander (2014) The individual and socioeconomic impact of osteoarthritis. Nat Rev Rheumatol 10 (7) pp 437 - 441

Hyldahl RD, Evans A, Kwon S, et al (2016) Running decreases knee intra-articular cytokine and cartilage oligomeric matrix concentrations: a pilot study. Eur J Appl Physiol 116 (11-12) pp 2305 – 2314

IASP (2004) IASP Terminology: Pain [Online] Available: http://www.iasp-pain.org/terminology?navItemNumber=576#Pain Accessed: October 2017
IPAQ (nd) IPAQ Scoring Protocol [online] Available: www.ipaq.ki.se Accessed: January 2018

Iwaki H, Pinskerova V, Freeman MA (2000) Tibiofemoral movement 1: the shapes and relative movements of the femur and tibia in the unloaded cadaver knee. J Bone Joint Surg Br 82(8) pp 1189 – 1195

Janssen WGM, Bussmann HBJ, Stam HJ (2002) Determinants of the Sit-to-stand movement: a review Physical Therapy 82 (9) pp 866 – 879

Janvier T, Jennane R, Toumi H et al (2017) Subchondral tibial bone texture predicts the incidence of radiographic knee osteoarthritis: data from the Osteoarthritis Initiative Osteoarthritis Cartilage 25 (12) pp 2047 – 2054

Jarvholm B, Lewold S, Malchau H, et al (2005) Age, bodyweight, smoking habits and the risk of severe osteoarthritis in the hip and knee in men. Eur J Epidemiol 20 (6) pp 537 - 542.

John D, Tyo B, Bassett DR (2010) Comparison of four ActiGraph accelerometers during walking and running. Med Sci Sports Exerc 42 (2) pp 368 – 374

Jones CJ, Rikli RE, Beam WC (1999) A 30-s chair-stand test as a measure of lower body strength in community-residing older adults Res Q Exerc Sport 70 (2) pp 113 - 119

Jordan JM (2015) An ongoing assessment of osteoarthritis in African Americans and Caucasians in North Caroline: The Johnston County Osteoarthritis Project Trans Am Clin Climatol Assoc 126 pp 77-86

Juhl C, Chrisensen R, Roos EM, et al (2014) Impact of exercise type and dose on pain and disability in knee osteoarthritis: a systematic review and meta-regression analysis of randomized controlled trials. Arthritis Rheumatol 66 (3) pp 622 – 636

Junghans C, Jones M (2007) Consent bias in research: how to avoid it Heart 93(9) pp 1024 - 1025

Junior LSH, Pillay JD, van Mechelen W et al (2015) Meta-Analyses of the Effects of Habitual Running on Indices of Health in Physically Inactive Adults Sports Med 45 (10) pp 1455 - 1468

Kadam UT, Jordan K, Croft PR (2004) Clinical comorbidity in patients with osteoarthritis: a case-control study of general practice consulters in England and Wales. Ann Rheum Dis 63 (4) pp 408 – 414

Kanko LE, Birmingham TB, Bryant DM, et al (2019) The star excursion balance test is a reliable and valid outcome measure for patients with knee osteoarthritis. Osteoarthritis and cartilage 27(4) pp.580-585.

Kaptchuk TJ (2001) The double-blind, randomized, placebo-controlled trial: gold standard or golden calf? J Clin Epidemiol 54 (6) pp 541 – 549

Karsdal MA, Bay-Jensen AC, Lories RJ et al (2014) The coupling of bone and cartilage turnover in osteoarthritis: opportunities for bone antiresorptives and anabolics as potential treatments? Ann Rheum Dis 2014;73 pp 336 – 348

Karsdal MA, Leeming DJ, Dam EB, et al (2008) Should subchondral bone turnover be targeted when treating osteoarthritis? Osteoarthritis and Cartilage 16 (6) pp 638 - 646

Kellgren JH, Lawrence JS (1957) Radiological assessment of osteo-arthritis Ann Rheum Dis 16 (4) pp 494 - 502

Kennedy DM, Stratford PW, Wessel J, et al (2005) Assessing stability and change of four performance measures: a longitudinal study evaluating outcome following total hip and knee arthroplasty BMC Musculoskel Disord 26 (6)

Kettunen JA, Kujala UM, Kaprio J, et al (2001) Lower-limb function among former elite male athletes. Am J Sports Med 29 (1) pp 2 - 8

Kidd BL (2006) Osteoarthritis and joint pain. Pain 123(1-2) pp 6 - 9

Klara K, Collins JE, Gurary E, et al (2016) Reliability and accuracy of cross-sectional radiographic assessment of severe knee osteoarthritis: role of training and experience. The Journal of Rheumatology 43 (7) pp 1421 - 1426

Kluitenberg B, Bredeweg SW, Zijlstra S (2012) Comparison of vertical ground reaction forces during overground and treadmill running. A validation study BMC Musculoskeletal Disorders pp 213 – 235

Kluitenberg N, van der Worp H, Husstede BM, et al (2016) The Nlstart2run study: Training-related factors associated with running-related injuries in novice runners J Sci Med Sport 19 (8) pp 642 - 646

Kluitenberg B, van Middelkoop M, Diercks R (2015) What are the Differences in Injury Proportions Between Different Populations of Runners? A Systematic Review and Meta-Analysis Sports Med 45(8) pp 1143 – 1161

Kline PW, Williams DSB (2015) Effects of normal aging on lower extremity loading and coordination during running in males and females Int J Sports Phys Ther 10 (6) pp 901 - 909

Ko V, Naylore JM, Harris IA, et al (2013) The six-minute walk test is an excellent predictor of functional ambulation after total knee arthroplasty BMC Musculoskelet Disord 14 145

Konradsen L, Hansen EM, Sondergaard L (1990) Long distance running and osteoarthrosis. Am J Sports Med 18(4) pp 379 – 381.

KOOS (2012) KOOS Scoring 2012 [Online] Available: http://www.koos.nu/KOOSscoring2012.pdf Accessed: July 2016

Kornaat PR, Bloem JL, Ceulemans RY (2006) Osteoarthritis of the knee: association between clinical features and MR imaging findings. Radiology 239 (3) pp 811 – 817

Kotlarz H, Gunnarsson CL, Fang H, et al (2010) Osteoarthritis and Absenteeism Costs: Evidence From US National Survey Data Journal of Occupational and Environmental Medicine 52 (3) pp 263 – 268

Krampla W, Mayrhofer R, Malcher R, et al (2001) MR imaging of the knee in marathon runners before and after competition Skeletal Radiology 30 (2) pp 72 - 76

Krampla WW, Newrkla SP, Kroener AH, et al (2008) Changes on magnetic resonance tomography in the knee joints of marathon runners: a 10-year longitudinal study Skeletal Radiol 37 (7) pp 619 – 626

Krasnokutsky S, Attur M, Palmer G et al. (2008) Current concepts in the pathogenesis of osteoarthritis. Osteoarthritis Cartilage 16 (3) pp S1-3

Kraus VB, Blanco FJ, Englund M (2015) Call for Standardized Definitions of Osteoarthritis and Risk Stratification for Clinical Trials and Clinical Use Osteoarthritis Cartilage 23 (8) pp 1233 - 1241

Krishnan Y, Grodzinsky AJ (2018) Cartilage diseases. Matrix Biol 71(72) pp 51 – 69

Kujala UM, Kaprio J, Sarna S (1994) Osteoarthritis of weight bearing joints of lower limbs in former elite male athletes BMJ 308 (6923) pp 231 - 234

Kujala UM, Sarna S, Kaprio, J (1999) Heart attacks and lower-limb function in master endurance athletes. Med. Sci. Sports Exerc 31 (7) pp 1041 - 1046

Kyu HH, Bachman VF, Alexander LT (2016) Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013 BMJ 354 pp 1 - 10

Landers KA, Hunter GR, Wetzstein CJ (2001) The interrelationship among muscle mass, strength, and the ability to perform physical tasks of daily living

in younger and older women. J Gerontol A Biol Sci Med Sci 56 (10) pp 443 – 448

Landis JR, Koch GG (1977) The Measurement of Observer Agreement for Categorical Data Biometrics 33 (1) pp 159-174

Lane NE, Bloch DA, Jones HH, et al (1986) Long-distance running, bone density, and osteoarthritis. JAMA 255 (9) pp 1147 – 1151

Lane NE, Oehlert JW, Bloch DA, et al (1998) The relationship of running to osteoarthritis of the 423 knee and hip and bone mineral density of the lumbar spine: a 9 year longitudinal study Journal of Rheumatology 25(2) pp 334 – 341

Lee DC, Pate RR, Lavie CJ, et al (2014) Leisure-time running reduces all-cause and cardiovascular mortality risk. J Am Coll Cardiol 64 (5) pp 472 – 481

Lee JM, Kim Y, Welk GJ (2014) Validity of consumer-based physical activity monitors Med Sci Scports Exerc 46 (9) pp 1840 – 1848

Leech RD, Edwards KL, Batt ME (2016) Does running protect against knee osteoarthritis? Or promote it? Assessing the current evidence. Br J Sports Med 49 (21) pp 1355 - 1356

Lenhart RL, Thelen DG, Wille CM (2014) Increasing running step rate reduces patellofemoral joint forces. Med Sci Sports Exerc 46 (3) pp 557 – 564

Lespasio MJ, Piuzzi N, Husni ME, et al (2017) Knee Osteoarthritis: A Primer Perm J 21 pp 16-183

Lethbridge-Cejku M, Scott WW, Reichle R, et al (1995) Association of radiographic features of osteoarthritis of the knee with knee pain: data from the Baltimore Longitudinal Study of Aging. Arthritis Care Res 8 (3) pp 182 - 188

Lequesne MG, Dang N, Lane NE (1997) Sport practice and osteoarthritis of the limbs Osteoarthritis Cartilage 5 pp 75 – 86

Levangie PK, Norkin CC (2011) Joint Structure and Function: A comprehensive analysis 5th Edition. FA Davis Company, Philadelphia, USA

Li Y, Bienias JL, Bennett DA (2007) Confounding in the Estimation of Mediation Effects. Comput Stat Data Anal 51 (6) pp 3173 – 3186

Li G, Yin J, Gao J, et al (2013) Subchondral bone in osteoarthritis: insight into risk factors and microstructural changes Arthritis Res Ther 15 (6) pp 223

Liao JJZ (2010) Sample size calculation for an agreement study Pharmaceutical statistics 9 (2) pp 125 - 132

Lim SS, Vos T, Flaxman AD (2012) A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380 (9859) pp 2224 – 2260

Lin LI (1989) Concordance correlation coefficient to evaluate reproducibility. Biometrics 45 (1) pp 255 - 268.

Lin MR, Hwang HF, Hu MH, et al (2004) Psychometric comparison of the timed up and go, one-leg stand, functional reach and Tinetti balance measures in community-dwelling older people J Am Geriar Soc 52 (8) pp 1343 - 1348

Lindle RS, Metter EJ, Lynch NA (1997) Age and gender comparisons of muscle strength in 654 women and men aged 20-93 yr. J Appl Physiol 83 (5) pp 1581 - 1587

Litwic A, Edwards MH, Dennison EM, et al (2013) Epidemiology and burden of osteoarthritis. Br Med Bull 105 pp 185-99

Livshits G, Zhai G, Hart DJ, et al (2009) Interleukin-6 Is a Significant Predictor of Radiographic Knee Osteoarthritis The Chingford Study Arthritis & Rheumatism 60 (7) pp 2037 - 2045

Lo GH, Driban JB, Kriska AM, et al (2017) Is There an Association Between a History of Running and Symptomatic Knee Osteoarthritis? A Cross-Sectional Study From the Osteoarthritis Initiative. Arthritis Care Res 69 (2) pp 183 - 191

Lo GH, Musa SM, Driban JB, et al (2018) Running does not increase symptoms or structural progression in people with knee osteoarthritis: data from the osteoarthritis initiative. Clin Rheumatol 37 (9) pp 2497 – 2504

Loeser RF (2011) Aging and Osteoarthritis Curr Opin Rheumatol 23(5) pp 492 - 496

Loeuille D, Chary-Valckenaere I, Champigneurlle J, et al (2005) Macroscopic and microscopic features of synovial membrane inflammation in the osteoarthritic knee: correlating magnetic resonance imaging findings with disease severity. Arthritis Rheum 52 (11) pp 3492 - 3501.

Logan S, Hunter I, Ty Hopkins JT, et al (2010) Ground reaction force differences between running shoes, racing flats, and distance spikes in runners. J Sports Sci Med 9 (1) pp 147 – 153

Logerstedt D, Lynch A, Axe MJ, et al (2013) Symmetry restoration and functional recovery before and after anterior cruciate ligament reconstruction. Knee Surgery, Sports Traumatology, Arthroscopy 21 (4) pp 859-868.

Lohmander LS, Gerhardsson de Verdier M, Rollof J, et al (2009) Incidence of severe knee and hip osteoarthritis in relation to different measures of body mass: a population-based prospective cohort study. Ann Rheum Dis 68 (4) pp 490 - 496

Lohmander LS, Ostenberg A, Englund M, et al (2004) High prevalence of knee osteoarthritis, pain, and functional limitations in female soccer players twelve years after anterior cruciate ligament injury. Arthritis Rheum 50 (10) pp 3145 – 3152

Lopez-Otin C, Blasco MA, Partridge L (2013) The hallmarks of aging. Cell 153(6) pp 1194 -1217

Losina E, Walensky RP, Reichmann WM et al (2011) Impact of obesity and knee osteoarthritis on morbidity and mortality in older Americans. Annals of internal medicine 154 (4) pp 217 – 226

Losina E, Weinstein AM, Reichmann WM, et al (2013) Lifetime risk and age at diagnosis of symptomatic knee osteoarthritis in the US Arthritis Care Res (Hoboken) 65 (5) pp 703 - 711

Loudon JK (2016) Biomechanics and Pathomechanics of the Patellofemoral Joint Int J Sports Phys Ther 11 (6) pp 820 – 830

Luyten FP, Denti M, Filardo G et al (2012) Definition and classification of early osteoarthritis of the knee. Knee Surg Sports Traumatol Arthrosc 20 (3) pp 401 – 406

MacAuley D, Bauman A, Frémont P (2016) Exercise: not a miracle cure, just good medicine Br J Sports Med 2016 50 pp 1107 - 1108

Macera CA, Hootman JM, Sniiezek JE (2003) Major public health benefits of physical activity. Arthritis Rheum 49 (1) pp 122 – 128

Mahjoub M, Berenbaum F, Houard X (2012) Why subchondral bone in osteoarthritis? The importance of the cartilage bone interface in osteoarthritis. Osteoporosis International 23 (8) pp 841 - 846

Makris EA, Hadidi P, Athanasiou KA (2011) The knee meniscus: structure-function, pathophysiology, current repair techniques, and prospects for regeneration. Biomaterials 32 (30) pp 7411 – 7431

Maly MR, Costigan PA, Olney SJ (2006) Determinants of self-report outcome measures in people with knee osteoarthritis. Arch Phys Med Rehabil 87 (1) pp 96 - 104.

Manninen P, Riihamaki H, Heliovaara, M et al (2001) Physical exercise and risk of severe knee osteoarthritis requiring arthroplasty Rheumatology 40 pp 432 - 437

Mansell JP, Bailey AJ (1998) Abnormal cancellous bone collagen metabolism in osteoarthritis. J Clin Invest 101 (8) pp 1596 – 1603

Mansell JP, Collins C, Bailey AJ (2007) Bone, not cartilage, should be the major focus in osteoarthritis. Nat Clin Pract Rheumatol 3 (6) pp 306 – 307

Mason JJ, Lesko F, Johnson, et al (2008) Patellofemoral joint forces J Biomech 41 (11) pp 2337-2348

Masouros SD, McDermott ID, Amis AA, et al (2008) Biomechanics of the meniscus-meniscal ligament construct of the knee Knee Surg Sports Traumatol Arthrosc 16 pp 1121 - 1132

Masuko K, Murata M, Suematsu N, et al (2009) A metabolic aspect of osteoarthritis: lipid as a possible contributor to the pathogenesis of cartilage degradation. Clin Exp Rheumatol 27 (2) pp 347 – 353

Mathiessen A, Conaghan PG (2017) Synovitis in osteoarthritis: current understanding with therapeutic implications Arthritis Research & Therapy 19 pp 18

Mills K, Dudley D, Collins NJ (2019) Do the benefits of participation in sport and exercise outweigh the negatives? An academic review Best Pract Res Clin Rhematol 33 (1) pp 172 - 187

Muthuri SG, McWilliams, Doherty M, et al (2011) History of knee injuries and knee osteoarthritis: a meta-analysis of observational studies. Osteoarthritis Cartilage 19 (11) pp 1286 – 1293.

Maughan, RJ Miller, JD, (1983). Incidence of training-related injuries among marathon runners. British journal of sports medicine 17 (3) pp.162-165

Mazzuca SA, Brandt KD, Katz BP (2007) Risk factors for early radiographic changes of tibiofemoral osteoarthritis Annals of the Rheumatic Diseases 66 pp 394 - 399

McAlindon TE, Bannuru RR, Sullivan MC (2014) OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage 22 (3) pp 363 – 388

McAlindon TE, Cooper C, Kirwan JR, et al (1993) Determinants of disability in osteoarthritis of the knee. Ann Rheum Dis 52 (4) pp 258 - 262.

McAlindon TE, Snow S, Cooper C, et al (1992) Radiographic patterns of osteoarthritis of the knee joint in the community: the importance of the patellofemoral joint. Ann Rheum Dis 51 (7) pp 844 – 849

McConnell S, Kolopack P, Davis AM (2001) The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): a review of its utility and measurement properties Arthritis Rheum 45 (5) pp 453 – 461

McDermott M, Freyne P (1983) Osteoarthrosis in Runners with Knee Pain Brit J Sports Med 17 (2) pp 84 - 87

McMillan G, Nichols L (2005) Osteoarthritis and meniscus disorders of the knee as occupational diseases of miners. Occup Environ Med 62 (8) pp 567 – 575

McNamee R (2003) Confounding and confounders. Occup Environ Med 60 (3) pp 227 – 234

McWilliams DF, Leeb BF, Muthuri SG, et al (2011) Occupational risk factors for osteoarthritis of the knee: a meta-analysis. Osteoarthritis Cartilage 19 (7) pp 829 - 839

Mendiguchia J, Ford KR, Quatman CE (2011) Sex Differences in Proximal Control of the Knee Joint Sports Medicine 41 (7) pp 541 – 547

Merchant AC, Arendt EA, Dye SF, et al (2008) The Female Knee: Anatomic Variations and the Female-specific Total Knee Design Clin Orthop Relat Res 466 (12) pp 3059 - 3065.

Merghani A, Malhotra A, Sharma S (2016) The U-shaped relationship between exercise and cardiac morbidity. Trends Cardiovasc Med 26 (3) pp 232 – 240

Messier, SP, Legault C, Schoenlank CR et al (2008) Risk factors and mechanisms of knee injury in runners. Medicine & Science in Sports & Exercise 40 (11) pp 1873-1879.

Messier SP, Martin DF, Mihalko SL, et al (2018) A 2-Year Prospective Cohort Study of Overuse Running Injuries: The Runners and Injury Longitudinal Study (TRAILS). Am J Sports Med 46 (9) pp 2211 - 2221

Messier SP, Mihalko SL, Legault C, et al (2013) Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among

overweight and obese adults with knee osteoarthritis: the IDEA randomized clinical trial. JAMA 310 (12) pp 1263 – 1273

Micheo W, Hernández L, Seda C (2010) Evaluation, management, rehabilitation, and prevention of anterior cruciate ligament injury: current concepts. PM R 2 (10) pp 935 - 944

Miller RH (2017) Joint Loading in Runners Does Not Initiate Knee Osteoarthritis. Exerc Sport Sci Rev 45 (2) pp 87 – 95

Miller RH, Edwards RB, Brandon SC, et al (2014) Why don't most runners get knee osteoarthritis? A case for per-unit-distance loads. Med Sci Sports Exerc 46 (3) pp 572 - 579

Mobasheri A, Batt M (2016) An update on the pathophysiology of osteoarthritis. Ann Phys Rehabil Med 59(5-6) pp 333 – 339

Mobasheri A, Matta C, Zakany R (2015) Chondrosenescence: Definition, hallmarks and potential role in the pathogenesis of osteoarthritis Maturitas 80 (3) pp 237 – 244

Morrow JR, DeFina LF, Leonard D, et al (2012) Meeting Physical Activity Guidelines and Musculoskeletal Injury: The WIN Study Med Sci Sports Exerc 44 (10) pp 1986 - 1992

Mosher TJ, Liu Y, Torok CM (2010) Functional cartilage MRI T2 mapping: evaluating the effect of age and training on knee cartilage response to running. Osteoarthritis Cartilage 18 (3) pp 358 – 364

Muadi QI, Nicholson LL, Refshauge KM (2009) Do elite athletes exhibit enhanced proprioceptive acuity, range and strength of knee rotation compared with non-athletes? Scand J Med Sci Sports 19 (1) pp 103 - 112

Mueller MJ, Maluf KS (2002) Tissue adaptation to physical stress: a proposed "Physical Stress Theory" to guide physical therapist practice, education, and research. Phys Ther 82 (4) pp 383 - 403.

Mündermann A, Stefanyshyn DJ, Nigg BM (2001) Relationship between footwear comfort of shoe inserts and anthropometric and sensory factors. Med Sci Sports Exerc 33 (11) pp 1939 – 1945

Murad MH, Asi N, Alsawas M, et al (2016) New evidence pyramid BMJ Evidence-Based Medicine 21 pp 125 - 127

Muraki S, Oka H, Akune T, et al (2009) Prevalence of radiographic knee osteoarthritis and its association with knee pain in the elderly of Japanese

population-based cohorts: the ROAD study. Osteoarthritis Cartilage 17 (9) pp 1137 – 1143

Murphy L, Helmick CG (2012) The impact of osteoarthritis in the United States: a population-health perspective. Am J Nurs 112 (3 Suppl 1) pp S13 - 19
Murphy L, Schwartz TA, Helmick CG, et al (2008) Lifetime risk of symptomatic knee osteoarthritis. Arthritis Rheum 59 (9) pp 1207 - 1213

Muthari SG, Hui M, Doherty M, et al (2011) What If We Prevent Obesity? Risk Reduction in Knee Osteoarthritis Estimated Through a meta-analysis of observational studies Arthritis Care & Research 63 (7) pp 982 – 990

Nagaosa Y, Lanyon P, Doherty M (2002) Characterisation of size and direction of osteophyte in knee osteoarthritis: a radiographic study. Ann Rheum Dis 61 (4) pp 319 – 324

Neogi T, Felson D, Niu J et al (2009) Association between radiographic features of knee osteoarthritis and pain: results from two cohort studies BMJ 339

Neogi T, Zhang Y (2013) Epidemiology of osteoarthritis. Rheum Dis Clin North Am 39 (1) pp 1-19

Neufer PD, Bamman MM, Muoio DM et al (2015) Understanding the Cellular and Molecular Mechanisms of Physical Activity-Induced Health Benefits. Cell Metab 22(1) pp 4-11

Ng M, Fleming T, Robinson M (2014) Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 384 (9945) pp 766 – 781

Nguyen US, Zhang Y, Zhu Y, et al (2011) Increasing prevalence of knee pain and symptomatic knee osteoarthritis: survey and cohort data. Ann Intern Med 155 (11) pp 725 – 732

NHS (2018) Knee pain and other running injuries [Online] Available: https://www.nhs.uk/live-well/exercise/knee-pain-and-other-running-injuries/ Accessed: February 2018

NHS Digital (2017) Statistics on Obesity, Physical Activity and Diet – England 2017 [Online] Available: https://digital.nhs.uk/data-and-information/publications/statistical/statistics-on-obesity-physical-activity-and-diet/statistics-on-obesity-physical-activity-and-diet-england-2017 Accessed: January 2018

NICE (2013) Physical activity: brief advice for adults in primary care [Online] Available: https://www.nice.org.uk/guidance/ph44/chapter/about-this-guidance Accessed: September 2017

NICE (2014) Osteoarthritis: care and management [Online] Available: https://www.nice.org.uk/guidance/cg177 Accessed: July 2016

Nigg BM, Bahlsen HA, Luethi SM (1987) The influence of running velocity and midsole hardness on external impact forces in heel-toe running Journal of Biomechanics 20 (10) pp 951 - 959

Nigg BM, Baltich J, Hoerzer S, et al (2015) Running shoes and running injuries: mythbusting and a proposal for two new paradigms: 'preferred movement path' and 'comfort filter'. Br J Sports Med 49 (20) pp 1290 - 1294

Nightingale EJ, Pourkazemi F, Hiller CE (2014) Systematic review of timed stair tests J Rehabil Res Dev 51 (3) pp 335- 350
Nilsson J, THostensson A (1989) Ground reaction forces at different speeds of human walking and running Acta Physiologica Scandinavica 136 (2) pp 217 - 227

NHS (2017) Couch to 5k [Online] https://www.nhs.uk/live-well/exercise/get-running-with-couch-to-5k/ Accessed: 3 September 2017

Noakes TD, Myburgh KH, Schall R (1990) Peak treadmill running velocity during the VO2 max test predicts running performance. J Sports Sci 8 (1) pp 35 - 45

Noordzij M, Tripepi G, Dekker FW (2010) Sample size calculations: basic principles and common pitfalls. Nephrol Dial Transplant 25 (5) pp 1388 - 1393

Novacheck (1998) The biomechanics of running Gait Posture 7 (1) pp 77 - 95

Noyes FR, Barber SD, Mangine RE (1991). Abnormal lower limb symmetry determined by function hop tests after anterior cruciate ligament rupture. The American journal of sports medicine 19 (5) pp 513-518

Nüesch E, Dieppe P, Reichenbach S, et al (2011) All cause and disease specific mortality in patients with knee or hip osteoarthritis: population based cohort study. BMJ 342 p 1165

Odum SM, van Doren BA, Springer BD (2016) National Obesity Trends in Revision Total Knee Arthroplasty. J Arthroplasty 31 (9 Suppl) pp 136 - 139

Offord DR, Kraemer HC (2000) Risk factors and prevention Evidence-Based Mental Health 3 pp 70-71

Oja P, Kelly P, Pedisic Z, et al (2016) Associations of specific types of sports and exercise with all-cause and cardiovascular-disease mortality: a cohort study of 80 306 British adults Br J Sports Med p 1 – 7

O'Keefe JH, Patil HR, Laview CJ, et al (2012) Potential Adverse Cardiovascular Effects From Excessive Endurance Exercise Mayo Clin Proc 87 (6) pp 587 – 595

Office for National Statistics (2019) Internet Users UK 2019 [Online] Available: https://www.ons.gov.uk/businessindustryandtrade/itandinternetindustry/bulletins/internetusers/2019 Accessed: May 2019
Oremus M, Oremus C, Hall GB, et al (2012) Inter-rater and test-retest reliability of quality assessment by nice student raters using Jadad and Newcastle-Ottawa Scales BMJ Open 2 (4)

Orchard (2010) The OSICS 10.1 [online] Available: https://www.johnorchard.com/osics-downloads.html Accessed: August 2017

O'Reilly SC, Muir KR, Doherty M (1996) Screening for pain in knee osteoarthritis: which question? Ann Rheum Dis 55 (12) pp 931 -933.

Ounpuu (1994) The biomechanics of walking and running. Clin Sports Med 13 (4) pp 843 – 863

Palastanga N, Soames R (2006) Anatomy and Human Movement 6th Edition. Churchill Livingstone; London, UK.

Pannucci CJ, Wilkins EG (2010) Identifying and avoiding bias in research. Plast Reconstr Surg 126 (2) pp 619 - 625

Panush RS, Hanson CS, Caldwell, et al (1995) Is running associated with osteoarthritis? An Eight-Year Follow-up Study J Clin Rheumatol 1 (1) pp 35 – 39

Parkrun (2018) Parkrun Runners in Britain [Online] http://www.parkrun.org.uk/results/historicalchart/ Accessed 4 January 2018

Paschos NK. (2017). Anterior cruciate ligament reconstruction and knee osteoarthritis. World journal of orthopedics, 8 (3) p.212

Pearle AD, Warren RF, Rodeo SA (2005) Basic science of articular cartilage and osteoarthritis. Clin Sports Med 24 (1) pp 1-12

Peat G, Greig J, Wood L, et al (2005) Diagnostic discordance: we cannot agree when to call knee pain 'osteoarthritis'. Family Practice 22 pp 96 - 102.

Peat G, McCarney R, Croft P (2001) Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. Ann Rheum Dis 60 (2) pp 91 – 97

Peat G, Thomas E, Handy J, et al (2006) The Knee Clinical Assessment Study – CAS(K). A prospective study of knee pain and knee osteoarthritis in the general population: baseline recruitment and retention at 18 months. BMC Musculoskeletal Disorders 7 (30)

Peer MA, Lane J (2013) The Knee Injury and Osteoarthritis Outcome Score (KOOS): a review of its psychometric properties in people undergoing total knee arthroplasty. J Orthop Sports Phys Ther 43(1) pp 20 - 28.

Peffers MJ, Balaskas P, Smagul A (2018) Osteoarthritis year in review 2017: genetics and epigenetics. Osteoarthritis Cartilage 26 (3) pp 304-311

Phillips K, Clauw DJ (2013) Central pain mechanisms in the rheumatic diseases: future directions. Arthritis Rheum 65 (2) pp 291 – 302

Podsiadlo D, Richardson S (1991) The timed up and go: a test of basic functional mobility for frail elderly persons J Am Geriatr Soc 39 (2) pp 142 – 148

Potter HG, Jain SK, Ma Y, et al (2012) Cartilage injury after acute, isolated anterior cruciate ligament tear: immediate and longitudinal effect with clinical/MRI follow-up. Am J Sports Med 40 (2) pp 276 - 285

Poulet B, Staines K (2016) New developments in osteoarthritis and cartilage biology Current Opinion in Pharmacology 28, pp 8 – 13

Prieto-Alhambra D, Judge A, Javaid MK, et al (2014) Incidence and risk factors for clinically diagnosed knee, hip and hand osteoarthritis: influences of age, gender and osteoarthritis affecting other joints. Ann Rheum Dis 73 (9) pp 1659 - 1664

Prince SA, Adamo KB, Hamel ME, et al (2008) A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. Int J Behav Nutr Phys Act 6 (5) pp 56 – 79

Prodromos CC, Han Y, Rogowski J, et al (2007) A meta-analysis of the incidence of anterior cruciate ligament tears as a function of gender, sport, and a knee injury-reduction regimen. Arthroscopy 223 (12) pp 1320-1325

Punzi L, Galozzi P, Luisetto R, et al (2016) Post-traumatic arthritis: overview on pathogenic mechanisms and role of inflammation RMD Open 2 p 1 - 9

Rabin R, de Charro F (2001) EQ-5D: a measure of health status from the EuroQol Group. Ann Med 33 (5) pp 337 - 343.

Racunica TL, Teichtahl AJ, Wang Y, et al (2007) Effect of physical activity on articular knee joint structures in community-based adults Arthritis Care & Research 57 (7) pp 1261 - 1268

Ramski DE1, Kanj WW2, Franklin CC, et al (2014) Anterior cruciate ligament tears in children and adolescents: a meta-analysis of nonoperative versus operative treatment. Am J Sports Med 42 (11) pp 2769 -2776

Rannou F, Poiraudeau S (2010) Non-pharmacological approaches for the treatment of osteoarthritis. Best Pract Res Clin Rheumatol 24 (1) pp 93 - 106.

Ratzlaff C, Ashbeck EL, Guermazi A (2018) A quantitative metric for knee osteoarthritis: reference values of joint space loss. Osteoarthritis Cartilage 26 (9) pp 1215 – 1224

Reichenheim ME (2004) Confidence intervals for the kappa statistic The Stata Journal 4 (4) pp 421 -428

Reid A, Birmingham TB, Stratford PW, Alcock GK, et al (2007) Hop testing provides a reliable and valid outcome measure during rehabilitation after anterior cruciate ligament reconstruction. Physical therapy 87 (3) pp.337-349.

Reijaman M, Pols HA, Bergink AP, et al (2007) Body mass index associated with onset and progression of osteoarthritis of the knee but not of the hip: the Rotterdam Study. Ann Rheum Dis 66 (2) pp 158 - 162

Reiner M, Niermann C, Jekauc et al (2013) Long-term health benefits of physical activity--a systematic review of longitudinal studies. BMC Public Health 8(13) p 813

Reyes C, Leyland KM, Peat G, et al (2016) Association between overweight and obesity and risk of clinically diagnosed knee, hip, and hand osteoarthritis: a population-based cohort study Arthritis Rheumatol 68 (8) pp 1869 - 1875.

Richmond SA, Fukuchi RK, Ezzat A et al (2013) Are joint injury, sport activity, physical activity, obesity, or occupational activities predictors for osteoarthritis? A systematic review. J Orthop Sports Phys Ther 43 (8) pp 515 – 519

Rishiraj N, Taunton JE, Lloyd-Smith R, et al (2011) Effect of functional knee brace use on acceleration, agility, leg power and speed performance in healthy athletes Br J Sports Med 45 (15) pp 1230 – 1237

Rodier F, Campisi (2011) Four faces of cellular senescence. J Cell Biol 192 (4) pp 547-556

Robinson RH, Gribble PA (2008) Support for a reduction in the number of trials needed for the star excursion balance test. Arch Phys Med Rehabil 89 (2) pp 364 – 370

Roos EM (2005) Joint injury causes knee osteoarthritis in young adults. Current Opinion in Rheumatology 17 (2) pp.195 – 200

Roos EM, Arden NK (2016) Strategies for the prevention of knee osteoarthritis. Nat Rev Rheumatol 12 (2) pp 92 – 101

Roos EM, Laurén M, Adalberth T, et al (1998) Knee osteoarthritis after meniscectomy: prevalence of radiographic changes after twenty-one years, compared with matched controls. Arthritis Rheum 41 (4) pp 687 - 693.

Roos EM, Lohmander LS (2003) The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis Health Qual Life Outcomes 1 pp 64

Roos EM, Roos HP, Lohmander LS, et al (1998) Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. J Orthop Sports Phys Ther 28 (2) pp 88 – 96

Rothman KJ, Greenland S (2005) Causation and causal inference in epidemiology. Am J Public Health 95 Suppl 1:pp 144 - 150

Running USA (1998) Running in the USA [Online] https://running.imiscloud.com/RUSA/Research/RUSA/Research/Research_Information.aspx?hkey=9f0d1251-55cb-44aa-b9a6-84ed79c23ad9 Accessed: 4 September 2017

Sackett DL, Rosenberg WM, Gray JA (1996) Evidence based medicine: what it is and what it isn't. BMJ 312 (7023) pp 71 – 72

Salaffi F, Ciapetti A, Carotti M (2014) The sources of pain in osteoarthritis: a pathophysiological review. Reumatismo 66 (1) pp 57 – 71

Sanson-Fisher RW, Bonevski B, Green LW, et al (2007) Limitations of the randomized controlled trial in evaluating population-based health interventions. Am J Prev Med 33 (2) pp 1155 - 1161

Saxon L, Finch C, Bass S (1999)Sports Participation, Sports Injuries and Osteoarthritis Implications for Prevention Sports Med 28 (2) pp 123 - 135

Scanzello CR, Goldring SR (2012) The role of synovitis in osteoarthritis

pathogenesis. Bone 51 (2) pp 249 - 257

Scanzello CR, Moskowitz NK, Gibofsky A (2008) The post-NSAID era: what to use now for the pharmacologic treatment of pain and inflammation in osteoarthritis. Curr Rheumatol Rep 10 (1) pp 49 – 56

Schindler OS (2007) Osteochondritis dissecans of the knee Orthopaedics Trauma 21(1) pp 47 - 58

Schiphof D, van Middelkoop M, de Klerk BM et al (2014) Crepitus is a first indication of patellofemoral osteoarthritis (and not of tibiofemoral osteoarthritis). Osteoarthritis Cartilage 22 (5) pp 631 – 638

Schnohr P, Marott JL, Lange P, Jensen GB (2013) Longevity in male and female joggers: the Copenhagen City Heart Study. Am J Epidemiol 177 (7) pp 683 – 689

Schnohr P, O'Keefe JH, Marott JL, et al (2015) Dose of jogging and long-term mortality: the Copenhagen City Heart Study. J Am Coll Cardiol 65 (5) pp 411 - 419

Schouten JS, van den Ouweland FA, Valkenburg HA (1992) A 12 year follow up study in the general population on prognostic factors of cartilage loss in osteoarthritis of the knee. Ann Rheum Dis 51 (8) pp 932 - 937

Seedhom BB, D Dowson D, V Wright V (1974) Proceedings: Functions of the menisci. A preliminary study. Ann Rheum Dis 33 (1) pp 111

Segal NA, Glass NA, Felson DT, et al (2010) The Effect of Quadriceps Strength and Proprioception on Risk for Knee Osteoarthritis Med Sci Sports Exerc 42 (11) pp 2081 - 2088

Sharma L, Cahue S, Song J et al (2003) Physical functioning over three years in knee osteoarthritis: role of psychosocial, local mechanical, and neuromuscular factors. Arthritis Rheum 48 (12) pp 3359 – 3370

Sharma L, Lou C, Cahue S, et al (2000) The mechanism of the effect of obesity in knee osteoarthritis: the mediating role of malalignment. Arthritis Rheum 43 (3) pp 568 - 575.

Sharma L, Lou C, Felson DT (1999) Laxity in healthy and osteoarthritic knees. Arthritis Rheum 42 (5) pp 861 - 870

Sharma L, Pai YC, Holtkamp K, et al (1997) Is knee joint proprioception worse in the arthritic knee versus the unaffected knee in unilateral knee osteoarthritis? Arthritis Rheum 40 (8) pp 1518 – 1525

Shephard RJ (2003) Limits to the measurement of habitual physical activity by questionnaires Brit J Sports Med 37 pp 197 – 206

Shrier I (2004) Muscle dysfunction versus wear and tear as a cause of exercise related osteoarthritis: an epidemiological update British Journal of Sports Medicine 38 (5) pp 526 - 535

Silva PFS, Quintino LF, Franco, et al (2014) Measurement properties and feasibility of clinical tests to assess sit-to-stand/stand-to-sit tasks in subjects with neurological disease: a systematic review Braz J Phys Ther 18 (2) pp 99 – 110

Silvers HJ, Giza ER, Mandelbaum BR (2005) Anterior cruciate ligament tear prevention in the female athlete. Curr Sports Med Rep 4 (6) pp 341 - 343

Silvers HJ, Mandelbaum BR Prevention of anterior cruciate ligament injury in the female athlete Br J Sports Med 41 (Suppl 1) pp 52–59

Silverling S, O'Sullivan E, Garofalo M, et al (2012) Hip osteoarthritis and the active patient: will I run again? Curr Rev Musculoskelet Med 5 (1) pp 24 – 31

Silverwood V, Blagojevic-Bucknall M, Jinks C, et al (2015) Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. Osteoarthritis Cartilage 23 (4) pp 507 – 515

Simic M, Hinman RS, Wrigley TV, et al (2011) Gait modification strategies for altering medical knee joint load: a systematic review Arthritis Care Res (Hoboken) 63 (3) pp 405-426

Simundic AM (2013) Bias in research Biochem Med 23 (1) pp 12 - 15

Singh T, Newman AB (2011) Inflammatory markers in population studies of aging. Ageing Res Rev 10 (3) pp 319 - 329

Slemenda C, Brandt KD, Heilman DK, et al (1997) Quadriceps Weakness and Osteoarthritis of the Knee Annals of Internal Medicine 127 (2) pp 197 - 204

Smith B, Chu LK, Smith TC, et al (2008) Challenges of self-reported medical conditions and electronic medical records among members of a large military cohort BMC Medical Research Methodology 8 pp 37

Smith J, Noble H (2014) Bias in research. Evid Based Nurs 17 (4) pp 100 – 101

Sohn RS, Micheli LJ (1985) The Effect of Running on the Pathogenesis of Osteoarthritis of the Hips and Knees Clinical Orthopaedics 198 pp 106 – 109

Soligard T, Schwellnus M, Alonso JM, et al (2016) How much is too much? (Part 1) International Olympic Committee consensus statement on load in sport and risk of injury Br J Sports Med 50 pp 1030 - 1041.

Souza RB (2016) An Evidence-Based Videotaped Running Biomechanics Analysis Phys Med Rehabil Clin N Am 27 (1) pp 217 - 236.

Spector TD, Cicuttini F, Baker J, et al (1996) Genetic influences on osteoarthritis in women: a twin study. BMJ 312 (7036) pp 940 - 943

Spector TD, MacGregor AJ (2004) Risk factors for osteoarthritis: genetics Osteoarthritis Cartilage 12 pp 39 – 44

Sport England (2016) Active Peoples Survey 2016 [Online] https://www.sportengland.org/research/about-our-research/active-people-survey/ Accessed: 11 December 2017

Springer BA, Marin R, Cyhan T, et al (2007) Normative values for the unipedal stance test with eyes open and closed. Journal of geriatric physical therapy 30 (1) pp.8-15

Stang A (2010) Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of non-randomized studies in meta-analyses Eur J epidemiol 25 (9) pp 603 - 605

Stanley LE, Kerr Zy, Dompier TP et al (2016) Sex Differences in the Incidence of Anterior Cruciate Ligament, Medial Collateral Ligament, and Meniscal Injuries in Collegiate and High School Sports: 2009-2010 Through 2013-2014. Am J Sports Med Jun 44 (6) pp 1565 - 1572

Stratford PW, Kennedy DM, Woodhouse LJ (2006) Performance measures provide assessments of pain and function in people with advanced osteoarthritis of the hip or knee. Phys Ther 86 (11) pp 1489 – 1496

Stribley RF, Albers JW, Tourtellotte WW et al (1974) A quantitative study of stance in normal subjects. Arch Phys Med Rehabil, 55 (2) pp 74-80.

Steultjens MP, Dekker J, van Baar ME et al (2000) Range of joint motion and disability in patients with osteoarthritis of the knee or hip. Rheumatology 39 (9) pp 955 – 961

Steultjens MP, Dekker J, van Baar ME (2001) Muscle strength, pain and disability in patients with osteoarthritis. Clin Rehabil 15 (3) pp 331 – 341

Steultjens MP, Roorda LD, Dekker et al, (2001) Responsiveness of observational and self-report methods for assessing disability in mobility in patients with osteoarthritis Arthritis Care and Research 45 (1) pp 56 – 61

Strath SJ, Kaminsky LA, Ainsworth BE et al (2013) Guide to the assessment of physical activity: Clinical and research applications: a scientific statement from the American Heart Association. Circulation 128 (20) pp 2259 – 2279

Strobl J, Cave E, Walley T (2000) Data protection legislation: interpretation and barriers to research. BMJ 321 (7265) pp 890 - 892.

Suri S, Gill SE, Massena de Camin S et al (2007) Neurovascular invasion at the osteochondral junction and in osteophytes in osteoarthritis. Ann Rheum Dis 66 (11) pp 1423 – 1428

Suri S, Walsh DA (2012) Osteochondral alterations in osteoarthritis. Bone 51 (2) pp 204 – 211

Susser M (1991) What is a cause and how do we know one? A grammar for pragmatic epidemiology. Am J Epidemiol 133 (7) pp 635 - 648

Swart NM, van Linschoten R, Bierma-Zeinstra SM, et al (2012) The additional effect of orthotic devices on exercise therapy for patients with patellofemoral pain syndrome: a systematic review. Br J Sports Med 46 (8) pp 570 - 577

Szebenyi B, Hollander AP, Dieppe P et al (2006) Associations between pain, function, and radiographic features in osteoarthritis of the knee. Arthritis Rheum 54 (1) pp 230 - 235

Taşkıran E, Taşkıran D, Duran T, et al (1998) Articular cartilage homeostasis after anterior cruciate ligament reconstruction Knee Surgery, Sports Traumatology, Arthroscopy 6 (2) pp 93 - 98

Tat SK, Lajeunesse D, Pelletier J-Pet al (2010) Targeting subchondral bone for treating osteoarthritis: what is the evidence? Best Pract Res Clin Rheumatol 24 (1) pp 51 – 70

Taunton JE, Ryan MB, Clement DB, et al (2002) A retrospective case-control analysis of 2002 running injuries Br J of Sports Med 36 pp 95 - 101

Teichtahl A, Wluka A, Cicuttini FM (2003) Abnormal biomechanics: a precursor or result of knee osteoarthritis? British Journal of Sports Medicine 37 (4) pp 289 – 290

Teichtahl AJ, Wluka AE, Wijethilake P, et al (2015) Wollf's law in action: a mechanism for early knee osteoarthritis. Arthritis Res Ther 1: 17 p 207

Terwee CB, Bot SD, de Boer MR, et al (2007) Quality criteria were proposed for measurement properties of health status questionnaires. J Clin Epidemiol 60 (1) pp 34 – 42

Terwee CB, Mokkink LB, Steuljens MP, et al (2006) Performance-based methods for measuring the physical function of patients with osteoarthritis of the hip or knee: a systematic review of measurement properties Rheumatology (Oxford) 45 (7) pp 890 - 902

Tesarz J, Schuster AK, Hartman M, et al (2012) Pain perception in athletes compared to normally active controls: a systematic review with meta-analysis Pain 153 (6) pp 1253 - 1262

Thomas E, Peat G, Croft P (2014) Defining and mapping the person with osteoarthritis for population studies and public health. Rheumatology 53 (2) pp 338 -345

Thomas MJ, Wood L, Selfe J, et al (2010) Anterior knee pain in younger adults as a precursor to subsequent patellofemoral osteoarthritis: a systematic review. BMC Musculoskelet Disord 9 (11) p 201.

Thorlund JB, Juhl CB, Roos EM, et al (2015) Arthroscopic surgery for degenerative knee: systematic review and meta-analysis of benefits and harms BMJ 350

Tiku ML, Sabaawy HE (2015) Cartilage regeneration for treatment of osteoarthritis: a paradigm for nonsurgical intervention. Ther Adv Musculoskelet Dis 7 (3) pp 76 - 87

Timmins KA, Leech RD, Batt ME et al (2017) Running and Knee Osteoarthritis: A Systematic Review and Meta-analysis. Am J Sports Med 45 (6) pp 1447 – 1457

Tolk JJ, Janssen RPA, Prinsen CAC, et al (Measurement properties of the OARSI core set of performance-based measure for hip osteoarthritis: a prospective cohort study on reliability, construct validity and responsiveness in 90 hip osteoarthritis patients Acta Orthopaedica 90 (1) pp 15 - 20

Toomey CM, Whittaker JL, Nettel-Aguierre A et al (2017) Higher Abdominal Fat in Youth and Young Adults 3–10 Years Following a Sport-related Knee Injury Osteoarthritis Cartilage 25 (S1) pp S338 –S339

Topolovec-Vranic J, Natarajan K (2016) The use of social media in recruitment for medical research studies: a coping review J Med Internet Res 18 (11) p 286

Torres L, Dunlop DD, Peterfy C et al (2006) The relationship between specific tissue lesions and pain severity in persons with knee osteoarthritis. Osteoarthritis Cartilage 14 (10) pp 1033 – 1040

Tortora GJ, Derrickson B (2007) Principles of Anatomy of Physiology 11th Edition. Biological Sciences Textbooks Inc, Hoboken, USA.

Tran G, Smith TO, Grice A, et al (2016) Does sports participation (including level of performance and previous injury) increase risk of osteoarthritis? A systematic review and meta-analysis British Journal of Sports Medicine 50 (23) pp 1459 – 1466

Trepczynski A, Kutzner I, Kornaropoulos E (2012) Patellofemoral Joint Contact Forces during Activities with High Knee Flexion Journal of Orthopaedic Research 30 pp 408 - 415

Troosters T, Gosselink R, Decramer M (1999) Six minute walking distance in healthy elderly subjects Eur Respir J 14 (2) pp 270 – 274

Trost SG, Blair SN, Khan KM (2014) Physical inactivity remains the greatest public health problem of the 21st century: evidence, improved methods and solutions using the '7 investments that work' as a framework Br J Sports Med 48 pp 169 - 170

Turkiewicz A, Petersson IF, Björk J et al. (2014) Current and future impact of osteoarthritis on health care: a population-based study with projections to year 2032. Osteoarthritis Cartilage 22 (11) pp 1826 – 1832

Urquhart DM, Tobing JF, Hanna FS et al (2011) What is the effect of physical activity on the knee joint? A systematic review. Med Sci Sports Exerc 43 (3) pp 432 – 442

Valdes AM, Doherty M, Spector TD (2008) The additive effect of individual genes in predicting risk of knee osteoarthritis. Ann Rheum Dis 67 (1) pp 124 – 127

Valdes AM, Loughlin J, van Oene M, et al (2007) Sex and Ethnic Differences in the Association of ASPN, CALM1, COL2A1, COMP, and FRZB With Genetic Susceptibility to Osteoarthritis of the Knee Arth Rheum 56 (1) pp 137 - 146

Valdes AM, Spector TD (2011) Genetic epidemiology of hip and knee osteoarthritis. Nat Rev Rheumatol 7 (1) pp 23 - 32

Van Belle G (2008). Statistical rules of thumb. Second edition. John Wiley & Sons Inc, New Jersey.

Van der Kraan PM, van den Berg (2007) Osteophytes: relevance and biology Osteoarthritis Cartilage 15 (3) pp 237 – 244

Van der Worp MP, Ten Haaf DS, van Cingel R et al (2015) Injuries in runners; a systematic review on risk factors and sex differences. PloS one *10*(2)

Vandenbroucke JP, von Elm E, Altman DG, et al (2007) Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration Epidemiology 18 (6) pp 805 - 835

Van Dijk GM, Dekker J, Veenhof C, et al (2006) Course of functional status and pain in osteoarthritis of the hip or knee: a systematic review of the literature. Arthritis Rheum 55 (5) pp 779 – 785

Van Gent R.N, Siem D, van Middelkoop M et al (2007) Incidence and determinants of lower extremity running injuries in long distance runners: a systematic review. British journal of sports medicine, 41 (8) pp.469 - 480.

Van Hout B, Janssen MF, Feng YS, et al (2012) Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health (5) pp 708 - 715

Van Laar M, Pergolizzi JV, Mellinghoff HU (2012) Pain treatment in arthritis-related pain: beyond NSAIDs. Open Rheumatol J 6 pp 320 – 330

Van Lummel RC, Walgaard S, Hobert MA, et al (2016) Intra-rater, inter-rater and test-retest reliability of an instrumented timed up and go (iTUG) test in patients with Parkinson's disease PLoS One 11 (3)

Van Mechelen W, Hlobil H, Kemper HC (1992) Incidence, severity, aetiology and prevention of sports injuries. A review of concepts. Sports Med 14 (2) pp 82 - 99.

Van Meer BL, Meuffels DE, van Eijsden WA et al (2015) Which determinants predict tibiofemoral and patellofemoral osteoarthritis after anterior cruciate ligament injury? A systematic review. Br J Sports Med 49 (15) pp 975 – 983

Van Melick N, van Cingel RE, Brooijmans F et al (2016) Evidence-based clinical practice update: practice guidelines for anterior cruciate ligament rehabilitation based on a systematic review and multidisciplinary consensus. Br J Sports Med 50 (24) pp 1506-1515

Verhagen E (2012) Prevention of running-related injuries in novice runners: are we running on empty? Br J Sports Med 46 (12) pp 836 - 837.

Viannini F, Spalding T, Andriolo L (2016) Sport and early osteoarthritis: the role of sport in aetiology, progression and treatment of knee osteoarthritis. Knee Surg Sports Traumatol Arthrosc 24 (6) pp 1786 – 1796

Vignon E, Valat JP, Rossignol M et al (2006) Osteoarthritis of the knee and hip and activity: a systematic international review and synthesis (OASIS). Joint Bone Spine 73 (4) pp 442 – 455

Vincent KR, Vincent HK (2012) Resistance Exercise for Knee Osteoarthritis PMR 4 (50) p S45–S52

Von Elm E, Altman DG, Egger M, et al (2007) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2370 (9596) pp 1453 – 1457

Vos T, Flaxman AD, Naghavi M, et al (2012) Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380 (9859) pp 2163 - 2196

Wachsmuth L, Soder S, Fan Z et al (2016) Immunolocalization of matrix proteins in different human cartilage subtypes Histology and Histopathology 21 pp 477 – 485

Walter SD, Elisasziw M, Donner A (1998) Sample size and optimal designs for reliability studies Statistics in Medicine 17 (1) pp 101 -110

Wang X, Hunter D, Xu J, et al (2015) Metabolic triggered inflammation in osteoarthritis. Osteoarthritis Cartilage 23 (1) pp 22-30

Warburton DE, Nicol CW, Bredin SS (2006) Health benefits of physical activity: the evidence. CMAJ 174 (6) pp 801 -809

Wellsandt E, Axe MJ, Snyder-Mackler L (2018) Poor performance on single-legged hop tests associated with development of posttraumatic knee osteoarthritis after anterior cruciate ligament injury. Orthopaedic Journal of Sports Medicine 6 (11)

Wenham CY, Conaghan PG (2010) The role of synovitis in osteoarthritis. Ther Adv Musculoskelet Dis 2 (6) 349 3-59

Whittaker JL, Woodhouse LJ, Netterl-Aguirre A, et al (2015) Outcomes associated with early post-traumatic osteoarthritis and other negative health consequences 3-10 years following knee joint injury in youth sport. Osteoarthritis Cartilage 23 (7) pp 1122 – 1129

WHO (2002) Towards a Common Language for Functioning, Disability and Health [Online] Available: http://www.who.int/classifications/icf/training/icfbeginnersguide.pdf Accessed: December 2017

Wilk KE, Romaniello WT, Soscia SM, et al (1994) The relationship between subjective knee scores, isokinetic testing, and functional testing in the ACL-

reconstructed knee. Journal of Orthopaedic & Sports Physical Therapy 20 (2) pp 60-73.

Wilkie R, Blagojevic-Bucknall M, Jordan KP, et al (2013) Reasons Why Multimorbidity Increases the Risk of Participation Restriction in Older Adults With Lower Extremity Osteoarthritis: A Prospective Cohort Study in Primary Care Arthritis Care and Research 65 (6) pp 910 – 919

Williams PT (2013) Effects of Running and Walking on Osteoarthritis and Hip Replacement Risk Med Sci Sports Exerc 45 (7) pp 1292 - 1297

Wilson MG, Ellison GM, Cable NT (2015) Basic science behind the cardiovascular benefits of exercise Heart 101 pp 758 – 765

Wong M, Wuethrich P, Eggli P et al (1996) Zone-specific cell biosynthetic activity in mature bovine articular cartilage: A new method using confocal microscopic stereology and quantitative autoradiography Journal of Orthopaedic Research 14 (3) pp 424 – 432

Xergia SA, Pappas E, Zampeli F, et al (2013) Asymmetries in functional hop tests, lower extremity kinematics, and isokinetic strength persist 6 to 9 months following anterior cruciate ligament reconstruction. J Orthop Sports Phys Ther 43 (3) pp 154 - 162

Yeung SS, Yeung EW, Gillespie LD (2011) Interventions for preventing lower limb soft-tissue running injuries. Cochrane Database of Systematic Reviews (7)

Yusuf E, Kortekaas MC, Watt I et al (2011) Do knee abnormalities visualised on MRI explain knee pain in knee osteoarthritis? A systematic review. Ann Rheum Dis 70 (1) pp 60 - 67

Zadpoor AA, Nikoooyan AA (2011) The relationship between lower-extremity stress fractures and the ground reaction force: a systematic review. Clin Biomech 26 (1) pp 23 -38

Zheng H, Chen C (2015) Body mass index and risk of knee osteoarthritis: systematic review and meta-analysis of prospective studies. BMJ Open 5 (12)

Zhang M, Egan B, Wang J (2015) Epigenetic mechanisms underlying the aberrant catabolic and anabolic activities of osteoarthritic chondrocytes Int J Biochem Cell Biol 67 pp 101 - 109

Zhang W, Nuki G, Moskowitz RW et al (2010) OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. Osteoarthritis Cartilage 18 (4) pp 476 – 499

10 Appendices

Appendix 1

1. osteoarthr*.tw.
2. exp osteoarthritis/
3. arthrosis.tw.
4. Chronic pain/
5. (Degenerative adj3 joint).tw.
6. 1 or 2 or 3 or 4 or 5
7. knee/
8. exp knee joint/
9. knee$.tw.
10. 7 or 8 or 9
11. 6 and 10
12. (knee adj3 pain*).tw.
13. (disabilit* adj3 knee*).tw.
14. exp osteoarthritis, knee/
15. 12 or 13 or 14
16. 11 or 15
17. exp Running/
18. run$.tw.
19. jog$.tw.
20. sprint$.tw.
21. treadmill$.tw.
22. orienteer$.tw.
23. triathlon$.tw.
24. $marathon$.tw.
25. athletics.tw.
26. (race* or racing).tw.
27. athlete*.tw.
28. "track and field".tw.
29. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. 16 and 29
31. exp animals/ not humans.sh.
32. 30 not 31
33. limit 32 to english language
34. limit 33 to yr="1883 - 2018"

S29	S15 AND S28
S28	S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27
S27	TX "track and field"
S26	TX (race* OR racing)
S25	TX athlet*
S24	DE "ATHLETICS"
S23	TX marathon*
S22	TX triathlon*
S21	DE "TRIATHLON" OR DE "IRONMAN triathlons"
S20	TX orienteer*
S19	TX treadmill*
S18	TX sprint*
S17	TX Run OR runs OR running
S16	DE "RUNNING" OR DE "CROSS-country running" OR DE "JOGGING" OR DE "LONG-distance" OR DE "MIDDLE distance running" OR DE "ROAD running" OR DE "SPRINTING" OR DE "MARATHON running" OR DE "ULTRAMARATHON running"
S15	S13 OR S14
S14	S9 AND S10
S13	S11 OR S12

S14	S9 AND S10
S13	S11 OR S12
S12	TX (disabilit* N3 knee*)
S11	TX knee N3 pain*
S10	S1 OR S2 OR S3 OR S4 OR S5 OR S6
S9	S7 OR S8
S8	TX knee or patella
S7	DE "KNEE"
S6	TX "degenerative N3 joint"
S5	TX "chronic pain"
S4	DE "CHRONIC pain"
S3	TX arthros*
S2	TX osteoarthr* OR "osteo arthr*"
S1	DE "OSTEOARTHRITIS"

Limited to 2018

☐	34	limit 33 to yr="1883 - 2018"
☐	33	limit 32 to english language
☐	32	30 not 31
☐	31	exp animal/ not exp human/
☐	30	16 and 29
☐	29	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
☐	28	"track and field".tw.
☐	27	athlete*.tw.
☐	26	(race* or racing).tw.
☐	25	athletics.tw.
☐	24	$marathon$.tw.
☐	23	triathlon$.tw.
☐	22	orienteer$.tw.
☐	21	treadmill$.tw.
☐	20	sprint$.tw.
☐	19	jog$.tw.
☐	18	run$.tw.
☐	17	exp running/
☐	16	11 or 15
☐	15	12 or 13 or 14
☐	14	exp osteoarthritis, knee/
☐	13	(disabilit* adj3 knee*).tw.
☐	12	(knee adj3 pain*).tw.
☐	11	6 and 10
☐	10	7 or 8 or 9
☐	9	knee$.tw.
☐	8	exp knee joint/
☐	7	knee/
☐	6	1 or 2 or 3 or 4 or 5
☐	5	(degenerative adj3 joint).tw.
☐	4	chronic pain/
☐	3	arthrosis.tw.
☐	2	exp osteoarthritis/
☐	1	osteoarthr*.tw.

Appendix 2

parkrun research summary



PHYSICAL ACTIVITY AND YOUR HEALTH

The beneficial impact of physical activity on health is well known. We also know that being inactive is linked to many diseases. In relation to running, one of the most popular pastimes in the UK, most individuals are at no greater risk of osteoarthritis and the health benefits far outweigh risks of injury/illness resulting from participation. One difficulty with this research is the lack detailed physical activity data, especially running data.

We are experienced sports Medicine clinicians and academics based at Queens Medical Centre, University of Nottingham. We regularly work with the general public, elite professional and Olympic athletes.

We seek to conduct world-leading research to help understand the relationship between chronic disease, such as osteoarthritis, and physical activity, such as running. We invite all parkrunners to become involved in our research. We hope that it will become the largest study ever undertaken that explores physical activity, other modifiable risk factors, and health.

If you are aged 18 or over, we encourage you to sign up, whether or not you have any health or knee problems. Also please sign up regardless of how often you run (or even if you never run!). We want to recruit people who are very active, those who are inactive, and everyone in-between!

If you enrol, we will ask you to complete a questionnaire when you join the study [http://tinyurl.com/haloquestionnaire]. This will enable us to get an understanding of who you are, how much physical activity/running you do and the effects on your overall health, including your knee joints.

If you agree for us to contact you again, a follow-up questionnaire will be sent after roughly 12 months, and regularly thereafter. We will invite a small number of people to be assessed by our physiotherapists at centres around the country to investigate the effect of running on joint function, the impact of performance on joint health and also to look at the link between genetics and risk of injury. Taking part in these sub-groups is entirely voluntary – participation is optional at every stage.

This study seeks to explore the long-term effect of physical activity, including running, and other risk factors (e.g. diet) and how these relate to the risk of disease, including osteoarthritis. One aim in particular will evaluate individuals who participate regularly in recreational running and the development of knee osteoarthritis over time. In doing so, it is hoped that novel clinical practices may be highlighted and developed.



Appendix 3

Participant Information Sheet for Q1 and Q2



Participant Information Sheet

Title: The health of adults' longitudinal observational study (HALO)

You have been invited to take part in this research study. Before you decide whether to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends and relatives if you wish to. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether you wish to take part or not. Should you wish to become involved in this study, please retain a copy of this information sheet for your records.

Thank you for reading this.

Name of Investigators:

Chief investigator: Dr Kim Edwards
Course Director: Sports and Exercise Medicine
Academic Orthopaedics, Trauma and Sports Medicine
University of Nottingham
C Floor, West Block, Queen's Medical Centre
Nottingham, NG7 2UH

Background

Many health conditions, including cardiovascular disease, type 2 diabetes, cancers and chronic lung disease, mental illness and osteoarthritis, are linked to what are called 'modifiable risk factors' which are physical inactivity, obesity, smoking and poor diet. The health burden of these conditions in developed countries is expected to worsen, mainly due to population ageing and continued rises in risk factors. This presents a large challenge to policy makers and researchers alike. One difficulty is the lack of data of sufficient quality, particularly detailed physical activity data, and lack of such data at multiple time points over many years.

What does the study involve?

No intervention is required as part of the study, we simply wish to observe your lifestyle choices and behaviours and how this relates to your health. This study would involve completing an initial online questionnaire (we can post you a hard copy if you prefer), which we anticipate will take approximately 30 minutes to complete.

At the end of the questionnaire we will ask you if we can contact you again about this study. If you consent we will send you the other two initial questionnaires (which also take about 30 minutes to complete). Then (if you wish) we will send a follow-up questionnaire after roughly 12 months, then further questionnaires every 2-5 years. We plan to collect data for at least 15 years. You can withdraw from the study at any time.

Some data to be collected is more onerous, e.g. in terms of the time or cost of collecting the data. Accordingly these data will only be gathered from smaller sub-groups of all participants. If you consent to being contacted again, from time to time we would invite you to participate in these studies. Full details about these studies would be provided at the time. Participation would be entirely optional and would not affect whether you continue to participate in the questionnaire element of the study or not. In short, you could do as much or as little as you wish.

Why have you been chosen?

We are recruiting people from all walks of life. We would like to recruit very active people, very inactive people, and everyone in-between. If you are aged 18 or over, we would like you to complete our questionnaire.

Do you have to take part?

It is up to you to decide whether or not to take part. Your completion of the online questionnaire is considered your consent to be involved in the study.

If you decide to take part you are still free to withdraw at any time and without giving a reason.

What do you have to do?

If you wish to take part, if you are reading this on our website, then the questionnaire will start automatically at the end of this page. If you are reading a paper version, please go to the following link (or contact us for a paper version of the questionnaire): http://tinyurl.com/haloquestionnaire

If you do not wish to take part, please feel free to close down this window/leave this website/throw away this document.

Please note, as a participant in our study, we would not require any alteration to your lifestyle choices. No change in running participation or any other sporting activity would be expected, nor any change in diet or other lifestyle behaviours. Should you make any changes to your behaviours (e.g. stopping running) in the future, we would hope that you would continue with your involvement in our study as this may provide significant information that is important as part of our analysis.

What are the side effects of any treatment or procedures received when taking part?

There is no intervention within this study, therefore there are no possible side effects.

What are the possible disadvantages and risks of taking part?

Participant data shall be securely protected throughout the study. There is a minimal risk, for example due to unforeseen circumstance or human error, that some data is accessible by someone other than the research authors. Thorough measures shall be put in place by the authors to ensure that the chances of this happening are negligible. All study data will be anonymised and password protected.

What if something goes wrong? Who can you complain to?

In case you have a complaint about your treatment by a member of staff or anything to do with the study, you can initially approach the lead investigator (Dr Kim Edwards), details below.

If this achieves no satisfactory outcome, you should then contact the University of Nottingham Faculty of Medicine and Health Research Ethics Committee Secretary:

Mrs Louise Sabir,
Division of Therapeutics and Molecular Medicine,
D Floor, South Block,
Queens Medical Centre,
Nottingham, NG7 2UH

Telephone 0115 8231063

E-mail louise.sabir@nottingham.ac.uk.

In the unlikely event that you suffer injury to yourself or damage to your property as a result in taking part in this research, the University does have an insurance policy to cover harm arising as a result of the defect in the design of the study. In addition, all medical practitioners taking part in the research have personal medical negligence cover.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept on a password-protected database and is strictly confidential. Any information about you that leaves the research unit will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?

Results from the study will be published in various sources, including PhD thesis, MSc dissertations, and academic peer reviewed journals. In addition, we hope to present this work at academic conferences internationally. No participants will not be identified in any report / publication.

Who is organising and funding the research?

This study is sponsored by the University of Nottingham. Academic support from tenured staff within Academic Orthopaedics, Trauma and Sports Medicine in the University of Nottingham, who are associated with the Arthritis Research UK Centre for Sport, Exercise and Osteoarthritis, will support the long term study. RL is funded by the University of Nottingham and Arthritis Research UK through the Arthritis Research UK Centre for Sport, Exercise and Osteoarthritis.

Who has reviewed the study?

This study has been reviewed and approved by the University of Nottingham Faculty of Medicine and Health Research Ethics Committee. It has also been agreed with the parkrun Research Board and the University of Sydney Research Ethics Committee.

Contact for Further Information

Primary point of contact for general enquiries:
Mr Richard Leech
Arthritis Research UK Centre for Sport, Exercise & Osteoarthritis
Academic Orthopaedics, Trauma and Sports Medicine
University of Nottingham
South Block C Floor
Queen's Medical Centre
Nottingham, NG7 2UH
Email: theHALOstudy@nottingham.ac.uk

Chief Investigator:
Dr Kim Edwards
Course Director: Sports and Exercise Medicine
Academic Orthopaedics, Trauma and Sports Medicine
University of Nottingham
C Floor, West Block, Queen's Medical Centre
Nottingham, NG7 2UH
Email: kimberley.edwards@nottingham.ac.uk

Appendix 3

Participant Information Sheet (Training diaries)

Title: The health of adults' longitudinal observational study (HALO)

The validity of self-reported physical activity measures from recreational athletes in the HALO Study

You have been invited to take part in this research study. Before you decide whether to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends and relatives if you wish to. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether you wish to take part or not. Should you wish to become involved in this study, please retain a copy of this information sheet for your records.

Thank you for reading this.

Name of Investigators:

Chief investigator: Dr Kim Edwards (principal supervisor and PI)
BSc (Hons), MMedSci, PhD, PGCAP, SFHEA
Course Director: Sports and Exercise Medicine
Academic Orthopaedics, Trauma and Sports Medicine
University of Nottingham
C Floor, West Block, Queen's Medical Centre
Nottingham, NG7 2UH

Background

Many health conditions, including cardiovascular disease, type 2 diabetes, cancers and chronic lung disease, mental illness and osteoarthritis, are linked to what are called 'modifiable risk factors' which are physical inactivity, obesity, smoking and poor diet. The health burden of these conditions in developed countries is expected to worsen, mainly due to population ageing and continued rises in risk factors. This presents a large challenge to policy makers and researchers alike. One difficulty is the lack of data of sufficient quality, particularly detailed physical activity data, and lack of such data at multiple time points over many years.

The HALO study is a large study investigating the relationship between physical activity and health. As part of this we need to understand physical activity in great detail and we are asking a small number of people for comprehensive physical activity data.

What does the study involve?

No intervention is required as part of the study, we simply wish to understand what physical activity you do.

Do you already keep a diary about your training? This could be a written diary, by hand or electronic; or use of an app; Nike+; GPS data; fitbit; pedometer; Garmin; heart rate monitor; etc. If yes, we would like a copy of these data. It doesn't matter whether you are very active or very inactive.

We plan to analyse them to understand more about your physical activity. This will give us very detailed information about your physical activity to compare to your health in the future. Thus participation in this study will only require you sending us copies of your existing data, preferably your data for the last 12 months.

Why have you been chosen?

You have been chosen because you are a participant of the HALO study who has consented to being contacted again and who has indicated that you keep a training diary.

Do you have to take part?

It is up to you to decide whether or not to take part. Your participation is entirely voluntary.

If you decide to take part you are still free to withdraw at any time and without giving a reason.

What do you have to do?

If you wish to take part, please respond to our invitation email sending us your training diary (which may or may not be in multiple formats).
If you do not wish to take part, please ignore this email.

What are the side effects of any treatment or procedures received when taking part?

There is no intervention within this study, therefore there are no possible side effects.

What are the possible disadvantages and risks of taking part?

Participant data shall be securely protected throughout the study. We will anonymise your training diary data upon receipt. There is a minimal risk, for example due to unforeseen circumstance or human error, that some data is accessible by someone other than the research authors. Thorough measures shall be put in place by the authors to ensure that the chances of this happening are negligible.

What if something goes wrong? Who can you complain to?

In case you have a complaint on your treatment by a member of staff or anything to do with the study, you can initially approach the lead investigator (Dr Kim Edwards), details below.

If this achieves no satisfactory outcome, you should then contact the University of Nottingham Faculty of Medicine and Health Research Ethics Committee Secretary:

Mrs Louise Sabir,
Division of Therapeutics and Molecular Medicine, D Floor, South Block,
Queens Medical Centre,
Nottingham, NG7 2UH
Telephone 0115 8231063

E-mail louise.sabir@nottingham.ac.uk.

In the unlikely event that you suffer injury to yourself or damage to your property as a result in taking part in this research, the University does have an insurance policy to cover harm arising as a result of the defect in the design of the study. In addition, all medical practitioners taking part in the research have personal medical negligence cover.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept on a password-protected database and is strictly confidential. Any information about you that leaves the research unit will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?

Results from the study will be published in various sources, including PhD thesis, MSc dissertations, and academic peer reviewed journals. In addition, we hope to present this work at academic conferences internationally. No participants will not be identified in any report / publication.

Who is organising and funding the research?

This study is sponsored by the University of Nottingham. Academic support from tenured staff within Academic Orthopaedics, Trauma and Sports Medicine in the University of Nottingham, who are associated with the Arthritis Research UK Centre for Sport, Exercise and Osteoarthritis, will support the long term study.

Who has reviewed the study?

This study has been reviewed and approved by the University of Nottingham Faculty of Medicine and Health Research Ethics Committee.

Contact for further information

Primary point of contact for general enquiries:

[intern name]: Academic Orthopaedics, Trauma and Sports Medicine
University of Nottingham
C Floor, West Block, Queen's Medical Centre
Nottingham, NG7 2UH

Email: theHALOstudy@nottingham.ac.uk

Chief Investigator:
Dr Kim Edwards
Course Director: Sports and Exercise Medicine
Academic Orthopaedics, Trauma and Sports Medicine
University of Nottingham
C Floor, West Block,
Queen's Medical Centre
Nottingham, NG7 2UH
Email: kimberley.edwards@nottingham.ac.uk

Appendix 4

Participant information sheet: functional testing

Participant Information Sheet

Title: The health of adults' longitudinal observational study (HALO)

You have been invited to take part in this research study. Before you decide whether to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends and relatives if you wish to. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether you wish to take part or not. Should you wish to become involved in this study, please retain a copy of this information sheet for your records.

Thank you for reading this.

Name of Investigators:

Chief investigator:

Dr Kim Edwards
Course Director: Sports and Exercise Medicine
Academic Orthopaedics, Trauma and Sports Medicine
University of Nottingham
C Floor, West Block, Queen's Medical Centre
Nottingham, NG7 2UH

Co-investigators:

Professor Mark Batt
Director: Arthritis Research UK Centre for Sport, Exercise and Osteoarthritis
Consultant Sport & Exercise Medicine
Arthritis Research UK Centre for Sport, Exercise & Osteoarthritis
Queen's Medical Centre, Nottingham, NG7 2UH

Professor Brigitte Scammell
Professor of Orthopaedics and Head of Academic Orthopaedics, Trauma and Sports Medicine
Academic Orthopaedics, Trauma and Sports Medicine
University of Nottingham
C Floor, West Block, Queen's Medical Centre
Nottingham, NG7 2UH

Mr Richard Leech
Arthritis Research UK Centre for Sport, Exercise & Osteoarthritis
Academic Orthopaedics, Trauma and Sports Medicine
University of Nottingham
South Block C Floor, Queen's Medical Centre
Nottingham, NG7 2UH

Background

It is well known that regular physical exercise has many health benefits including protection against obesity, type 2 diabetes and cardiovascular disease. Sport and exercise are the most obvious forms of physical activity and recreational running is one of the most popular pastimes in the UK. Yet, conversely, running participation suffers from negative press that reinforces the widely held perception running will have a detrimental effect on weight-bearing joints, especially the knee. However the balance of previous research suggests that this is not the case - but these were small investigations and a larger study is needed. Another problem with the data is that detailed information about running participation and functional ability are not collected.

Knee osteoarthritis is one of the most common musculoskeletal conditions requiring healthcare intervention, and can be very disabling. Because of the paradox between the known link between regular physical activity and good health and the fear of running leading to knee osteoarthritis, it is imperative that the association between running and the risk of knee osteoarthritis is clarified.

What does the study involve?

The purpose of this testing is to assess function and knee joint health. In total, the testing should take no more than one hour on two occasions. You will need to come to the Queens Medical Centre [insert other location for participants in the other UK city locations if we know where that participant lives (optional question on baseline questionnaire) or list all locations if address not known] for these tests.

This assessment will comprise of a short discussion with a physiotherapist to review current knee health and any history of injury. The 12 physical tests are very simple to complete. Please wear comfortable clothing. In summary the tests involve:

- Moving from a seated position to a standing position for half a minute;
- Walking up a flight of nine stairs;
- Walking 40m as fast as you can;
- Raising from a chair to standing with a short walk;
- Seeing how far you can walk in six minutes;
- How far you can hop (in three hops)
- Balancing on one leg;
- Another balancing on one leg exercise (slightly different);
- Measurement of knee joint and thigh circumference;
- Assessment of range of movement;

- The presence or absence of crepitus (noise) during movement
- Seated knee joint height

We would like to carry out these tests in the next month or so and then to repeat these tests after roughly 12 months. We would assess the data to identify any change in values and how these relate to any symptoms relating to your knee joint reported on your questionnaire.

Why have you been chosen?

You may remember that you completed a questionnaire for this study recently. As you indicated a preference that you would be interested to participate in further aspects of our research, this information is provided for your consideration.

Do you have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason.

What do you have to do?

If you wish to take part in the study, please do so by contacting the authors directly via the email address (or telephone number) provided below to arrange a mutually convenient appoint for the tests.

What are the side effects of any treatment or procedures received when taking part?

There is no intervention within this study, therefore there are no possible side effects.

What are the possible disadvantages and risks of taking part?

No. The tests are non-invasive and there are no risks to taking part.

That said, we will ask you to declare any reasons that may cause problems to complete the test. Specifically:

- No undiagnosed, acute knee joint injury that the participant feels would prevent them from being able to undertake the tests in a pain free manner
- No recent surgery (for any reason) that would otherwise prevent full participation in normal physical and functional requirements
- No co-morbidities that alter balance such as any condition that causes dizziness or light-headedness

This should prevent anyone from completing the test that could potentially feel soreness or discomfort during the test. Despite the simplicity of the test, there still may be some who complete the tests that have minimal discomfort. A qualified physiotherapist shall be present throughout testing.

Participant data shall be securely protected throughout the study. There is a minimal risk, for example due to unforeseen circumstance or human error, that some data is accessible by someone other than the research authors. Thorough measures shall be put in place by the authors to ensure that the chances of this happening are negligible. All study data will be anonymised and password protected.

What are the possible benefits of taking part in this study?

You will not benefit directly from participation in this study but the results from the study may allow us to better understand the association between running and the risk of knee osteoarthritis, for optimal joint health in runners.

What if something goes wrong? Who can you complain to?

In case you have a complaint on your treatment by a member of staff or anything to do with the study, you can initially approach the lead investigator (Dr Kim Edwards), details below.

If this achieves no satisfactory outcome, you should then contact the University of Nottingham Faculty of Medicine and Health Research Ethics Committee Secretary:

Mrs Louise Sabir,
Division of Therapeutics and Molecular Medicine,
D Floor, South Block,
Queens Medical Centre,
Nottingham, NG7 2UH

Telephone 0115 8231063

E-mail louise.sabir@nottingham.ac.uk.

In the unlikely event that you suffer injury to yourself or damage to your property as a result in taking part in this research, the University does have an insurance policy to cover harm arising as a result of the defect in the design of the study. In addition, all medical practitioners taking part in the research have personal medical negligence cover.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept on a password-protected database and is strictly confidential. Any information about you that leaves the research unit will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?

Results from the study will be published in various sources, including PhD thesis and academic peer reviewed journals. In addition, we hope to present this work at academic conferences internationally. No participants will not be identified in any report / publication.

Who is organising and funding the research?

This study is sponsored by the University of Nottingham. Academic support from tenured staff within Academic Orthopaedics, Trauma and Sports Medicine in the University of Nottingham, who are associated with the Arthritis Research UK Centre for Sport, Exercise and Osteoarthritis, will support the long term study. RL is funded by the University of Nottingham and Arthritis Research UK through the Arthritis Research UK Centre for Sport, Exercise and Osteoarthritis.

Who has reviewed the study?

This study has been reviewed and approved by the University of Nottingham Faculty of Medicine and Health Research Ethics Committee.

Contact for Further Information

Primary point of contact for general enquiries:
Mr Richard Leech
Arthritis Research UK Centre for Sport, Exercise & Osteoarthritis
Academic Orthopaedics, Trauma and Sports Medicine
University of Nottingham
South Block C Floor
Queen's Medical Centre
Nottingham, NG7 2UH
Email: msxrl5@nottingham.ac.uk [change to study email address when available]

Chief Investigator:
Dr Kim Edwards
Course Director: Sports and Exercise Medicine
Academic Orthopaedics, Trauma and Sports Medicine
University of Nottingham
C Floor, West Block, Queen's Medical Centre
Nottingham, NG7 2UH
Email: kimberley.edwards@nottingham.ac.uk

Appendix 5

Consent Form

(this all fits on to one side of A4 when formatted on its own)



Consent Form

Title: The health of adults' longitudinal observational study (HALO)

Name of Investigator:

Mr Richard Leech

Arthritis Research UK Centre for Sport, Exercise & Osteoarthritis,
Academic Orthopaedics, Trauma and Sports Medicine, University of Nottingham
South Block C Floor, Queen's Medical Centre, Nottingham, NG7 2UH

Please read this form and sign it once the above named or their designated representative, has explained fully the aims and procedures of the study to you. Please initial each box once you have read and understood each statement.

I voluntarily agree to take part in this study.	☐
I confirm that I have been given a full explanation by the above named and that I have read and understand the information sheet given to me which is attached.	☐
I have been given the opportunity to ask questions and discuss the study with the above investigator, or their deputies, on all aspects of the study and have understood the advice and information given as a result.	☐
I agree to comply with the reasonable instructions of the investigator and will notify him immediately of any unexpected unusual symptoms or deterioration of health.	☐
I authorise the investigators to disclose the results of my participation in the study but not my name.	☐
I understand that information about me recorded during the study will be kept in a secure database. If data is transferred to others it will be made	☐

anonymous. Data will be kept for 7 years after the results of this study have been published.

I authorise the investigators to disclose to me any abnormal test results. ☐

I understand that I can ask for further instructions or explanations at any time. ☐

I understand that I am free to withdraw from the study at any time, without having to give a reason for withdrawing. ☐

I confirm that I have disclosed relevant medical information before the study. ☐

For completion by the participant:

Name: .....

Signature: ..... Date: .....

For completion by the investigator:

I confirm that I have fully explained the purpose of the study and what is involved to:

.....

I have given the above named a copy of this form together with the information sheet.

Investigators Signature: ..... Date: .....

Investigators Name:.....

Participant Unique ID Number: .....

Appendix 6



Participant Information Sheet

Title: **The health of adults' longitudinal observational study (HALO)**

You may remember that you have previously completed one (or more) questionnaire(s) already for this study, and you consented to being contacted again. Accordingly, you are invited to take part in this next stage of the project. Before you decide whether to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends and relatives if you wish to. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether you wish to take part or not. Should you wish to become involved in this study, please retain a copy of this information sheet for your records.

Thank you for reading this.

Name of Investigators:

Chief investigator:

Dr Kim Edwards
Course Director: Sports and Exercise Medicine
Academic Orthopaedics, Trauma and Sports Medicine
University of Nottingham
C Floor, West Block, Queen's Medical Centre
Nottingham, NG7 2UH

Co-investigators:

Professor Mark Batt
Director: Arthritis Research UK Centre for Sport, Exercise and Osteoarthritis
Consultant Sport & Exercise Medicine
Arthritis Research UK Centre for Sport, Exercise & Osteoarthritis
Queen's Medical Centre, Nottingham, NG7 2UH

Professor Brigitte Scammell
Professor of Orthopaedics and Head of Academic Orthopaedics, Trauma and Sports Medicine
Academic Orthopaedics, Trauma and Sports Medicine
University of Nottingham
C Floor, West Block, Queen's Medical Centre
Nottingham, NG7 2UH

Mr Richard Leech

Arthritis Research UK Centre for Sport, Exercise & Osteoarthritis
Academic Orthopaedics, Trauma and Sports Medicine
University of Nottingham
South Block C Floor, Queen's Medical Centre
Nottingham, NG7 2UH

Background

Many health conditions, including cardiovascular disease, type 2 diabetes, cancers and chronic lung disease, mental illness and osteoarthritis, are linked to what are called 'modifiable risk factors' which are physical inactivity, obesity, smoking and poor diet. The health burden of these conditions in developed countries is expected to worsen, mainly due to population ageing and continued rises in risk factors. This presents a large challenge to policy makers and researchers alike. One difficulty is the lack of data of sufficient quality, particularly detailed physical activity data, and lack of such data at multiple time points over many years.

At this time, we are especially interested in physical activity (e.g. running) completed during the last 12 months and whether or not these have had any effect on your musculoskeletal health (e.g. your muscles, bones, joints) or if there has been any change in symptoms (e.g. joint pain or stiffness).

What does the study involve?

No intervention is required as part of the study, we simply wish to observe your lifestyle choices and behaviours and how this relates to your health. To take part, you will be required to complete the online questionnaire (we can post you a paper copy if you prefer), which we anticipate will take 15-20 minutes to complete. Some of the questions you will have answered before in previous questionnaires, but by answering them again, we can see if there has been any change.

We plan to send you further follow-up questionnaires roughly every 2-5 years. You can withdraw from the study at any time.

Why have you been chosen?

Runners from the UK and Australia were invited to take part in our study. You may remember that you completed an initial questionnaire for this study about a year ago. In that questionnaire you consented to being contacted again. You may have completed other questionnaires, but everyone is invited to take part in this questionnaire regardless of how much or how little you have previously done. Accordingly, you have been invited to take part in this research study.

Do you have to take part?

It is up to you to decide whether or not to take part. Your completion of the online questionnaire is considered your consent to be involved in the study.

If you decide to take part you are still free to withdraw at any time and without giving a reason. Participation shall have no effect on your involvement in parkrun or any other running or exercise.

What do I have to do?

If you wish to take part, the questionnaire can be accessed via the link in the email.

If you would prefer to complete a paper version of the questionnaire, please contact the researchers using the email address given below and we will post one to you.

If you do not wish to take part, please feel free to close down this window/leave this website.

Please note, as a participant in our study, we would not require any alteration to your lifestyle choices. No change in running participation or any other sporting activity would be expected, nor any change in diet or other lifestyle behaviours. Should you make any changes to your behaviours (e.g. stopping running) in the future, we would hope that you would continue with your involvement in our study as this may provide significant information that is important as part of our analysis.

What are the side effects of any treatment or procedures received when taking part?

There is no intervention within this study, therefore there are no possible side effects.

What are the possible disadvantages and risks of taking part?

Participant data shall be securely protected throughout the study. There is a minimal risk, for example due to unforeseen circumstance or human error, that some data is accessible by someone other than the research authors. Thorough measures shall be put in place by the authors to ensure that the chances of this happening are negligible. All study data will be anonymised and password protected.

What if something goes wrong? Who can I complain to?

In case you have a complaint on your treatment by a member of staff or anything to do with the study, you can initially approach the lead investigator (Dr Kim Edwards), details below.

If this achieves no satisfactory outcome, you should then contact the University of Nottingham, Faculty of Medicine and Health Research Ethics Committee Secretary:

Mrs Louise Sabir,
Division of Therapeutics and Molecular Medicine,
D Floor, South Block,
Queens Medical Centre,
Nottingham, NG7 2UH

Telephone 0115 8231063

E-mail louise.sabir@nottingham.ac.uk.

In the unlikely event that you suffer injury to yourself or damage to your property as a result in taking part in this research, the University does have an insurance policy to cover harm arising as a result of the defect in the design of the study. In addition, all medical practitioners taking part in the research have personal medical negligence cover.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept on a password-protected database and is strictly confidential. Any information about you that leaves the research unit will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?

Results from the study will be published in various sources, including PhD thesis, MSc dissertations, and academic peer reviewed journals. In addition, we hope to present this work at academic conferences internationally. No participants will not be identified in any report / publication.

Who is organising and funding the research?

This study is sponsored by the University of Nottingham. Academic support from tenured staff within Academic Orthopaedics, Trauma and Sports Medicine in the University of Nottingham, who are associated with the Arthritis Research UK Centre for Sport, Exercise and Osteoarthritis, will support the long term study. RL is funded by the University of Nottingham and Arthritis Research UK through the Arthritis Research UK Centre for Sport, Exercise and Osteoarthritis.

Who has reviewed the study?

This study has been reviewed and approved by the University of Nottingham Faculty of Medicine and Health Research Ethics Committee. It has also been agreed with the parkrun Research Board.

Contact for Further Information

Primary point of contact for general enquiries:

Mr Richard Leech
Arthritis Research UK Centre for Sport, Exercise & Osteoarthritis
Academic Orthopaedics, Trauma and Sports Medicine
University of Nottingham
South Block C Floor
Queen's Medical Centre
Nottingham, NG7 2UH
Email: thehalostudy@nottingham.ac.uk

Chief Investigator:
Dr Kim Edwards
Course Director: Sports and Exercise Medicine
Academic Orthopaedics, Trauma and Sports Medicine
University of Nottingham
C Floor, West Block, Queen's Medical Centre
Nottingham, NG7 2UH
Email: kimberley.edwards@nottingham.ac.uk