Stratification of patellofemoral pain using clinical, biomechanical and imaging features

Benjamin Timothy Drew

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Co-author contribution

This research has been carried out by a team with my own contributions and the contributions of the other members explicitly indicated below**:**

Chapter 3 - Which patellofemoral joint imaging features are associated with patellofemoral pain? Systematic review and meta-analysis

BD carried out the conception and design of the study with supervision of AR, TS and PC. BD and FP conducted the collection and assembly of the data with any discordance resolved by TS. All the authors (BD, AR, FP, TS and PC) contributed to the analysis and interpretation of the data. BD drafted the chapter and all the authors revised the chapter. BD takes the responsibility for the integrity of the work as a whole from inception to the finished chapter.

Chapter 4 - Patellofemoral joint morphology of middle aged people with patellofemoral pain measured using 3D MRI quantitative technology: data from the Osteoarthritis Initiative

BD, MB and PC conceived the idea and design of the study with support from AR, SK and BDu. BD collected and assembled the data with statistical support from BDu and technical support from MB. All authors (BD, MB, AR, BDu, SK and PC) contributed to the analysis and interpretation of the data. BD drafted the chapter and all the authors revised the chapter. BD takes the responsibility for the integrity of the work as a whole from inception to the finished chapter.

Chapter 5 - The development of data-derived subgroups in patellofemoral pain using modifiable clinical, biomechanical and imaging features

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Chapter 6 - The effect of targeted treatment on people with patellofemoral pain: a pragmatic randomised controlled feasibility study

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- **Drew BT**, Bowes MA, Redmond AC, Dube B, Kingsbury S, Conaghan PG. (2017). Patellofemoral morphology is not related to pain when using 3D quantitative analysis: data from the Osteoarthritis Initiative. *Rheumatology*. 56 (12), 2135-2144.

Conference oral presentations

- **Drew BT**, Redmond AC, Smith TO, Penny F, Conaghan PG. Which patellofemoral joint imaging features are associated with patellofemoral pain? Systematic review and meta-analysis*. International Patellofemoral Pain Research Retreat, September 2015.*

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Conference Poster presentations

- **Drew BT**, Redmond AC, Conaghan PG. StrOPP: Stratification of patellofemoral pain using clinical, biomechanical and imaging features. *AR UK Sports, Exercise & Osteoarthritis Conference 2014, December 2014.*

- **Drew BT,** Conaghan PG, Smith TO, Selfe J, Redmond AC. Targeted treatment for young people with knee pain. *NIHR Annual Trainee Conference 2016, December 2016.*

- **Drew BT,** Conaghan PG, Smith TO, Selfe J, Redmond AC. Targeted treatment for young people with knee pain. *Annual Postgraduate Research Symposium, April 2017.*

- **Drew BT**, Bowes MA, Redmond AC, Dube B, Kingsbury S, Conaghan PG. Patellofemoral bone morphology is related to gender but not pain: 3D quantitative data analysis from OAI. *Osteoarthritis Research Society International (OARSI) 2017, April 2017.*

- **Drew BT**, Bowes MA, Redmond AC, Dube B, Kingsbury S, Conaghan PG. Patellofemoral bone morphology is not associated to pain using 3D quantitative analysis: data from the OAI. *4th British Association of Sport & Exercise Medicine Annual Conference, October 2017.*

Abstract

Patellofemoral pain (PFP) is a common musculoskeletal complaint and the efficacy of current therapies aimed at PFP is limited. The aetiology of PFP is widely considered to be multifactorial and as a result the clinical presentation is often heterogeneous. In an attempt to address this issue, an international PFP consensus statement, published in 2013, highlighted the need to sub-group patients with PFP to enable more stratified interventions.

A multi-methodological approach was used in this thesis. A systematic review of the existing imaging literature in PFP demonstrated that PFP is associated with a number of imaging features in particular MRI bisect offset and CT congruence angle and that some of these features should be modifiable with conservative treatment. A retrospective analysis investigating the overall 3D shape and 3D equivalents of commonly used PFJ imaging features demonstrated no differences between a group with and without PFP, challenging the current perceptions on the structural associations to PFP. A cross-sectional cluster analysis using modifiable clinical, biomechanical and imaging features identified four subgroups that are present in PFP cohort with a Weak group showing the worst prognosis at 12 months. Lastly, a pragmatic randomised controlled feasibility study comparing matched treatment to usual care management showed that matching treatment to a specific subgroup is feasible in terms of adherence, retention and conversion to consent.

In summary, the findings of this thesis improves our understanding of the structural associations to PFP; the subgroups that exist within the PFP population; the natural prognosis of these PFP subgroups; and the feasibility of targeting treatment at PFP subgroups within a clinical trial.

Benjamin Drew
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List of Abbreviations

2D	Two-dimensional
3D	Three-dimensional
AAM	Active appearance model
AAR	Active angle reproduction
ADLS	Activities of daily living
AKP	Anterior Knee Pain
AKPS	Anterior Knee Pain Score
ANOVA	Analysis of variance
ASIS	Anterior superior iliac spine
ASM	Active shape model
BFR	Blood flow restriction
BMI	Body Mass Index
BSO	Bisect offset
BW	Body weight
CA	Congruence angle
CAST	Calibrated anatomical systems technique
CI	Confidence intervals
Cine PC	Cine Phase Contrast
CKC	Closed kinetic chain
COG	Centre of gravity
CONSORT	Consolidated Standards of Reporting Trials
CT	Computed tomography
DAG	Directed acyclic graph
dGEMRIC	Delayed gadolinium enhanced MRI of cartilage
EMG	Electromyography
FIQ	Functional Index Questionnaire
fMRI	Functional magnetic resonance imaging
FPI	Foot Posture Index
FWB	Full weight bearing
GAG	Glycosaminoglycan
GEE	Generalised estimating equations
GP	General Practitioner
GROC	Global rating of change scale
HCA	Hierarchical cluster analysis
ICC	Intraclass correlation coefficient
IFP	Infrapatellar fat pad
IKD	Isokinetic dynamometer
IKDC	International Knee Documentation Committee
IMMPACT	Initiative on Methods, Measurement and Pain Assessment in Clinical Trials
IRB	Institutional review board

ITB	Iliotibial band
kg/BW	Kilograms per body weight
KL	Kellgren & Lawrence
KOOS	Knee injury and osteoarthritis outcome score
LBP	Lower back pain
LDA	Linear discriminant analysis
LPA	Lateral patellofemoral angle
LR	Likelihood ratio
MAR	Missing at random
MCFIQ	Modified functional index questionnaire
MCID	Minimal clinically important difference
MD	Mean difference
MOAKS	MRI Osteoarthritis Knee Score
MP:LP ratio	Medial patella : Lateral patella ratio
MRC	Medical Research Council
MRI	Magnetic resonance imaging
MT	Matched treatment group
N/E	Not examined
NIHR	National Institute for Health Research
NOS	Newcastle-Ottawa Scale
Nm	Newton metre
NRS	Numerical rating scale
NWB	Non weight-bearing
OA	Osteoarthritis
OAI	Osteoarthritis Initiative
OKC	Open kinetic chain
OR	Odds ratio
PAR	Passive angle reproduction
PCA	Principal component analysis
PFJ	Patellofemoral joint
PFJRF	Patellofemoral join reaction force
PFOA	Patellofemoral osteoarthritis
PFP	Patellofemoral pain
PFPS	Patellofemoral pain syndrome
PPT	Pain pressure threshold
PROM	Patient reported outcome measure
PSIS	Posterior superior iliac spine
PTA	Patella tilt angle
RCT	Randomised controlled trial
RMS	Root mean square
ROM	Range of movement
RPE	Rate of perceived exertion
SA	Sulcus angle
SD	Standard deviation

SEM	Standard error of the mean
SMD	Standardised mean difference
SSM	Statistical shape models
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
tAB	Total area of subchondral bone
TFJ	Tibiofemoral joint
TiDiER	Template for Intervention Description and Replication
TKR	Total knee replacement
TNJ	Talonavicular joint
TwoStep CA	SPSS TwoStep cluster analysis
UC	Usual care group
UK	United Kingdom
US	Ultrasound
UTD	Unable to detect
VAS	Visual Analogue Score
VAS-u	Usual Visual Analogue Score
VAS-w	Worst Visual Analogue Score
VL	Vastus lateralis
VMO	Vastus medialis obliquus
WB	Weight bearing
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
WPAIQ	Work Productivity and Activity Impairment Questionnaire
X^2	Chi squared test
XR	X-ray

Chapter 1 - Introduction

1.1 Background

Patellofemoral pain (PFP), is a term often used synonymously with anterior knee pain [1]. PFP is characterised by a gradual onset of pain related to changes to the patellofemoral joint (PFJ) and not associated with any other knee condition [2]. It is often exclusively linked to loaded activities such as stairs, running etc.[3] and is rarely reported with unloaded activities except for reported pain with prolonged flexion [4]. Experts believe that PFP may be a precursor to patellofemoral osteoarthritis [5] forming a disease continuum, however, this link remains unsubstantiated at present [6].

The typical age range for people with PFP is from adolescence up to 40 years. A recent UK epidemiological study estimates that one in six adults consulting their general practitioner for knee pain will be diagnosed with PFP [7] and in adolescents the reported point prevalence of PFP is 6% [8]. Given that UK population estimates show that the 15-39 age group equates to over 26% of the whole population [9] and with longitudinal studies revealing that 77 to 91% of people with PFP will experience pain for over 10 years [10]; the potential societal burden from PFP is of concern. People with PFP are known, as a result of the pain, to reduce their physical activity [11] which instils negative beliefs toward physical activity and may lead to a major impact on their future health [3].

A variety of theories on the origins of pain in PFP have been proposed. These include patellar malalignment, abnormal tissue homeostasis, lateral retinacula hyper-innervation and subchondral bone irritation [12, 13]. There is still, however, no consensus with regards to pathogenesis of PFP. The cause of PFP is widely accepted to be multifactorial in nature and an extensive number of associated factors have been identified [14]. These factors have been classified as distal (e.g. foot), local (e.g. patellofemoral joint) and proximal (e.g. hip) comprising of clinical, biomechanical and imaging features.

Consensus does exist, however, that non-surgical, conservative management is the primary treatment of choice [15] . Multimodal treatment is widely considered best practice [16] which can include combinations of interventions such as taping, knee orthoses , gait-retraining, foot orthoses, muscle strengthening and muscle stretching [17, 18]. Despite this being the accepted treatment approach, 62% of adolescents with PFP still report an unfavourable outcome following treatment and 40% of young adults from pooled data (n=330) report a

similar unfavourable outcome one year following rehabilitation [19]. This shows that the variability in treatment outcome remains considerable.

The inconsistency in treatment outcomes suggests sub-groups may exist within the PFP population [14]. Currently, there is limited hard evidence to support the existence of sub-groups or potential for stratification in treatment of PFP. This notion is however supported by an international consensus statement, developed by international PFP experts, which states: “identification of the subgroups remains the ‘holy grail’ for PFP research” [20]. There is a paucity of research investigating the interrelationship between the local, distal and proximal factors [20], which may refine potential subgroups further.

Stratified approaches to care for other musculoskeletal conditions have demonstrated improved treatment outcomes [21]. With a widespread belief that separate, identifiable subgroups exist within the PFP population [20, 22], then there is a clear need to attempt to identify these sub-groups. Aligning imaging features to both clinical and biomechanical features provides a greater holistic assessment of PFP and an opportunity to develop definitive sub-groups. The modelling of outcomes may then allow stratified interventions to be developed and limit the likely progression of pathology.

1.2 Aims & objectives

The central hypothesis underpinning this thesis is:

Improved subgrouping of people with PFP based on modifiable features will enable stratification and targeting of interventions

The overarching aim of the thesis is to identify PFP subgroups with modifiable features that could be targeted with stratified treatment. To fulfil this aim the following objectives were identified:

- To determine which imaging features are most associated with PFP

- To analyse the structure of the patellofemoral joint using commonly used imaging features converted into their 3D quantitative equivalents

- To determine which diagnostic subgroups are present in a PFP cohort by combining modifiable clinical, biomechanical and imaging features.

- To explore the prognosis of these data derived subgroups

- To explore the feasibility of a targeted intervention, matched to the characteristic of a selected subgroup, compared to usual care management

1.3 Thesis structure & overview

Chapter Two: *Narrative literature review*

This narrative literature review comprises of five main themes that underpin the thesis: i) current clinical, biomechanical and imaging features associated with PFP; ii) current interventions for treating PFP; iii) proposed mechanism of action for these interventions; iv) predictors of response for these interventions; v) current stratification and classification methods used for PFP. These themes are used to demonstrate the need for stratification in PFP. This chapter also includes a detailed background to the natural history, pathogenesis, risk factors and clinical examination of PFP thus providing context to this thesis.

Chapter Three - *Which patellofemoral joint imaging features are associated with patellofemoral pain? Systematic review and meta-analysis*

This is a systematic literature review and meta-analysis of the imaging features associated with PFP. This review aims to control for confounding factors such as loading and knee flexion angle in order to compare imaging features and their association to PFP. The strengths and weakness of the current literature are discussed in terms of their methodological quality and the impact of full weight bearing imaging is also analysed.

Chapter Four - *Patellofemoral joint morphology of middle aged people with patellofemoral pain measured using 3D MRI quantitative technology: data from the Osteoarthritis Initiative*

This is a retrospective analysis of the Osteoarthritis Initiative database using 3D quantitative technology. This chapter aims to investigate whether commonly reported imaging features converted into their 3D quantitative equivalents differ between those with and without PFP,

and between genders. In this chapter, 13 PFP imaging features are investigated between an older group (>45 years) with PFP but without osteoarthritis (KL grade =0) and a similar group without PFP. Finally, the overall bone shape is explored between groups.

Chapter Five - *The development of data-derived subgroups in patellofemoral pain using modifiable clinical, biomechanical and imaging features*

This is a longitudinal cohort study with a cross-sectional analysis exploring the presence of diagnostic subgroups in a PFP cohort by combining modifiable clinical, biomechanical and imaging features. This chapter uses a SPSS TwoStep cluster analysis of ten features, applied within a two-stage approach, to derive modifiable data driven subgroups from a PFP cohort. Relevant patient characteristics such as age, gender BMI etc. are used as descriptors within these groups to provide further context. Using a logistic regression, adjusted for known confounders, the prognosis of these subgroups is assessed at 12 month follow up.

Chapter Six - *The effect of targeted treatment on people with patellofemoral pain: a pragmatic, randomised controlled feasibility study*

This is a feasibility study investigating targeted treatment in PFP. This chapter aims to explore the feasibility of a targeted hip strengthening intervention, matched to a subgroup with baseline hip weakness, compared to usual care management. In addition, the chapter explores the mechanism of effect of the hip strengthening in a group defined as ‘weak’. This chapter aims to inform a larger randomised controlled trial in the future as well as improving our understanding of why hip strengthening may improve symptoms in people with PFP.

Chapter Seven: *Discussion, future directions and conclusions*

This closing chapter discusses the main findings of the thesis with reference to any updated literature, limitations of the thesis as a whole, the future directions for research and the eventual conclusions that can be drawn.

Chapter 2 - Literature review

This literature review will aim to explore the need for stratification by showing that patellofemoral pain (PFP) is a condition of: i) multifactorial aetiology; ii) with multiple relevant targets for intervention; and iii) multiple treatment options with heterogeneous responses. Each section of the literature review is summarised critically showing how it links to stratification. The addition of sections devoted to terminology, epidemiology and outcomes provide context to the review. This review includes literature published up until May 2016. An update of the research from May 2016 to present is provided in Chapter 7.

2.1 Definition

There is no universally accepted definition of patellofemoral pain (PFP). Table 2.1 shows the definitions used in the latest three Cochrane reviews published on the subject of PFP. Despite these definitions being different, they do show common themes regarding: the location of pain (e.g. pain in the patella region), functional limitations (e.g. pain with load activities such as stairs etc.) and exclusion of other differential diagnosis (e.g. patellar tendinopathy etc.). It has been suggested that PFP may in essence be a diagnosis by exclusion [23].

Table 2.1: Definitions of PFP

Study	Definition
van der Heijden *et al.* (2015) [24]	Patellofemoral pain syndrome (PFPS) is characterised by retropatellar pain (behind the kneecap) or peripatellar pain (around the kneecap), mostly occurring when load is put on the knee extensor mechanism such as when climbing stairs, squatting, running, cycling or sitting with flexed knees The diagnosis is based on these symptoms after excluding other distinct knee pathologies, which potentially cause anterior knee pain
Smith *et al.* (2015) [25]	PFPS is characterised by pain behind and around the patella, which is aggravated during prolonged sitting, descending stairs or slopes, squatting or kneeling
Callaghan *et al.* (2012) [26]	Patellofemoral pain syndrome refers to the clinical presentation of knee pain related to changes in the patellofemoral joint. Patellofemoral pain syndrome usually has a gradual onset of pain with none of the features associated with other knee injuries or diseases

2.2 Terminology

The terminology and nomenclature surrounding PFP is widely accepted as being ambiguous [1].This poses a problem clinically as there are number of reported examples of mismanagement in terms of surgery and conservative treatment [1]. The first published description of the PFP clinical presentation we consider today used the term “internal derangement of the knee”[27], however, in reality this encompassed both PFJ and tibiofemoral joint (TFJ) conditions [28]. In the early 1900s, surgeons began to attribute patellar chondral lesions as the source of pain following meniscal surgery. Slowly the term “chondromalacia patellae’ was coined and began to be ascribed to the current PFP presentation seen today [28]. The presence of chondromalacia patellae has repeatedly been shown to be poorly correlated to pain [29] and notably Scott Dye allowed a colleague to perform an arthroscopy under no anaesthesia in order to establish which knee structures are symptomatic[30]. They found an absence of any sensation over the articular patella cartilage suggesting the chondromalacia patellae is very unlikely to be the source of pain in PFP.

The movement away from using the term chondromalacia patellae meant that by the 1970s, ‘patella malalignment’ begun to be used to describe this clinical presentation [31] and this resulted in other terms such as lateral patella pressure syndrome etc. However, due to the fact that not all people presenting with PFP have malalignment and with the reported failure of many alignment surgeries [31], the term lateral patella pressure syndrome is not currently recognised, despite malalignment still being attributed as one of the primary causes for the condition.

The terms anterior knee pain (AKP), patellofemoral pain syndrome and patellofemoral pain have been used interchangeably. The International Patellofemoral Study Group, with a membership of predominantly orthopaedic surgeons, currently advocates the term ‘anterior knee pain’ [32]. Thomeé *et al.* (1999) [33] suggested that AKP encompasses a number of distinct pathologies and once these have been excluded patellofemoral pain (syndrome) can then be diagnosed. This in essence suggests that PFP is a diagnosis by exclusion. The terms anterior knee pain syndrome and patellofemoral pain syndrome, Grelsamer *et al.* (2009) [1] argues, are useless, nonspecific and potentially inappropriate as a *syndrome* is collection of consistent clinical signs and symptoms [1], which due the multifactorial nature of PFP, is a definition that PFP does not satisfy. Of particular note is the change in terminology

used in the International Patellofemoral Pain Research Retreat consensus documents[14, 20, 34], published biennially, in which the first consensus statement [34] used patellofemoral pain syndrome whereas subsequent publications[14, 20] have dropped the term *syndrome* potentially in reaction to the published views of Grelsamer *et al.* (2009) [1]. Currently, it appears that the most widely accepted terminology to be patellofemoral pain with the majority of publications on this condition choosing to use this nomenclature. Hereafter, 'patellofemoral pain' (PFP) will be the preferred term used in this thesis to encompass all synonymous terms including patellofemoral pain syndrome, anterior knee pain and chondromalacia patellae.

2.3 Natural History/ Epidemiology

2.3.1 Natural history of PFP

PFP was long considered a benign, self-limiting condition that would improve with time [10]. A number of longitudinal studies [10, 35-37] have refuted this, with data showing the presence of pain persisting in the majority of cases at three to 16 years following diagnosis.

It was firstly shown [36, 37] that, at an average of four years follow up, 94% (51/54) people still reported pain. Of these people, 54% reported the pain to be the same or worse and 52% reported some activity restriction. At an average 5.7 years, Blond and Hansen (1998) [35] found that 73% still complained of pain with 48% reporting pain worse or the same and 74% reporting a reduction in athletic activity. At an 11 year follow-up following diagnosis, Stathopulu and Baildam (2003) [10] reported that 91% (20/22) still had pain and that 45% (10/22) reported that their daily life is affected. In the largest follow up conducted at 16 years [36], 77% (38/49) people were found to still report pain.

These studies show that pain is still present in 73-94% of people up to 16 years follow-up, which strongly rejects the view of PFP as a self-limiting condition. They demonstrate that pain severity and functional restriction remain unchanged or increased in 48-54% and 45-74% respectively, although this functional restriction varies in terms of expected demand e.g. athletic ability versus daily life[37]. On the other hand, this would still suggest that over half experience an improvement in pain over time and supports data which is often omitted in the literature, that at 16 years follow up, 73% of the 38 patients with pain reported at least some improvement in symptoms. This may explain how PFP was once considered self-limiting.

2.3.2 Link between PFP and PFOA

There is a concern that approximately 50% of PFP cases who report on-going pain and functional limitation may develop future patellofemoral osteoarthritis (PFOA), with PFP having been implicated as a potential precursor to PFOA [5]. A few studies have supported this theory. Utting *et al.* (2005) [38] found that 22% of patients who had undergone an arthroplasty for isolated PFOA reported experiencing PFP symptoms in adolescence and early adulthood. This was supported by the results of Thorstensson *et al.* (2009) [39] who showed in a cohort of people with chronic knee pain aged 35-54 years, that 32% (9/28) developed isolated PFOA at seven year follow-up having shown no radiographic OA at baseline. A comprehensive review of the literature [6] suggests most studies that support the associations between PFP and PFOA were not primarily designed to answer this question and conclude, despite expert opinion proposing this relationship [5], that current literature is unable to substantiate a clear link between both conditions.

2.3.3 Prevalence and incidence of PFP

The prevalence data surrounding PFP has been widely criticised for its unrepresentative sources and so the real-world prevalence remains unknown [40]. Prevalence is defined as the number of cases of a particular condition at a single point in time [41]. Callaghan and Selfe (2007) [40] conducted a review of the sources of prevalence data, finding that much of the prevalence data cited is based on secondary or even tertiary referencing with some of the source data considered unrepresentative. The current figures cited in the literature for the adult population are typically based on athletes [42] and military personnel [43]. In these studies the prevalence is cited to be between 14% and 25% of all knee injuries [42, 43]. In the general public, Wood *et al.* (2011) [7] analysed 57,555 GP diagnostic codes annually in the UK to show that ‘patellofemoral disorders’ comprised of 17% (303/1782) of all knee consultations. This is comparable to data from the Netherlands [44] which showed that 11% of GP diagnostic codes for knee pain was given as ‘patellofemoral pain syndrome’.

Incidence is defined as the number of new cases of a particular condition within the same population during a set time period [41]. A review of the literature showed that the incidence range was between 9% (over 12 weeks) and 17% (over two years) [45]. This comprised almost solely of sporting and military participants, however, it is perhaps understandable considering that increased physical activity is a risk factor for the development of PFP. In contrast, Boling *et al.* (2010) [43] followed 1525 midshipman finding a significantly lower

incidence rate of 2.2% (over 2.5 years). It is unclear what may have contributed to this lower figure, however, the same study does demonstrate that females were over twice as likely to develop PFP compared to males suggesting that the female to male ratio of any cohort will likely influence the overall incidence reported.

There is a tendency across the majority of epidemiological studies related to PFP to focus on a group greater than 18 years old; a feature which may be the result of ethical restrictions [46]. A few studies have explored age groups between 10 – 19 years old [8, 47-49]. Two studies explored the prevalence of AKP (encompassing a range of conditions including PFP) and two specifically focused on PFP [8, 49]. The studies focused on AKP show very similar prevalence rates of 27% (183/688) [47] and 27% (331/1210) [48]. Foss *et al.* (2012) [47], under the umbrella term of 'anterior knee pain', showed that the other specific conditions such as patella tendinopathy, Osgood-Schlatter disease represented 11% of the overall figure thus leaving 16% to account for the prevalence of PFP. In adolescent athletes, PFP had a prevalence of 16% [49], which is comparable to the data from Foss *et al.* (2012) [47] minus the other conditions e.g. Osgood- Schlatter etc. Mølgaard *et al.* (2011) [8], [49] only found that PFP showed a younger population prevalence of 6%, based on Danish students. As prevalence data is often compiled from large distinct populations, it is likely that an athletes will present with different risk factors to the general student population [20]. Prevalence data recording is also reliant on people seeking treatment from a primary clinician. Rathleff *et al.* (2013) [50] looked at the care seeking behaviour of adolescents with PFP showing that 47% (163/344) with insidious knee pain had not sought treatment. The reason for this figure is unknown but the authors did show that individuals were more likely to seek treatment for traumatic rather than an insidious onset.

As well as the established prevalence of PFP within adolescents, Rathleff *et al.* (2016) [11] has recently showed in a cohort aged 15-19 years (n=504) that compared to other knee pathologies, people with PFP showed a significant reduction in both sports and leisure time participation over a two year follow up period. As highlighted by the authors, this significant reduction in activity for young people with PFP could lead to serious lifestyle consequences and a more sedentary lifestyle [11].

2.3.4 Health economics

In terms of health economics, Tan *et al.* (2010) [51] provides the only cost-utility analysis of exercise for PFP. Based on data from a high quality RCT [52] they showed that whilst direct

medical costs were significantly higher in an intervention group, likely as a result of the additional physiotherapy intervention. The overall societal costs for the intervention group (€1011) were significantly less than control group (€1166) because they included productivity costs. Productivity costs were based on the cost of absenteeism and reduced efficiency at work (presenteeism). This seems very pertinent considering the PFP population is typically a working-age population. However, the results of this study cannot be extrapolated to UK healthcare system where healthcare models and direct medical costs are likely to vary.

2.3.5 Risk factors

The potential risk factors for the development of PFP, taken from prospective cohorts, is presented here, with the known associated factors discussed in later sections. The most comprehensive work to date [53] systematically reviewed all known risk factors. Table 2.2 shows the risk factors that have shown significance in leading to the development of PFP. Pooling of data was only possible for the following variables: height, weight, BMI, age, peak knee extensor torque and peak knee flexor torque. Only reduced knee extensor strength was significantly associated as a high risk for future PFP [53] based on variety of testing procedures. The results of the review are based on only seven available studies however, and as the authors highlight, the cohorts investigated include a disproportionate number of military cohorts and so do not necessarily represent the general population [53].

Table 2.2: Risk factors for the development of PFP
Adapted from Lankhorst *et al.* (2012) [53]

	Risk Factors	Mean difference (MD) (95% CI) ±*
Demographic	Less height (cm) [54]	MD -3.10 (-5.73, -0.47)
Psychological	Less looking for social support [55]	MD -1.78 (-3.44, -0.12)
Physical fitness	Less sports participation (hours/week) [56]	MD -2.38 (-4.03, -0.73)
	More push ups (number) [57]	MD 1.60 (0.22, 2.98)
	Reduced vertical jump (cm) [57]	MD -3.39 (-5.95, -0.83)
Ground reaction force	Less vertical ground reaction force [58]	MD -0.30 (-0.58, -0.02)
Isometric strength	Greater knee extension strength (at 85°) [58]	MD 24.60 (0.69, 48.51)
	Less knee flexion strength (% BW) [58]	MD -0.02 (-0.04, 0.00)
	Less knee extension strength (% BW) [58]	MD -0.06 (-0.10, -0.02)
Isokinetic strength	Greater ratio of peak torque flexors and extensors (60 °s) [56]	MD 0.06 (0.01, 0.11)
	Greater ratio of peak torque flexors to extensors (240 °s) [56]	MD 0.07 (0.01, 0.13)
	Less concentric knee extension (60°s, Nm)	MD -17.48 (-28.89, -6.07)[56] MD -17.60 (-30.70, -4.50)[54]
	Less concentric knee extension (240 °s, Nm) [56]	MD -8.27 (-14.22, -2.32)
	Less concentric knee extension (60°s, Nm / BW)	MD -0.23 (-0.41, -0.05)[56] MD -0.24 (-0.42, -0.06)[54]
	Less concentric knee extension (240°s, Nm / BW) [56]	MD -0.11 (-0.20, -0.06)
	Less concentric knee extension (60°s, Nm / BMI)	MD -0.67 (-1.20, -0.14)[56] MD -1.08 (-1.72, -0.44)[54]

	Risk Factors	Mean difference (MD) (95% CI) ±*
	Less concentric knee extension (240°s, Nm / BMI) [54]	MD -0.4 (-0.73, -0.07)
Kinetics	Less knee extension moment (% BW x Height) [58]	MD 0.03 (0.00, 0.04)
	Less hip external rotation moment (% BW X Height) [58]	MD 0.02 (0.00, 0.04)
Static Posture	Greater medial tibial intercondylar distance in standing (cm) [57]	MD 1.50 (0.60, 2.40)
	Greater navicular drop (mm) [58]	MD 0.90 (0.04, 1.76)
Flexibility	Less quadriceps flexibility (°) [55]	MD -7.59 (-24.35, -0.83)
	Less gastrocnemius flexibility (°) [55]	MD -3.10 (-5.83, -0.37)
General Joint laxity	Greater thumb to forearm [55]	MD -3.10 (-5.83, -0.37)
Plantar pressure	Less time to maximal pressure on 4th metatarsal head (s)[59]	MD -0.02 (-0.06, -0.01)
	Reduced maximal velocity of mediolateral component of the COP during forefoot contact[59]	MD -30.29 (-46.01, -14.57)
Muscle activation	Reduced reflex response time of VMO (ms) [55]	MD -1.11 (-2.04, -0.18)
	Reduced reflex response time of VL (ms) [55]	MD -1.36 (-2.25, -0.47)
	Greater VMO before VL onset (ms) [55]	MD 6.53 (6.13, 6.93)

± Mean difference between those that develop PFP (case) and those that didn't (controls). Only statistically significant results are reported (p <0.05)

*Positive values favour the cases

As expanded on in section 2.8.1, the association of hip dysfunction with PFP has been the subject of increasing interest. Since the publishing of the Lankhorst *et al.* (2012) [53] review, a number of studies have added to the literature. In contrast to current belief, recent evidence in adolescent athletes has suggested that hip abduction strength [60] and increased knee abduction moments [61] were risk factors for PFP, with the authors proposing that this may represent an increased effort to control for knee valgus. The available data does not allow for this explanation to be substantiated. The only systematic review of the literature [62] to date that has explored hip strength as a risk factor for PFP, found that despite cross-sectional studies showing that hip weakness is associated to PFP, there is no evidence to suggest that a reduction of isometric hip strength leads to PFP. It is worth considering however, that isometric strength is the most commonly used measure of hip strength in these types of studies. It might be that other types of muscle contraction e.g. concentric or eccentric may be more functionally relevant to PFP [62]

2.4 Aetiology

The aetiology of PFP is unknown [13]. Numerous theories have been proposed, although no consensus has yet been reached [14]. Below provides an overview of the suspected structures and causes of pain. These theories, however, should not be considered exclusive and experts [63] believe they will likely overlap.

2.4.1 Subchondral bone

The localised stress transmitted through the PFJ is thought to be important in the development of PFP and there is a growing support for the *patellofemoral stress theory* shown in Figure 2.1 [12] . The term ‘stress’ is used to describe a loading force applied to an object whereas ‘strain’ is the response and deformation of that object from the applied stress [64]. It has been shown that people with PFP demonstrate greater PFJ stress [65, 66]. Ho *et al.* (2014) [66] showed that a PFP group demonstrated a 67-118% increase in patellar bone strain. Similarly, Farrokhi *et al.* (2011) [65] showed that PFP demonstrated a 35-66% increase in octahedral shear stress (reflects the portion of the stress field that tends to distort tissue [65]). It is agreed that articular cartilage is aneural so cannot be considered the source of pain [30]. Conversely, subchondral bone, lying immediately beneath the calcified cartilage [67] is highly innervated and a possible source of nociceptive pain [12]. Three mechanisms

have been proposed for the subchondral bone leading to pain. The first mechanism is based on the observed increases in intraosseous fluid [68] as a consequence of increase stress and loading. This is known to increase the intermeduallary hypertension, which leads to nociceptors in the bone, sensitive to pressure changes to be stimulated [69]. Another potential mechanism could be the increase in metabolic activity within the subchondral bone. A few studies have found that people with PFP display an increase in tracer uptake within the patella and articulating femur when analysed using scintigraphy [70, 71]. However, this only correlates with approximately one third of structural damage quantified using MRI [72], with scintigraphy showing a greater level of metabolic activity. This discordance may be the result of scintigraphy being better at identifying early structural damage or it may be that the poor specificity of scintigraphy [71] means that the increased metabolic activity could be indicative of another disease or injury [71]. The third possibility is the known presence within the subchondral bone of substance P, a nociceptive neurotransmitter found within nerves, which have been identified within the subchondral plate of the patellae [73].

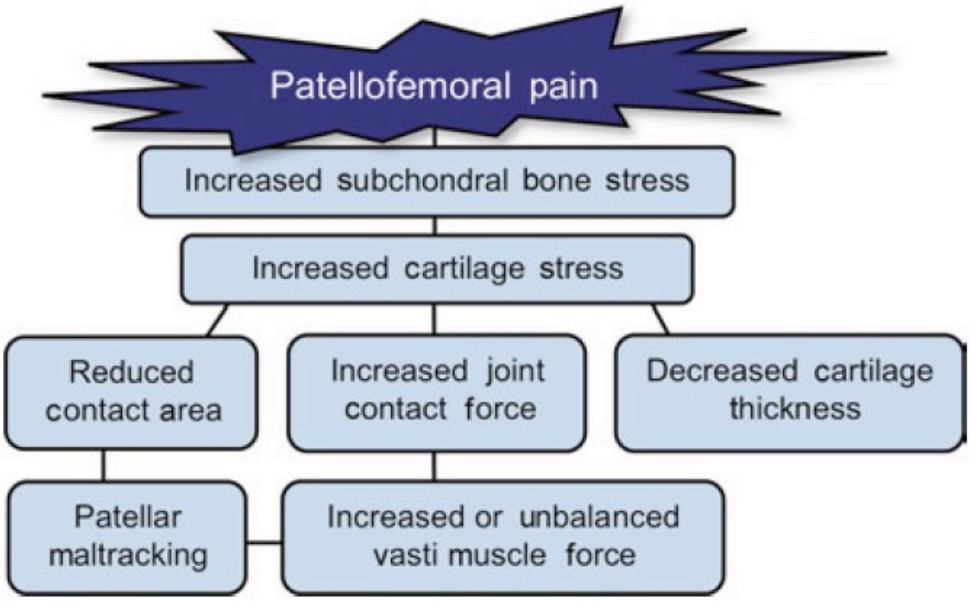


Figure 2.1: Factors which lead to increased subchondral bone stress
Reprinted with permission from Springer, Imaging and Musculoskeletal Modelling to Investigate the Mechanical Etiology of Patellofemoral Pain [12]

2.4.2 Homeostasis

Scott Dye's seminal paper published in 1996 [74] proposes the now well recognised tissue homeostasis theory to explain the pathogenesis in patellofemoral pain (Figure 2.2). This holistic theory considers that PFP may be the result of a multitude of causes including some of PFJ structures discussed above. In a collection of papers [13, 74, 75], he proposes that these tissues become overloaded once the person moves out of their *zone of tissue homeostasis* and beyond their *envelope of function[13, 74]* – a term given to the safe capacity of a joint to accept, transmit and dissipate load without leading to damage and dysfunction. The author stresses that the model should considered dynamic and is one which varies significantly between individuals (Dye et al 1996). The envelope of function is influenced by four distinct group of factors: i) anatomic e.g. joint morphology; ii) kinematic e.g. motion control; iii) physiological e.g. cellular healing capacity; and iv) treatment e.g. exercise. Dye *et al.* (1999) [75] surmises that commonly prescribed treatment such as taping, exercise, bracing etc. are primarily restoring the PFJ to its zone of homeostasis. This provides theoretical support to the concept of load management, recently advocated by a number of experts [16]. Despite the near-universal acceptance of this model, it does appear only speculative, as no current method exists to sensitively measure soft tissue homeostasis [76]

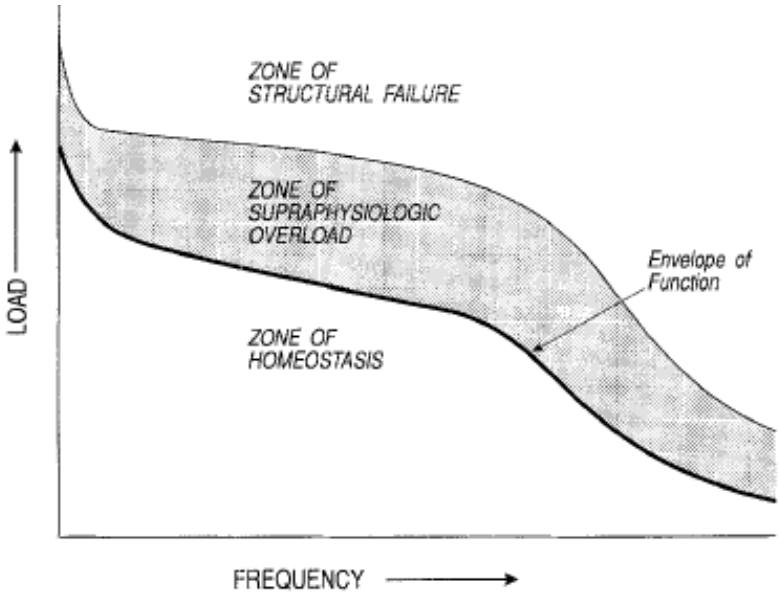


Figure 2.2: A graph representing the envelope of function.
The zone within the envelope of function ('zone of homeostasis) is where one can safely dissipate loading and avoid injury. The zone above the envelope of function ('zone of supraphysiological overload') is insufficient to cause macro structural failure but repetitive loading within this zone may lead to injury. The uppermost zone ('zone of structural failure') is where macro structural failure occurs often the result of extreme traumatic loading e.g. skiing accident. Reprinted with permission from Elsevier, Operative Techniques in Sports Medicine [74]

2.4.3 Lateral retinaculum

The lateral retinaculum is a structure on the lateral aspect of the patella, which comprises of converging and interdigitating structures [77, 78]. This complex structure consists of three layers: superficial, intermediate and deep [77]. The superficial layer comprises of deep fascia which is not attached to patella but laterally thicken to form the iliotibial band (ITB) in the lateral thigh. The intermediate layer forms the longitudinal retinaculum with the longitudinal fibres of ITB adhering to patella quadriceps tendon and joint capsule adjacent to patellar tendon. The deep layers form the transverse retinaculum with superficial and deep fibres of the ITB. The substantial deep fibres anchor the lateral edge of the patella to the ITB [77].

In people with PFP, Fulkerson *et al.* (1985) [79] found that 33% (26/75) of their cohort located their pain to either the lateral or medial retinaculum. The cause of these symptoms

has been explored by a number of groups histologically. People with PFP have been shown to have increased perineural fibrosis, reduced myelinated fibres [79], vascular hyperinnevation, increased substance P and increased neural growth within the retinacula [80]. This concept of neural growth within the retinacula has been explored further with Sanchis-Alfonso *et al.* (1998) [81] showing that those people with high levels of PFP had increased nerve diameter and the presence of neuromas. This is in contrast to the people with moderate levels of PFP who had a large number of small nerve fibres. Recent ultrasound findings have also suggested that the thickness of the retinaculum is greater in PFP compared to a group without pain [82]. The reason for this thickening is not explored by the authors but may be explained by the histological changes detailed in the earlier studies [81]. The generalizability of these findings, however, remains questionable as the findings are only based on small sample sizes of ten [82] to sixteen [81] knees. The small samples are likely the result of the fact that histological analysis is conducted *in vitro* using either excised tissue from surgery, or cadaveric knees which is less available in young cohort whose primary management is conservative treatment.

2.4.4 Infrapatellar fat pad

The infrapatellar fat pad (IFP) is an extracapsular, extrasynovial structure that is located in the anterior compartment of the knee [83] (see Figure 2.3). Despite its exact function being unknown, it is seen as serving as reservoir for reparative cells after injury [83]. The IFP has been identified as a potential source of pain. Dye *et al.* (1998) [30] reported severe, localised pain when IFP was arthroscopically palpated with only local anaesthesia at the portal sites. Saline induced injection into the IFP has shown to reproduce pain pattern associated with PFP-pain located to anteromedial and retropatellar region [84, 85]. The cause of the pain may also be linked to IFP biomechanics and histology. The pressure applied to the fat pad is greatest at full extension (< 20) and also shows a marked increase at extremes of flexion (>100) [86]. Histological analyses of fat pad in those with PFP show increases in substance P and S-100 protein; however, the association with PFP cannot be substantiated due to the lack of control group [87]. A link between IFP oedema and PFJ morphology and malalignment has also been explored. Jibri *et al.* (2012) [88] showed significant differences in Insall-Salvati index, a measure of patella height, and patella tilt angle (see *2.7.1*) when comparing a group with MRI confirmed IFP oedema and a group with normal fat pads. This link to PFJ structural changes is supported by more recent work [89] showing that IFP oedema correlates with an increase in T2 values in the medial cartilage. In contrast, cadaveric studies in which fat pad oedema was simulated, using an inflatable fluid cell

positioned by ultrasound, showed no changes in lateral translation or lateral patellar tilt [87]. However, this cadaveric model did demonstrate a significant reduction in PFJ contact area at near full extension (0-30) [87].

The basic science appears to support the premise that the fat pad may contribute to PFP; however, the prevalence of IFP pathology in PFP has not been established.

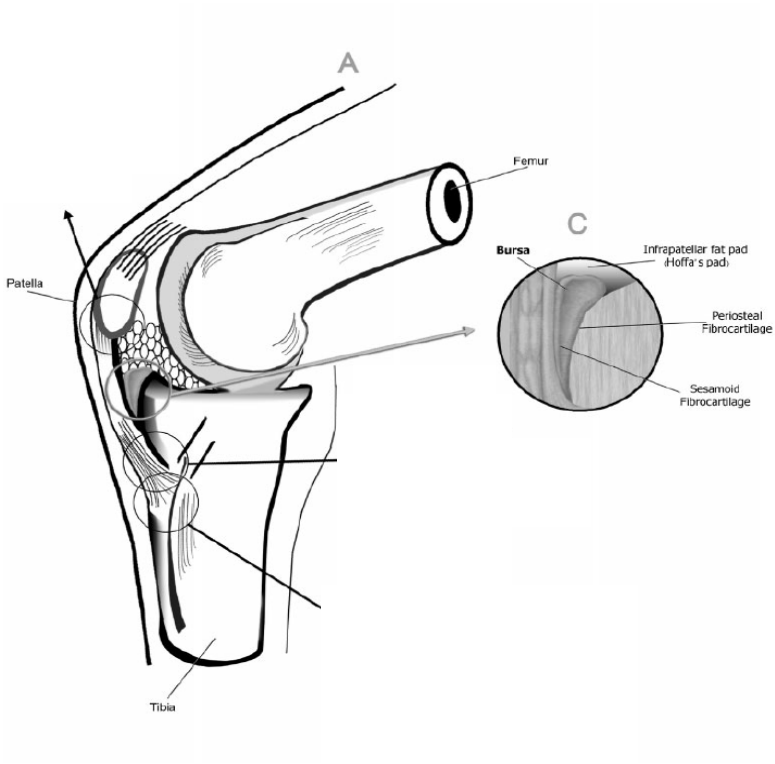


Figure 2.3: Anatomy of the infrapatellar fat pad
Reprinted with permission from Taylor & Francis, Physical Therapy Reviews [90]

2.4.5 Synovium

The synovial membrane of the knee is the largest in the body [91].The membrane attaches to the upper border of the patella and forms a large pouch beneath the quadriceps femoris on the distal anterior femur. Below the patella it is separated from the infrapatellar fat pad before projecting downward, either side of the femur, to its point of attachment on the menisci [91].The synovium is a semipermeable membrane that controls molecular traffic in and out of the joint space, maintaining the composition of the synovial fluid which provides

nutrients and removes metabolic products for the health of the articular cartilage [92]. Similar to the IFP, direct arthroscopic palpation of the synovium was reported as being moderately to severely painful [30]. This may be explained by the level of substance P within the synovium as it has shown to be higher in a AKP group compared to a group of people with total knee replacements and a group of post-operative meniscectomy and anterior cruciate ligament reconstructions [93]. This is supported by Bohnsack *et al.* (2009) [87] who observed the same increase of substance P within the synovium of people with AKP as well as an increase S-100 protein which is suggestive of a chronic inflammatory state [94].

2.4.6 Sensory dysfunction

Any tissue injury is thought to lead to some peripheral sensitisation and sensory change [95]. Sensory changes may also reflect the level of chronicity that his often found in individuals with PFP [95]. Jensen *et al.* (2007) [96] were the first group to investigate this phenomenon in PFP. They found quantitative sensory differences between PFP and healthy controls in terms of tactile stimulation, detection threshold for warmth and detection threshold for cold. Nevertheless, they were unable to observe any homogenous subgroups within a PFP population of n=91 despite using a range of somatosensory testing variables. This work has been expanded subsequently by Rathleff and colleagues in a collection of studies [95, 97] that have focused on pain pressure threshold (PPT) measured using algometry. They found that people with PFP have a lower PPT than healthy controls across both local sites (patella) and distal site (tibialis anterior) [97]. PPT was found to correlate with the duration of symptoms supporting algometry as a tool for measuring chronicity [97]. More recent work investigated the efficiency of the diffuse noxious inhibition of the nervous system by measuring the conditioned pain modulation [95]. It was found by applying pressure to the elbow (the conditioned stimulus) and then the knee (the test stimulus) that people with PFP have less increase in pain detection and tolerance thresholds[95]. An inability to increase thresholds is seen as deficiency in the body's pain modulatory and inhibitory system [95].

This emerging evidence may explain pain in subgroup of people PFP but the generalizability are limited as most of these findings are based on all female cohorts many of which are aged between 15-19 years [95, 97]. Age is considered a determinant of pain perception [98] and thus these findings may not reflect the typical PFP aged group up to 40 years.

2.4.7 Vascular dysfunction

In a series of studies [99-101], Selfe and colleagues highlight the possibility of PFP heterogeneity in terms of vascular and thermoregulatory function. They found that 18% (14/77) of individuals with PFP answer 'yes' to the question: '*Do your legs feel cold even in warm surroundings?*' These people also demonstrated greater pain, less physical activity and a worse response to exercise. Furthermore, they showed that individuals with objectively cold knees (cold to palpation) had a lower activity levels and a worse Modified Functional Index Questionnaire (MFIQ) score [101]. This reduced temperature may be linked to vascular abnormalities that have been explored by Naslund *et al.* (2005) [71]. Using a novel, non-invasive photoplethysmography, which assess blood volume changes in the microvascular bed of tissue [102] they showed significant differences between a PFP and healthy individuals in terms of pulsatile blood flow during a knee flexion arc. The explanation for how this vascular dysfunction links to pain is unknown. However it has been proposed that vascular bending or torsion, a mechanical disruption to the vascular supply, occurs leading to episodes of ischemia [103]. This may then create a hypoxic environment, which stimulates the production of numerous neurotransmitters within the local tissue, as discussed above.

Despite a growing body of literature on this subject, the importance of the vascular system in those with PFP still remains highly speculative. One of the biggest challenges is the accessibility and validity of the equipment needed to measure these vascular features clinically. These features may identify an important subgroup of PFP but future research would need to link these vascular changes with more established features of PFP e.g. knee strength etc. to demonstrate their clinical significance.

2.4.8 Proprioceptive dysfunction

Proprioception is the ability to sense the position and movement of limb segments [104]. It is widely considered to be important with all knee injuries [104]. However the temporal relationship between proprioception and pain is unclear. Callaghan (2011) [105] summarised the commonly used measures of proprioception within knee pain research which includes: active/passive joint position reproduction; detecting the initiation of passive movement; detecting a sensation of vibration; measuring the delay of muscle contraction; reproducing a muscle force; and postural sway. Specifically within PFP, the most commonly reported

measure of proprioception is active/ passive joint position reproduction. The studies using this methodology [106-110] show contradictory results. Some studies show that differences between a PFP group and asymptomatic control group exist [106, 107, 111] while others show no difference [109, 110, 112] . Callaghan *et al.* (2008) [107] sub-classified his cohort using the accuracy scores from the target angle, revealing subgroups of people with PFP who demonstrate either good or poor proprioception. It is plausible that the contradiction in the previous studies lies in the innate proprioceptive ability of the individuals recruited. Of note, is the work of Selfe *et al.* (2006) [113] who investigated the optimum number of trials to conduct during active/ passive joint position reproduction. They showed that five trials for active angle reproduction and six trials for passive angle reproduction allowed the data to achieve stabilisation. A subsequent review of the literature shows that the studies finding no significant difference [109, 110] performed three repetitions [109], two repetitions [112] and unclear the number of repetitions [110]. This is in contrast to the studies that found a difference between groups, which performed the optimum number of trials: five trials [106], six trials [111] and six trials [107]. The exact mechanism behind this alteration in proprioception is unknown.

Proprioceptive dysfunction can also be improved by interventions such as strengthening exercises [108] and taping [107, 114]. It has been suggested that taping may stimulate cutaneous receptors on the skin, which contribute to proprioceptive information [107, 114]. Alternatively, the changes may lie within the brain, as suggested by a study of application of patella tape to an asymptomatic group, which resulted in increased activity within the cerebellum and decreased activation in the supplementary motor cortex [26, 105]. Improved proprioception following strength training may be the result of either reducing the pain inhibition or greater patella stability with less tissue stress [108].

The temporal relationship of proprioception remains unclear, thus it is not known whether abnormal proprioception causes altered neuromuscular control and leads to the development of PFP or whether the pain from PFP disrupts the central processes and reduces proprioception [109].

2.4.9 Psychosocial dysfunction

The inconsistencies in treatment outcomes for PFP [115] as well as the inability to identify a sole, organic cause for the pain; has led to a greater focus on psychosocial factors [116]. Catastrophizing, the belief that pain will worsen and nothing that can prevent that [117], has

been identified as one of the key psychological attributes associated with PFP. Doménech *et al.* (2014) [118] showed that catastrophizing was the only variable that could be identified as a predictor of PF pain. In their study [118], catastrophizing explained 19% variance for pain and 28% for disability. This is supported by previous work [119] which has identified that people with PFP had a significant reduction in their perception of health control, which will contribute to the overall feeling of catastrophization. In a comparison between professional and amateur athletes, both with PFP, it was shown that professional athletes demonstrated a 44% greater perceived role limitation, which the authors [120] suggest might signify an increased level of catastrophizing. This would imply that the expected level of performance/ function might make one more susceptible to catastrophization. Other psychosocial factors that have been have been shown to be significantly associated with PFP include stress [121], anxiety [122] and fear avoidance behaviour [122] . Hostility has also been recognised as a potentially important personality trait in PFP. However, the direction of its effect is contentious, with Witoński *et al.* (1998) [123] identifying an increase and Carlsson *et al.* (1993) [121] finding a reduction in hostility. This may be result of Witoński *et al.* (1998) [123] comparing against a group of ACL rupture patients rather than asymptomatic controls.

Despite this emerging evidence, there still remains a paucity of evidence supporting the role of psychosocial factors in the development of PFP. The variety of constructs that have been explored makes comparison challenging, limiting the adoption into clinical research at present.

2.4.10 Link between PFP aetiology and stratification

This section shows that the aetiology of PFP is multifactorial, one of the first indications for stratification [124]. Nine causes of PFP are presented here and many of these remain speculative based on a small number of underpowered studies. As highlighted, these proposed aetiologies are unlikely to be exclusive [63] and furthermore there is likely to be differences in the causes of PFP along the age continuum e.g. adolescents vs. 40 years olds [125]. These uncertainties would make stratifying based on aetiology very challenging and therefore limits its inclusion within a stratified treatment approach.

2.5 Clinical examination

2.5.1 Clinical history

Pain is the predominant symptom in PFP and often localized to the patella region as depicted in Figure 2.4. PFP is rarely reported in unloaded activities (e.g. lying down) [3] with exception of prolonged sitting which has been shown to be associated with a presentation of PFP compared to other knee pathologies [126]. Other symptoms often described subjectively include joint crepitus, restricted functional activities and joint stiffness [3]. The multifactorial nature of PFP continues to make diagnosis difficult. No definitive clinical test exists to identify people with PFP [3].

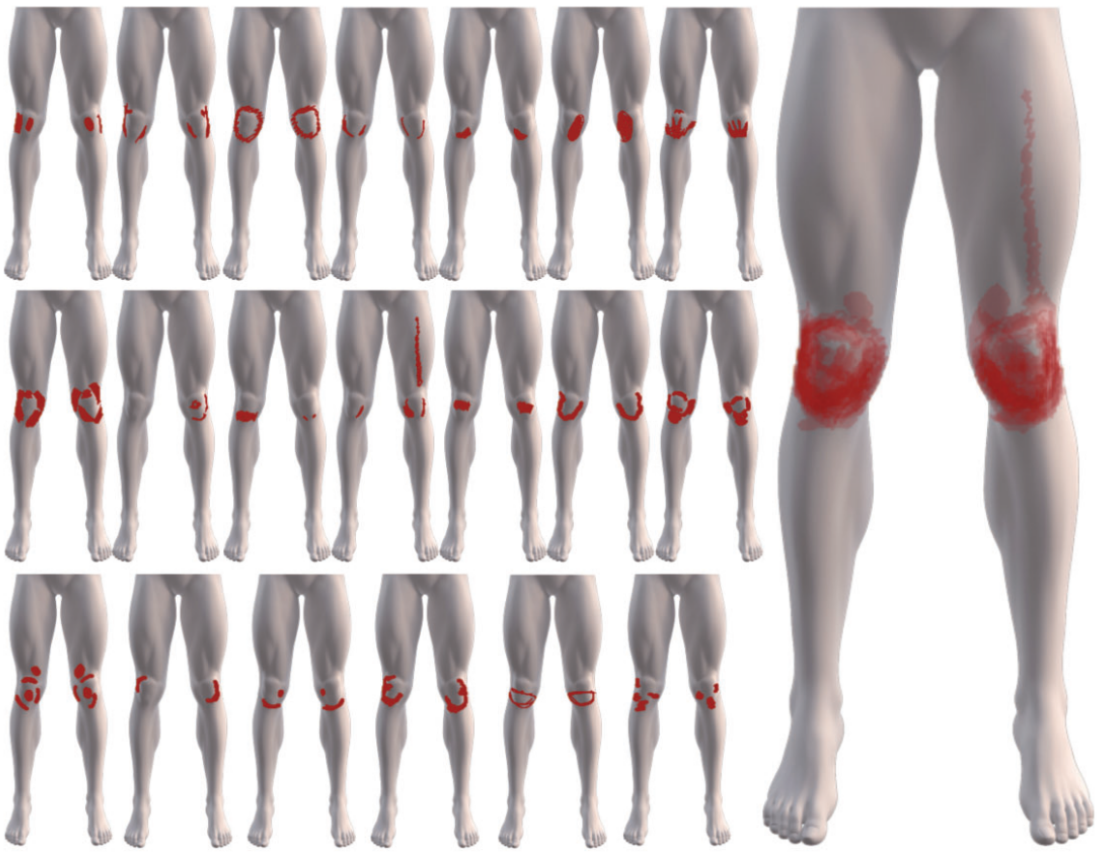


Figure 2.4: Self-reported pain
Pain location measured using the Navigate pain app. The small images represent the pain location of each participant with PFP (n=20). The large image represents an average pain location. Reprinted with permission Oxford University Press, Pain Medicine[95].

2.5.2 Objective examination

A number of studies have investigated the diagnostic utility of musculoskeletal tests for PFP [127-129] and two studies [23, 130] have reviewed the literature with the aim of selecting the best clinical test to aid diagnosis. In the early 1980s, it was shown [128] that the 'patella friction test' (synonymous with the Clarke test), considered at the time an important test for diagnosing PFP, was still positive in 66% of a healthy cohort highlighting the poor diagnostic accuracy of clinical tests in PFP. Further work has investigated the diagnostic test probability of the following single tests [129]. Using positive likelihood ratios (LR+) (how much to increase the probability of the disease if the test is positive) and negative likelihood ratios (LR-) (how much to decrease the probability of the disease if the test is negative) the following results were found: vastus medialis coordination test (LR+ 2.26; LR- 0.90); the patellar apprehension test (LR+ 2.26; LR- 0.79); eccentric test (LR+ 2.34; LR- 0.71). All the single tests showed a clinically relevant LR+ of > 2.0 but with no tests reached the <0.5 LR- deemed clinically relevant by the authors [129]. It has been suggested that test accuracy may be improved by combining tests [131].

The review by Cook *et al.* (2012) [23] focused on the diagnostic applicability of a combination of tests. They showed that two of three of the following tests: pain with resisted contraction; pain during squatting; and pain with medial or lateral patella palpation demonstrated LR+ 4.0, LR- 0.5 and a post-test probability of 89%. This combination of tests was challenged by the outcome of another review [130] which concluded that due to the LR- 0.2 yielded by the single lest of *pain during squatting test,* that the combination of tests was not diagnostically superior to this single test. Both LR+ and LR- are important in determining the accuracy of a diagnostic test. However, as PFP is widely considered a diagnosis of exclusion [23] it could be suggested that greater importance be given to the LR+ as this is ruling in the condition. This would mean that the LR+ 4.0 yielded by the combined pain with resisted contraction; pains during squatting; and pain with medial or lateral patellar palpation may be better to employ in clinical practice. The combined model also showed a greater post-test probability compared to *pain during squatting test* (89% vs. 79%).

There are a number of difficulties with assessing diagnostic test accuracy in this population [23]. Firstly, there is no agreed reference test available in which to compare the clinical test. MRI and arthroscopy have been used in some studies [23, 132, 133] to rule out competing pathology, however, MRI abnormalities have been shown to be highly prevalent with 89% (631/710) of older adults without radiographic OA demonstrating MR findings, thus questioning the specificity of MRI [134] . Consequently, most studies use the widely

accepted diagnostic algorithm which relates to pain reproduction with at least more than two functional activities [3]. This system, however, has been questioned by Callaghan *et al.* (2009) [126] who reported that there was no difference in reported pain for these activities between a PFP group and group with other soft tissue knee problems. Another consideration is that the case-control design does not accurately reflect true clinical practice when a level of uncertainty exists which influences the decisions made [23]. This is made more challenging by the fact that PFP is known to be heterogeneous in terms of its presentation [3].

In summary, debate surrounds whether the combined tests are superior to the single test (pain during squatting) when attempting to diagnose PFP. The comparison of post-test probability values (above) would suggest that the combined tests should be considered current best practice. However, if PFP continues to be considered a diagnosis by exclusion then perhaps more emphasis should directed to improving the diagnostic accuracy of differential diagnoses such as patella tendinopathy etc.

2.6 Patient reported outcome measures

A range of patient reported outcome measures (PROMs) have been applied to PFP. Adapted from two systematic reviews[135, 136] , Table 2.3 details the description and psychometric properties of the main outcomes used in both PFP research and in clinical practice. Additional data is provided as a result of a further letter to editor [137] highlighting the omission of the Modified Functional Index Questionnaire.

Published thresholds for intraclass correlation coefficients (ICC)[138], effect sizes [139] and Cronbach alpha[140] were used to interpret the data in Table 2.3. It shows that all the PROMs demonstrate an excellent test-rest reliability [138] except for the Visual Analogue Scale (VAS) which shows only good reliability (ICC = 0.60). Using the effect size as measure of responsiveness, Anterior Knee Pain scale (AKPS), Functional Index Questionnaire (FIQ), VAS, worst VAS (VAS-w), International Knee Documentation (IKDC) and Activity of Daily Living Scale (ADLs) all show good responsiveness [139]The Eng & Pierrynowski questionnaire and usual VAS (VAS –u) show a moderate responsiveness. Internal consistently has only been evaluated for five outcome measures using Cronbach alpha, showing that both ADLs and IKDC have excellent [141] and MFIQ, AKP and FIQ have good internal consistency. Concurrent validity was established based on looking at the outcome in

relation to other established measures. The Eng & Pierrowski questionnaire, Flandry questionnaire, VAS-U and VAS-W demonstrate strong validity [139] and AKP, ADLs and MFIQ demonstrated moderate validity.
In addition to the to the psychometric properties of the outcomes, Bennell *et al.* (2000) [142] evaluated the questionnaires by asking people to rank the outcome measures in terms of the easiest, the hardest, the most confusing, requires most explanation and best depicts symptoms. The Flandry questionnaire was reported to be the most confusing (48.7%), requires the most explanation (50%) but was considered to best depict symptoms (45.7%). The FIQ was considered the easiest (38.3%) and Eng & Pierrynowski (39.5%) the hardest.

Based on the available data, the systematic review by Esculier *et al.* (2013) [135] concludes that ADLs, AKPS and IKDC are the most recommended PROMs, however, the studies in the final recommendation differ considerably from Green *et al.* (2014) [136] despite only a years difference in the search completion (August 2012 vs. August 2013). Only 6 of the 24 studies used by Esculier *et al.* (2013) [135] were included by Green *et al.* (2014) [136]. This may be result of Esculier *et al.* (2013) [135] including studies of mixed knee pain that included PFP and other pathologies. This potentially affects the external validity of their findings and recommendations. Overall, no consensus exists to which specific PROM should be used, however, the latest consensus statement [20] suggests that a combination of PROMs to capture pain, function and quality of life should be included.

Table 2.3: Psychometric properties of patient reported outcomes
Adapted from [129, 135, 136]

Instrument name	Description	Test-retest reliability (ICC)	Validity (*r*)	Responsiveness (effect size)	Internal consistency (Cronbach α)
Eng & Pierrynowski Questionnaire	Visual analogue rating evaluated during activity e.g. stairs etc.	0.83-0.92	0.66 (vs. Flandry)	0.76	N/E
Flandry questionnaire	28-item questionnaire in a visual analogue response format that evaluates the severity of symptom and activity limitation. Score of out 280 (absence of symptoms)	0.95	0.66 (vs. Eng)	N/E	N/E
Anterior Knee Pain Scale	13-item questionnaire that evaluates pain and functional limitation. Score out of 100 (absence of symptoms)	0.81-0.90	0.58 (vs. FIQ)	1.15	0.81-0.84
Functional Index Questionnaire	8 item questionnaire that evaluate functional limitations. Total scores range from 0 to 16 (no limitation) with scores ranked from 0 (unable) – 2 (no problem)	0.48-0.94	0.66 (vs. Flandry)	0.32-1.29	0.83-0.86
Visual analogue Pain Scale / Numerical Pain Rating Scale	Visual or numerical pain scale which evaluates perceived current level of pain	0.60	N/E	0.26-1.22	N/E
Visual Analogue Pain Scale when least pain (VAS-L)	Visual or numerical pain scale which evaluates perceived current level of least pain	0.64-0.74	N/E	N/E	N/E
Visual Analogue Pain Scale when usual pain (VAS-U)	Visual or numerical pain scale which evaluates perceived current level of average pain	0.56-0.77	0.63 (vs. VASW-W)	0.15-0.75	N/E
Visual Analogue Pain Scale when worst pain (VAS-W)	Visual or numerical pain scale which evaluates perceived current level of worst pain	0.56-0.79	0.63 (vs. VAS-U)	0.02-1.15	N/E
Activity of Daily Living Scale (ADLS)	14 item scale which evaluates how the symptoms affect daily activities and specific functional tasks. Scored out of 100 (absence of symptoms)	0.93-0.99	>0.50 (vs. GROC)	0.63-1.26	0.89-0.93

International Knee Documentation Subjective Knee Form (IKDC)	18 item scale which evaluates symptoms, function and sports activities due to knee pain. Scored out of 100 (absence of symptoms)	0.92-0.99	N/E	1.13	0.88-0.93
Modified Functional Index Questionnaire (MFIQ)	10-item questionnaire developed to combine both FIQ and AKPs. Scored out of 100 (worst possible symptoms)	95% CI ± 11.2 (SD ± 5.47)	rho = 0.42-0.50 (vs. VAS with movement)	N/E	0.83

ICC = intraclass correlation coefficients; GROC = global rating of change scale; NE = not examined.

2.7 Imaging

2.7.1 Patella malalignment

Malalignment or maltracking is still considered an important factor in PFP and still the prevailing cause of pain [14]. The term malalignment can be misleading as other authors have used this term to encompass differences in skeletal alignment and biomechanics throughout the whole lower limb [143]. For the sake of clarity, in this review malalignment will be used to describe “the translational or rotational deviation of the patella relative to any axis” [63] with other biomechanical dysfunction discussed in a later section.

The idea of malalignment begin in the 1970s based on the work of Hughston (1968) [144] who suggested that patella malalignment might be a distinct diagnosis, as up until then the only diagnoses for AKP were either patella dislocation or chondromalacia patellae. During the 1970s, radiographic assessment became more widely used at the PFJ in terms of malalignment, and popular measures such as patella tilt [145] were developed to provide a mechanistic cause for this presentation of pain. This brought with it the development of a number of surgical techniques to address the malalignment. Despite Insall *et al.* (1983) [146] demonstrating that AKP correlated with malalignment; other studies [147] revealed the presence of malalignment in asymptomatic populations. This questioned the importance placed on the malalignment in PFP. Grelsamer (2000) [63] proposed the idea that patellofemoral malalignment may predispose an individual to developing PFP but that a ‘trigger’ is required such as trauma, overuse etc.

The common features considered during an assessment of PFJ alignment are that of tilt and lateral displacement. The most commonly considered features applied are patella tilt angle and bisect offset. Patella tilt angle was popularised by Ficat *et al.* (1975) [145] as a cause for hyper-pressure within the lateral patella facet and hypo-pressure, leading to malnutrition, in the medial patellar facet. There are a number of recognised techniques for measuring the lateral patella displacement (Table 2.4). This is also true of patella tilt angle (Table 2.5) with a number methods having been applied. Lateral patellar displacement is thought to either lead to aberrant loading of the lateral patella facet [148] or hyperinnervation of the retinacula [79]. Based on our systematic review of the literature (see Chapter 3), bisect offset, first described in 1988 [149] and developed over the 1990s [150], is one of the most commonly reported measures of lateral displacement.

Table 2.4: Bisect offset assessment methods

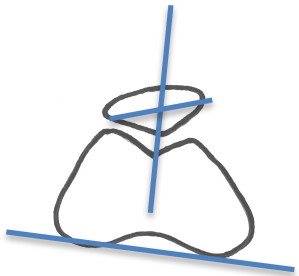
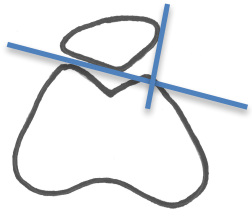
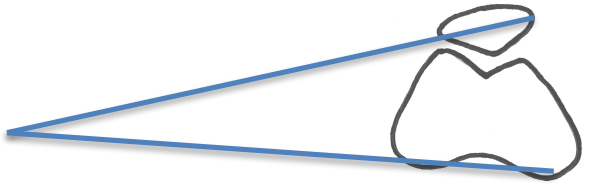
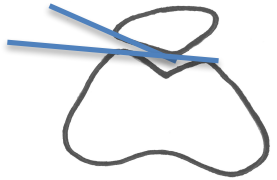
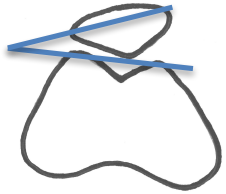
Lateral displacement	Description	Schematic
Bisect offset	Determined by drawing a line connecting the posterior femoral condyles and then projecting a perpendicular line anteriorly through the deepest portion of the trochlear groove to a point where it bisected the patella width line. The bisect offset is reported as the percentage of patella width lateral to the midline [144].	
Absolute patella displacement	Determined by a line projected anteriorly through most anterior point of medial condyle. Distance from this line to medial edge of patella is expressed either positively or negatively in millimeters, (depending on lateral or medial position) respective of the perpendicular line [150].	
Lateral patella displacement	Determined by drawing a line joining the summits of the medial and lateral femoral condyles and dropping a perpendicular line at the level of the summit of the medial condyle. The distance of the medial margin of the patella from this perpendicular line is measured [151].	

Table 2.5: Patella tilt assessment methods

Patella tilt	Description	Schematic
Patella Tilt Angle	Determined by the angle formed by lines joining the posterior femoral condyles and the maximum width of the patella [148].	
Lateral patellofemoral angle	Determined by the angle between a line drawn along the lateral joint surface of the patella and a line drawn along the anterior aspect of the femoral condyles [152].	
Patella tilt angle II	Determined by the angle between the posterior condylar line and the maximal patella width line. [153].	

The overall importance of PFJ alignment has been questioned in recent years in response to the limited correlation between the radiographic measures and symptoms [147]. Other theories including the above mentioned tissue homeostasis theory [74] are considered more encompassing, however, no theory remains exclusive. With reference to the thoughts of Grelsamer (2000) [63], it is likely that patellofemoral malalignment may make an individual more predisposed to moving out of the *envelope of function* and thus leading to pain. The fact that not all people presenting with PFP will have radiographical malalignment should not be seen a reason to ignore PFJ alignment but a need to identify these subgroups and their link to other known features.

The systematic review conducted for Chapter 3 provides an extensive review of the common imaging features, and is primarily linked to the known malalignment and maltracking features. With increased access to finite modelling techniques, other features have begun to be explored that rely on many inputs including MRI, joint reaction force etc. to derive the data. These features are discussed below.

2.7.2 Patellofemoral joint stress

Subchondral bone as a source of pain in PFP has led to research investigating the stress that is applied to the PFJ. Structurally, patellofemoral joint stress is influenced by the contact force, the contact area and the composition of articular surface [154]. Stress is proportional to force and inversely proportional to the surface area it acts on [155]. As a result increases in patellofemoral contact area may serve to distribute forces over a greater surface area and, theoretically, decrease stress to the patellofemoral articular surface [156]. In people with PFP, patellofemoral joint stress has been shown to increase with greater flexion during weight bearing and with greater extension during non-weight bearing [157, 158]. However in vitro studies have shown that PFJ reaction force (PFJRF) has a nonlinear relationship with PF contact area (Figure 2.5) despite PFP contact area initially increasing with PFRF there is a plateau at 500N loads - the approximate load of normal walking [155]. Thus with any greater activity demand e.g. running, fast walking, the PFJ contact area plateaus and is unable to disperse the increase in PFJRF. Brechter and Powers (2002) [159] found no difference in patellofemoral stress during stair ascent or descent and with application of a knee brace between groups, however, they did find that people with PFP reached peak PFJ stress earlier during early flexion (0-30°). It was hypothesised [159] this was the result of reduced contact area at early flexion angles. These findings are consistent with Salsich and Perman (2013) [160] who found a significantly lower contact area at 0-20°

flexion in a relatively larger group of PFP participants (n= 27) compared to a pain free group. PFJ contact area is discussed further in section 2.7.3.

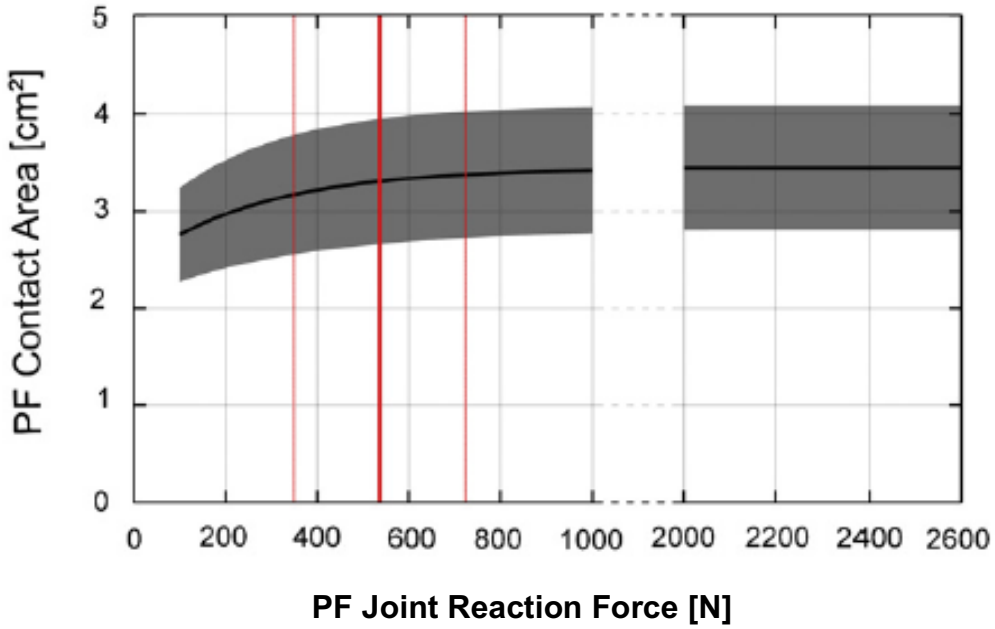


Figure 2.5: Relationship between contact area and joint reaction force
Mean values (solid black lines) together with 95% confidence intervals (grey areas) are presented for all eight knees for a representative instance of the stair climbing gait cycle (30 knee flexion). Note the plateauing around 500N (solid red line). Reprinted with permission of Elsevier, Journal of Biomechanics [155]

Rather than seeing patellofemoral stress as a single entity, patellofemoral stress has been broken down into separate components; octahedral stress and hydrostatic pressure [65] using finite element modelling informed from gait analysis, electromyography (EMG) during squat movement and knee MRI. Octahedral stress reflects the portion of stress that distorts the tissue whereas hydrostatic pressure reflects the magnitude of the portion of the stress that uniformly compress the cartilage [65]. Both octahedral stress and hydrostatic pressure have been shown to be increased in both the patella and femur compared to a pain-free control group [65]. These findings conflict with the more recent findings of Besier *et al.* (2015) [161] who demonstrated no difference in stress between a PFP and a pain-free group using similar measures. These reported differences may be explained by analysing stress at different knee flexion angles or by the use of the stair ascent task compared to a squat. Figure 2.6 shows that the position of the femur has also been shown to impact PFJ stress [162]. An increase in femoral internal rotation of only 5° lead to a significant elevation in

hydrostatic stress and octahedral stress with the PFJ [162] supporting the premise that even small changes in femoral control are important.

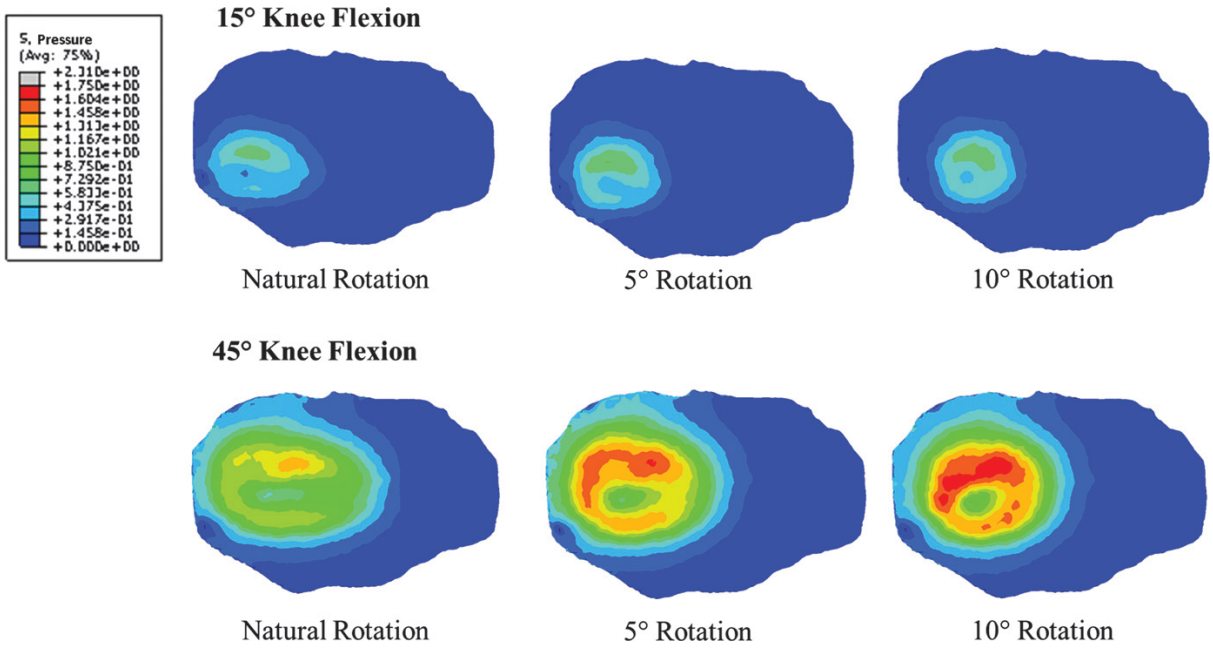


Figure 2.6: Increases in cartilage stress in relation to femur rotation
The increase in darkness of colour is representative of increasing hydrostatic pressure at 5° and 10° knee flexion. Reprinted with permission of Wolters Kluwer Health Inc, Medicine & Science in Sports Exercise [162]

Changes in patellar water content (suggestive of subchondral bone oedema) has been used as a surrogate measure for stress [68]. The water content of the patella can be observed by using a combination of T2 relaxation and multi fat peak spectral modelling under MRI. Ho *et al.* (2014) [68] measured the patellar water content at three time points: i) prior to running ii) following 40 minute run and iii) 48 hours post-running. They showed that patella water content increased immediately following activity and returned to pre-running levels after two days. These changes were importantly associated with significant changes in pain thus providing a potential explanation for the intermittent symptoms experienced by runners with PFP. More recently, it has been suggested that bone *strain* may be a more superior bone failure predictor than stress models [66]. Ho *et al.* (2014) [66] using similar finite element modelling showed that people with PFP demonstrated significantly greater peak and

average principal strain magnitudes in the patella region. Furthermore they demonstrated that cartilage thickness appears negatively associated with peak strain.

2.7.3 Patellofemoral contact area

As mentioned previously, it has been suggested that people with PFP have a reduced contact area during the early part of the flexion [159, 160]. However, these findings are dependent upon the method of analysis and quantification. A number of the studies have used biomechanical modelling to quantify the stress and contact area at the patellofemoral joint [65, 159, 161, 163, 164]. Besier *et al.* (2005) [154] proposed that patellofemoral contact area is influenced by the testing variables such as knee flexion position and physiological weight bearing. They showed that the variation between unloaded and loaded conditions can lead to an increase in anything between 10 -100% in contact area with an average of 24%. This suggests that any PFJ imaging data findings need to be interpreted with consideration of loading and the knee flexion position. Whereas Besier *et al.* (2005) [154] used a healthy cohort, Salsich and Perman (2007) [165] investigated which factors explained patellofemoral contact area in people with PFP. They showed that patellar width and tibiofemoral rotation explained 46% of the variation in contact area. The concept of patellar width is also supported by Besier *et al.* (2005) [154] who found a difference between males and females in terms of patellofemoral contact area but no difference was found once normalised for patellar height and width. This highlights the importance of gender in the interpretation of the findings. This gender difference is highlighted in Chapter 4. Due to the differences in patellofemoral joint anatomy, data should only be interpreted using gender-specific thresholds.

Observing a change in patellofemoral contact area is noteworthy; however, its importance can only be considered in relation to the clinical symptoms. There is a paucity of literature using contact area as an outcome of intervention and linking this to clinical symptoms. The few studies that have explored the link [166, 167] do suggest a relationship between contact area and pain. The application of a patellofemoral brace has been shown to increase patellofemoral contact area in people PFP with an associated 56% reduction in pain [167] thus demonstrating a potential link between structure and pain. Chiu *et al.* (2012) [166] also investigated that effect of an intervention on patellofemoral joint contact area. Using a within - group comparison they showed a significant change in contact area following an eight week quadriceps strengthening intervention. The combined sample size from both studies of people with PFP was relatively small (n =24) suggesting caution is advised when interpreting

these findings, however, this demonstrates a promising link between PFJ structure and the mechanistic effect of treatment.

All these findings are in contrast to Connolly *et al.* (2009) [168] who demonstrated higher contact area in PFP versus a control group at 15°. It may be that this inconsistency in findings may simply be the result of small PFP sample size (n=10) and a type II error. However, despite all studies using MRI, the analysis of the images varies greatly. Connolly *et al.* (2009) [168] scored from a digitised image capturing the 3D nature of the patellofemoral joint whereas the other studies [159, 167], despite using complex biomechanical models to quantify the overall patellofemoral stress, quantify the contact area based on only axial MR slices which fail to represent the 3D nature of the PFJ (see Chapter 4 for further details). This shows that measuring patellofemoral stress and contact area is dependent upon a number of factors including MR assessment as well as gender, physiological loading, and knee angle position [154]. As a result, a level of caution is required when interpreting and generalising the results.

2.7.4 Cartilage thickness

The composition of articular surface is an important component of PFJ stress and as such remains a feature of interest [154]. Cartilage thickness in patellofemoral pain was initially explored by quantifying the cartilage thickness at three locations on the patella and femur. Draper *et al.* (2006) [169] demonstrated that males with PFP had a significantly reduced patellar cartilage thickness compared to a control group but that there was no difference in femoral cartilage. Females demonstrated no difference between PFP and controls for either patella or femoral cartilage. However, when results were adjusted for body mass there was no difference in either group or gender. This pattern of results is consistent with the findings of Connolly *et al.* (2009) [168] who showed no difference in patellar cartilage thickness between a PFP and a healthy control group. In contrast, a number of more recent studies [66, 170], both of which used all-female cohorts, found significantly reduced patella cartilage thickness compared to pain free control groups. There may be a number of methodological reasons for the contrast in findings. Draper *et al.* (2006) [169] used the modified Outerbridge system which aims to classify joint cartilage breakdown. It is apparent that the author was attempting to rule out the presence of degenerative change, however, it is also arguable that using the Outerbridge classification as an inclusion criteria can introduce a selection bias as the classification tool focuses on the loss of cartilage. Perhaps most importantly, both Farrokhi *et al.* (2011) [170] and Ho *et al.* (2014) [66] used a matched control group that

controlled for known confounding factors such as age, body mass index and physical activity. This level of adjustment may have led to the detection of differences in cartilage thickness between groups.

2.7.5 Quantitative MRI

Quantitative MRI techniques have recently been explored to further understand the composition of cartilage and to offer some link between PFP and PFOA [171]. A number of quantitative techniques can be applied. T1 relaxation time detects the changes in proteoglycan content of the cartilage [172]. Whereas T2 relaxation time detects the ability of the free water protons to move within the cartilage matrix; a measure of cartilage integrity [172]. Within PFP, a few studies have shown no difference between PFP and controls in terms of T2 relaxation [170, 171]. Differences have been noted in T1 relaxation times in the lateral facets with people with PFP demonstrating higher T1 values [173]; however, this is not a consistent finding. van der Heijden *et al.* (2016) [171] found with a much larger sample size no difference in T1 relaxation between a PFP and control group. They attribute this to the adjustment made for known confounders such as physical activity level. However, in contrast to the other variables they investigated T1 values in the lateral femur and patella were consistently higher in PFP suggesting a trend towards an agreement with the previous study [173]. van der Heijden *et al.* (2016) [171] also used the most validated method of measuring cartilage composition, [174] delayed contrast-enhanced MRI of cartilage (dGEMRIC) technique, which measures the change in glycosaminoglycans (GAGs). GAGs are thought to precede the loss of cartilage in OA so are considered a suitable indicator of early cartilage loss and degeneration [171, 172]. A intravenous contrast agent is given and distributes in the cartilage with an inverse relationship to the negatively charged GAGs [175, 176]. The GAG content can be calculated by differences in T1 values. Despite it being considered the most validated method, no differences were noted between groups for T1 values [171].

2.7.6 Kinematic MRI

The application of kinematic MRI for the patellofemoral joint appears to originate from the early work of Shellock and colleagues [177]. As PFP is primarily considered to be related to dynamic maltracking, the need to visualise tissue during movement seems important. Kinematic MRI in its simplest form has been applied to people with patellofemoral pain, with individuals positioned supine and the knee adjusted to a variety of angles and with low resolution images captured [178, 179]. More recently, groups have begun to explore different

techniques. Cine phase contrast (Cine-PC) MR Imaging has been utilised to investigate patellofemoral motion in vivo [180-182]. Cine-PC imaging combines two techniques to generate tissue velocities in the x, y, and z planes. Cine PC MRI is considered very accurate and precise [183], however to ensure this accuracy the procedures requires a number of accurate repetitions which is challenging with a symptomatic patient, likely more prone to fatigue [184]. The better variant to limit fatigue is Real Time MRI which only requires one motion cycle [185]. Real-time imaging has been used by Draper *et al.* (2009) [148] with patellofemoral pain during full weight. This technique is arguably more clinically accurate to assess PFP in which pain is elicited in weight bearing [148]. Real time MRI has the added advantage that the imaging plane can be continuously defined to track an object [185].

2.7.7 Link between PFP imaging and stratification

In summary, this section has identified a number of imaging features which could be targeted with treatment - an indication for stratification. It clearly shows that there is a growing interest in more complex PFJ imaging features. PFP has been shown to be associated with: an increase in PFJ stress and strain; a reduction in PFJ contact area; and an increase T1 relaxation times in the lateral patella. These features may have the potential to be future treatment targets but currently there is a limited evidence to support interventions that would elicit a clinical change in these measures. Patella malalignment features e.g. bisect offset, patella tilt etc., in contrast, remain the most commonly investigated measures within PFP and known to be modifiable with knee orthoses (see section *2.9.4.2*) and taping (see section *2.9.3.2*). These features should therefore be considered for future subgrouping. With a variety of imaging techniques in terms of knee flexion position, weight bearing etc. a greater understanding of how these factors affect PFJ imaging features and their association with PFP is also warranted.

2.8 Biomechanics

2.8.1 Hip biomechanics

2.8.1.1 Strength deficits

Over the last 10 years more attention has been paid to the role of the hip in PFP [186]. Research has sought to quantify and objectify the influence of the hip people with PFP and establish hip-specific interventions. It is now well established in the literature that some people with PFP demonstrate weakness in concentric [187]; isometric [186, 188-191] and

eccentric [192, 193] hip abduction. Furthermore, a recent meta-analysis showed that hip abduction strength was a significantly associated to PFP [194]. Many academics and clinicians alike support the idea that hip external rotation is also an associated deficit in people with PFP [186, 188, 189, 191, 192], however, studies have found contrasting findings [193, 195]. The exact reason for this inconsistency is unclear, however, variations in strength testing procedures and measurements are likely to have had an influence on the eventual findings. The concept of hip strength and activation deficits has been further explored by investigating the effect of fatigue on hip kinematics. There is consistent evidence that these muscle groups weaken following exertion and that people with PFP show a significantly greater reduction than a control group [196, 197]. As highlighted clearly by Lack *et al.* (2015) [198] there is a tendency for 'strength' to be used to be used to encompass all types muscle contractions whilst these are likely to derive different results. A recent review [199] attempted to investigate muscle endurance but was unable to pool the data from studies investigating hip muscle endurance in PFP but did find conflicting evidence for differences in hip muscle endurance. Souza and Powers (2009) [200] showed 49% and 40% less hip extension and pelvic drop repetitions were performed respectively in females with PFP. Whereas McMoreland *et al.* (2011) [201] showed no difference between groups using a isokinetic dynamometer to measure total work (in joules) after 30 concentric contractions. The influence of bilateral and unilateral pain on hip muscle strength has also been briefly considered [202]. It has been shown that people with bilateral PFP have weakness in all hip muscle groups compared to those with unilateral PFP who demonstrated no weakness in their medial rotators and adductors [202]. The reason for this disparity is unknown yet considering the fact that a typical cohort of PFP will include both unilateral and bilateral PFP patients so this becomes an important consideration when planning interventions and comparing groups.

2.8.1.2 Hip kinematics & kinetics

An array of tasks have been used to explore the presumed movement dysfunction in people with PFP [20]. Running, jumping, stairs and walking have all been investigated, each providing unique task demands [200]. Hip internal rotation and hip adduction angle displacement are the common metrics investigated [203], however, other proximal features might include pelvic obliquity and drop [204, 205]. Stair descent has been selected by a number of studies as a task to explore hip kinematics [188, 200, 203, 206, 207] due to the fact it is a commonly reported aggravating activity for people with PFP [3], creating a known increase in joint load of up to eight times body weight compared to level walking [208].

Contrasting findings in hip kinematics during stair descent have been reported, with some studies reporting significant differences in hip internal rotation [200, 207] and hip adduction [207] with others finding no differences in either movement plane [188, 203]. Explanation of these differences in unclear, however, one of the authors did normalise the hip joint angle to zero based on their standing posture during the calibration phase whereas the other study quantified hip joint angle regardless of standing posture [200]. The differences observed may also reflect differences in baseline pain, step height, stepping duration [206] and possibly baseline hip muscle strength.

2.8.1.3 Neuromuscular activity

Using EMG, authors have attempted to specifically identify the muscle activity that is occurring at the hip joint. A number of studies have shown that the gluteus medius in people with PFP, responsible for controlling the transverse and coronal plane of the lower limb, has delayed activity and shorter duration in both stairs [195, 209, 210] and running [211] compared to healthy controls. Despite being more recognised as a primary hip extensor, gluteus maximus is also the primary external rotator of the hip [200]. There is evidence that gluteus maximus activation is different between PFP and healthy controls [200] whereas other studies have found no difference [211, 212]. These conflicting findings could be explained by studying different points within the stance phase e.g. toe off, heel strike etc. It is known, for instances, that the amount of stance phase will influence the amount of gluteus maximus activation [213].

2.8.2 Knee biomechanics

2.8.2.1 Strength deficits

Quadriceps weakness remains one of the most recognised associated features of PFP. A review of the literature shows that people with PFP display more quadriceps atrophy than healthy controls [214] and quadriceps weakness is also the only risk factor for PFP that is supported consistently across multiple studies [194].

2.8.2.2 Vastus Medialis Oblique

In 1986, McConnell published a seminal paper highlighting the importance of vastus medialis oblique (VMO) strength in PFP [215]. Since then a number of studies [85, 216-221] have supported this hypothesis suggesting that the VMO has a decreased and delayed activity compared to the vastus lateralis (VL). In contrast, other studies [222-227] have disputed this

findings by finding no such delay in activity. With consideration of the anatomy, it has been suggested that the VMO is most active at increased angles of knee flexion [31]. However, the stabilising effect of VMO is less required at these angles when the patella has greater containment within the trochlea [31]. In contrast, Jan *et al.* (2009) [228] showed using ultrasound with mean measurement error of 0.22 º, that a PFP group (n=51) had a VMO with a more proximal attachment on the patella and lower horizontal fibre angle suggesting a less effective medial pull. Nonetheless the clinical meaningfulness of differences in fibre angle of 3.5 º and insertion attachment of 0.4 mm remains questionable. The clinical implications of the findings are convoluted, as there is paucity of literature to support the minimal clinically meaningful difference of the EMG readings. It has been suggested that differences in timing lower than 5ms can lead to biomechanical difference in healthy male subjects [229], but this may not then relate to a symptomatic, commonly female PFP population. It may also be that the heterogeneous nature of the PFP population has led to inconsistencies in findings. A recent study sub-categorised people into 'maltrackers' with excessive patella tilt and bisect offset and found that this population had that largest correlation to VMO activation delay [230] suggesting VMO might have a clinical effect on patella kinematics.

A few authors have considered the whole of the literature surrounding VMO in PFP. Chester *et al.* (2008) [231] systematically reviewed the current literature and highlighted the on-going discrepancy in findings. They suggested number of potential source of heterogeneity that surrounds the methodology, population and procedural variations e.g. EMG electrode placement, onset determination methods etc. Wong (2009) [232] in their literature review categorised studies according to EMG procedural variations demonstrating a large variability in the onset determination, with applied onset thresholds varying from one to five standard deviations. These onset parameters are important, however, as long as studies standardise these onset thresholds for both muscles (VL and VMO) and both groups then this is thought to have little effect on the relative activation times and the between group differences observed [231].

2.8.2.3 Knee kinematics & kinetics

One gait measure that has been shown to differ between PFP and healthy controls is the amount of knee flexion in free walking [233-235] and stair use [159, 206, 210, 236, 237]. It has been suggested that people with PFP show a reduced knee flexion during stance phase. This finding, however, is not universally supported by all the literature [235] and may be the result of small sample sizes leading to type II error. Increases in knee flexion have

been noted when pain is reduced by the application of tape [238]. This would suggest that observed reduction in knee flexion in previous studies might be a pain avoiding strategy. Reducing the knee flexion angle is thought to reduce the knee extensor moment thus reducing the strength of the overall contraction required [234] . This is considered a common strategy for an inhibited muscle group.

Joint coupling variability is an index of the inter-segment system variations necessary to allow the movement system to adapt to changing constraints from one situation to the next [239]. Joint coupling variability has been highlighted as important for maintaining a healthy musculoskeletal system [240]. Lower variability in joint coordination (reduced ability to adapt to movement perturbations) is purported to increase soft tissue loading and increase the likelihood of pathology [241]. PFP is a condition long thought to be impacted by this reduced joint coupling variability [240] in particular across the knee in three movement planes. Nevertheless this is not a consistent finding. No differences were found between people with and without PFP whilst running at a self-selected pace [242]. Furthermore, a more recent study with a larger sample size showed that PFP demonstrated a *greater* joint coupling variability [241] contradicting the historical view. This contrasting finding may be explained by only including people with a greater baseline pain (three out of 10 VAS). The increase in variability would lend itself to a pain avoiding strategy, reducing stress on inflamed tissue [241]. It also conceivable that people with a higher baseline pain will have decreased motor control and thus greater movement translation [243].

2.8.2.4 Flexibility

Stretching often forms a key component of most multimodal programmes used in interventional research studies and reflects the widespread use in clinical practice [16]. The muscles targeted for stretching in PFP interventions almost always comprise of muscles around the knee joint, which include quadriceps, hamstrings and calf complex. Despite the common prescription of such stretches, there are only a few studies to support the association of muscle inflexibility and PFP [55, 244-247]. Quadriceps [55, 245, 246] and calf (gastrocnemius and soleus) [55, 246] flexibility have been shown to be significantly worse in people with PFP compared to asymptomatic controls. Hamstring flexibility is the subject of conflicting evidence, with a few studies [244, 247], from the same research group, demonstrating a significant difference in hamstring length for PFP, which conflicts with other findings [55]. These differences may be the result of different testing procedures, with the latter study [55] using the straight leg raise test and measuring the angle of the hip in

contrast to the popliteal angle used in the other studies. The popliteal angle has been suggested to have a potential ceiling effect, with a number of people found to be able to reach full knee extension [248]. The straight leg raise on the other hand has been criticised for being difficult to stabilise the pelvis during testing and for the increased engagement of sciatic nerve which may influence the specificity (hamstring length) of the test [249]. It is also worth noting that Patil *et al.* (2010) [244] and White *et al.* (2009) [247] from the same research group actually report the popliteal angle differently in PFP, with the former reporting the angle from 0° (full knee extension) despite arriving at the same conclusions. The effect of testing procedure is highlighted by the study by Peeler and Anderson (2007) [245]. They had patients undergo a three-week quadriceps programme and then assessed their pre interventional changes in quadriceps length using three different testing procedures. For the PFP group, significant differences were noted in the pre vs post results obtained using the Kendall test (Mean difference [MD] 4º) but no differences noted using the Thomas (MD 0º) or Elvey (MD 1º) tests despite all procedures intended to measure the same thing.

2.8.2.5 Joint mobility

Generalised hypermobility has long been associated with PFP [250] and is anecdotally considered to be important factor in the development of PFP . It is surprising, therefore, that a limited amount of evidence exists to support any association. Al-Rawi and Nessan (1997) [250] compared 115 people with AKP compared to 110 controls finding significantly greater hypermobility scores in the AKP group, based on the Beighton score. The understanding of why people with hypermobility get PFP may lie in the fact that ligament laxity reduces the joint constraints leading to malalignment and subsequent joint stress [181]. Conversely, Al-Rawi and Nessan (1997) [250] also reveal that 44% of people diagnosed with AKP have normal hypermobility scores (0-3) suggesting that subgroups of joint mobility exist. Witvrouw *et al.* (2000) [55] explored whether general joint hypermobility, which included measures of thumb apposition to the forearm and knee, elbow and little finger hyperextension (components of the Beighton score) predicted the development of PFP. Of all these measures, only a greater thumb to forearm was significant in developing PFP. This contrast to the study by Al-Rawi and Nessan (1997) [250] would refute the causative nature of general laxity in developing PFP.

The lateral and medial mobility of patella is known to vary within the patellofemoral population with some people with excessive and others with limited mobility [251]. The effect of patellar mobility is unknown but, in accordance to generalised hypermobility, when a

patella is deemed hypermobile there is a perceived loss of patella restraint integrity [252]. There are a number of methods to measure patellar mobility: lateral glide only [181]; medial glide only [253]; medial and lateral displacement with Patella pusher (a hand-held force gauge) [252]; patellofemoral arthrometer [251] and medial, lateral and total displacement with ruler [55, 254]. Witvrouw *et al.* (2000) [55] showed that baseline patella mobility was not predictive of the development of PFP. This is supported by a case-control study [251] that analysed patella mobility using a patellofemoral arthrometer showing no difference between a group with and without PFP. However, recent statistical subgrouping of a PFP cohort [254] has revealed that patella hypermobility was significantly associated with one of their three subgroups highlighting its potential importance for the management of PFP.

2.8.3 Foot & Ankle biomechanics

2.8.3.1 Foot plantar pressure

The link between PFJRF and PFJ stress is discussed in section 2.7.2. showing how ground reaction force of the foot has the potential to affect proximal structures i.e. knee, hip etc. It has been shown that people with PFP display less ground reaction force during heel strike [255]. Despite an overall lower resultant PFJRF, Chen and Powers (2014) [256] did find a higher PFJRF in the lateral component of the PFJ. Prospectively, people who develop PFP demonstrate a greater and more laterally directed foot pressure at initial contact [59] which would support the larger lateral force vector within the PFJ. Focusing on the specific phases of gait lateral directed force of the foot was also noted [257]. However, there is some discrepancy with the latter study finding significant lateral directed force during the propulsion phase rather than initial (heel) contact.

2.8.3.2 Static vs. Dynamic assessment

Excessive pronation has been widely considered to be associated with PFP [258] however, there is an inconsistency in findings [259]. Static measures of foot posture offer clinically viable tools that can be used to assess features such as pronation [259]. It has been demonstrated that people with PFP are four times more likely than healthy controls to have a larger difference between arch height in non-weight bearing compared to weight bearing [259]. This measure is similar to navicular drop test, which has purported to be good measure of pronation. However, despite the some reported high inter-rater reliability [248] is susceptible to error if relying completely on navicular palpation [259]. Ideally assessment of

the foot and identification of possible pronation should be determined dynamically, which represents real world function. More recently, static pronation determined by the foot posture index (FPI), a six-point scoring criteria encompassing many single static measures [260], has shown fair to moderate association with dynamic pronation for both peak angle of forefoot abduction and earlier rear foot eversion timing in people with PFP [258]. This shows some promise that a static tool can predict dynamic function, however, the associations are likely muted by the interaction and potential relationship with other kinematic measures such tibial or hip rotation. Understanding how the FPI interacts with whole limb kinematics remains an important consideration especially when attempting to identify PFP subgroups.

Recently, a series of studies [261-263] provide contrast to previous biomechanical studies for PFP by considering the ‘eversion buffer’. The eversion buffer is based on dynamic excursion during movement expressed as the quantity of available passive eversion (eversion buffer = passive eversion range of movement [ROM] – dynamic eversion ROM) (Figure 2.7). This allows calculation of the amount of time the foot has to respond until making contact (time to contact = eversion buffer / eversion velocity). Theoretically, this appears a logical approach for combining static and dynamic measures by considering the range of available movement and the motion control. They showed that runners with PFP had a significantly shorter time to contact than healthy runners and this was mostly the result of having less eversion ROM [263].The success of interventions such as orthoses may be influencing the time to contact, however, based on these results the motion control appears less important than the available eversion ROM that might be targeted with joint flexibility.

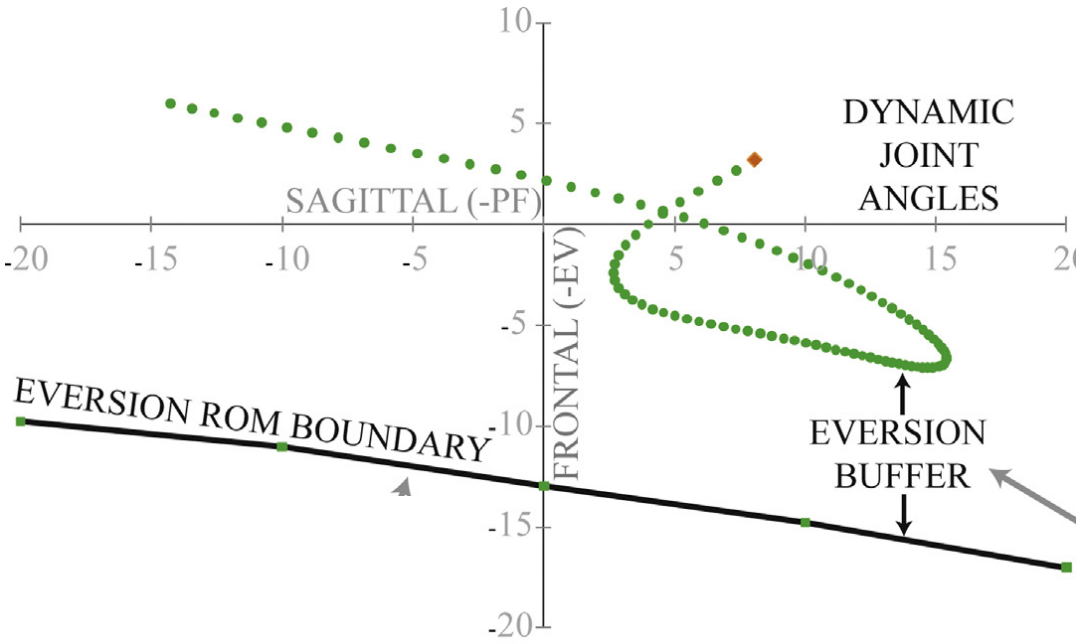


Figure 2.7: Eversion buffer.
The difference between the eversion range of movement (black line) and the dynamic excursion (green line). Reprinted with permission from Elsevier, Gait & Posture [263]

2.8.4 Link between PFP biomechanics and stratification

In summary, similar to the imaging section (2.7.7) this section shows a range of biomechanical features which could be targeted with treatment and provides a further indication for stratification. Conflicting evidence is available to support abnormal hip activation patterns, delayed VMO activity, abnormal patella mobility and increased PFJRF. In contrast, there is more evidence to show that PFP is associated with reduced knee strength, hip strength, abnormal hip kinematics, abnormal knee kinematics, increased static foot pronation and reduced flexibility. These remain viable treatment targets with established treatment options (see section 2.9) and thus should be considered for future subgrouping.

2.9 Interventions

2.9.1 Hip targeted interventions

2.9.1.1 Efficacy

Exercise is a common feature of almost all PFP treatment. Other adjunctive treatment interventions have been explored in isolation that target the hip including bracing [264] and trigger point release [190], however, exercise is the mainstay of treatment. This was first demonstrated by a case series (n=2) [186] that a purely hip specific strengthening programme performed over 14-weeks could improve pain and function. Subsequently, further research has aimed at exploring hip specific interventions in a PFP population. These positive findings has been supported by a RCT [265] and a case series [266] that have shown hip strengthening alone will improve both pain and functional outcomes [265, 266]. Differences between a hip-strengthening and a knee strengthening programme have supported the assertion that hip specific strengthening can show greater improvement at 4 weeks [267], 6 weeks [268], 6 months [269] and 2 years [270]. Despite these conclusions, it is worth considering that in these studies there were improvements in pain and function for both interventions suggesting both exercise types can be used or should be combined. This probably explains why further research has explored the combination of knee and hip exercises compared to knee exercises alone. Three RCTs [271-273] have shown that the combined intervention has a greater improvement compared to knee exercise alone up to 12 months follow-up [271].

Whilst considering the favourable results for employing hip strengthening, it is worth noting a recent systematic review [274] which actually calculated the correlation coefficient between the percentage change in strength and the percentage change in VAS score. They found no correlation between hip abductor strength change and pain change ($R^{2=}$ -0.010; p= 0.873) or between hip lateral rotator strength change and pain change (R^2 = 0.003; p = 0.935). Furthermore, they along with a number of other recent reviews [198, 199] have highlighted that a large variance exists in the number of treatment sessions (from 7 to 24 sessions), which in practice is likely to influence the outcome. There is also the factor that exercise interventions are largely dependent on the type and application of each exercise [198] ; which again varied greatly between studies. This point is demonstrated by a recent RCT [275], which compared functional stabilisation training to standard treatment. Functional stabilisation training, in essence, shares many features of previous published *hip strengthening* protocols, however, comparisons with hip strengthening would be difficult to

make due the different exercises utilised. Furthermore, with interventional-based studies there is always a potential for publication bias, which preclude negative findings for comparison.

A recent systematic review [276] has identified a number of case-control studies that have looked at isolated gait and movement retraining as possible treatment strategies with PFP. Prompts given during real-time running, that focus on hip and trunk position, have been shown to demonstrate a marked improvement in both pain and function [204, 205]. In running, a targeted intervention aimed at addressing gait retraining had a very significant reduction in pain of 87% [204] and 91% [205] which are considerably greater reductions than a previous reported studies [204]. This approach has been employed outside of running, showing that during a single leg squat exercise prompts to correct hip movement and control resulted in less pain being reported [277]. These findings strengthen the idea of incorporating optimal movement education and instructions into treatment plans.

2.9.1.2 Mechanism of effect of interventions

People with PFP are thought to present with increased hip adduction and internal rotation during movement tasks [278]. It is widely believed that altered kinematics may lead to altered patellofemoral joint stress, initiating the first nociceptive input [12]. Subsequently, correcting this movement is often seen as desired outcome in interventional studies and maybe required to achieve long-term resolution of PFP [276]. Studies have shown that following a hip-strengthening regime that significant changes in lower limb kinematics were achieved [275, 279]. In contrast, however, a similar number of studies [266, 280] have found that despite a significant improvement in strength that no significant differences were found in hip and knee kinematics. The reason for these conflicting results is unknown, however, there is a growing movement with the field suggesting that improvements in hip and proximal strength are is not necessarily essential for changes in kinematics. With consideration of the literature, it is worth noting that major differences exist between the studies. Ferber *et al.* (2011) [280] utilised only a three week strengthening program despite the same author suggesting that at least a six week program is required to achieve the desired treatment effect [268]. Earl and Hoch (2011) [266] utilised an eight week strengthening program and did not find any significant differences in in hip adduction, internal rotation, knee abduction, or rear foot eversion ROM during running. However, closer inspection of the participants shows that their baseline hip abduction strength was 33% kg/BW, which is much larger than the values of 16-29% kg/BW used in other PFP studies [266]. It may be that different people

respond to different types of regime and possibly subgrouping could aid this understanding. A recently described treatment paradigm [281] suggests that rehabilitation has three distinct stages: muscle activation followed by muscle strengthening and finally movement control (see *2.10.1* for further details). With consideration of this paradigm in relation to the Earl and Hoch (2011) [266] paper, it may be that these individuals with optimal strength may have benefited more from motor control, which may have led to significant changes in kinematics. Being able identify groups would allow better selection of treatment and would improve the understanding of which groups respond best to certain interventions. This stratification approach is discussed further in Chapter 6.

The other potential mechanism surrounds the effect of hip strengthening protocols on knee strength. Two RCTs [268, 275] that have recorded pre and post intervention strength measures have demonstrated that hip strengthening also provides a significant increase in strength for knee extensors [268] and knee flexors [275]. This is probably the result of the closed chain nature of the exercises employed in the included studies [198, 275]. This suggests that perhaps the mechanism of effect for hip strengthening shares similarities with knee strengthening, as detailed in 2.9.2.2. Based on this evidence, future studies should investigate mechanisms that are assumed in both approaches, which include lower limb kinematics, lower limb kinetics and PFJ alignment changes.

2.9.2 Knee targeted interventions

2.9.2.1 Efficacy

It is well established in both clinical practice and current evidence that quadriceps strengthening is effective in PFP management [282]. The precise method of delivery for most effective quadriceps strengthening is not so clear. A number of RCTs have compared open kinetic chain (OKC) to closed kinetic chain (CKC) with results showing no difference between exercise intervention at six weeks [283] and three months [284]. In contrast, other studies [285, 286] have showed significant differences in favour of CKC in terms of pain VAS [285] and function [286] (e.g. step down test) at eight weeks. This difference may be the result of type 1 error with these studies [285, 286] only using a relatively small sample (n < 24) compared to the other studies (n> 45). However, in the studies [283, 284] that show no difference, on closer inspection there is a trend towards CKC showing a greater improvement in terms of pain with functional activity. Furthermore, a few RCTs [287, 288] have investigated whether VMO specific exercise produces a different affect to general

quads specific exercise. Both found no difference in terms of pain and disability between groups at eight weeks [288] and six months [287].

2.9.2.2 Mechanism of effect

Despite quadriceps exercises being the mainstay of PFP rehabilitation, there is a paucity of evidence detailing the mechanistic effect of stronger quadriceps on PFP symptoms. The VMO was traditionally seen as cause of PFP and the VMO activity has been seen as a potential mechanistic outcome following knee-targeted exercise despite recent work questioning its mechanistic importance [289]. Generally the exercises that have utilised predominantly knee targeted exercise have demonstrated no significant change in VMO response time or changes in VL: VMO timing [285, 290, 291]. However, Ng *et al.* (2008) [290] showed that in a group that used biofeedback in conjunction with the knee exercises that a significant change occurred. This could, however, be simply explained by the fact that biofeedback increases body awareness, allowing one to selectively activate specific muscle groups e.g. VMO more independently [292].

New evidence has begun to further elucidate the mechanism through which knee strengthening affects PFP. Chiu *et al.* (2012) [166] showed that following an eight week knee strengthening protocol, significant changes were noted in PFJ contact area, analysed using MRI. This was associated with significant reductions in pain and disability. No differences were noted in patella tilt angle. This is in agreement with a recent study [293] that assessed patella tilt and lateralisation using CT and found no difference following eight weeks of knee strengthening. They unfortunately did not assess PFJ contact area so no comparisons can be made. The findings of these studies provide a plausible relationship between knee extensor strength and PFJ contact area but not with the other common PFJ imaging features. Changes in patellofemoral contact area provide a potentially plausible mechanism of effect, as this would theoretically mediate the patellofemoral joint stress as discussed in section *2.7.3*.

2.9.2.3 Predictors of response for multimodal treatment

Multimodal physiotherapy is widely considered the accepted standard of treatment for PFP [16]. Quadriceps and hip strengthening remain a fundamental component of these programmes [282] but whether all patients will benefit strengthening is unknown. The importance of identifying predictors of this type of intervention is thus important. A number of studies [19, 294-296] have investigated the factors that predict a response to multimodal treatment and have identified a range of prognostic factors. It has been highlighted that there

is a difficulty with differentiating between prediction and prognostic factors [297]. Prognostic factors do not relate to a specific intervention and thus are unable to guide clinical decisions [297]. For purpose of this section, the term predictors of poor response has been chosen reflecting predictors that determined an unsuccessful response following multimodal treatment. The following predictors are shown in Table 2.6. This list demonstrates the large degree of inconsistency in the current literature. The precise reason for this inconsistency is unclear, however the heterogeneity of the chosen outcomes is likely to have an impact on the comparability. The largest cohort(n=330) analysed [19] which was combination of two large RCT showed that the duration of symptoms (> 2 months) and baseline knee pain and function (AKPS < 70) were the strongest predictors of poor response. However, this study highlights another systemic problem with these post-hoc, pre-post study designs that the outcome is very dependent upon the selection of the participants. Collins *et al.* (2013) [19] show that knee pain greater than 2 months is a predictor of poor outcome but their inclusion criteria was pain for greater than 6 weeks and overall their cohort consisted of 81% (252/310) with over two months of pain.

Table 2.6: Predictors of poor response to multimodal treatment

Predictors of poor response (at baseline)	Standardised coefficient (β) unless otherwise stated
Smaller CSA at the mid-thigh [294]	0.56
Higher frequency of pain [294]	-0.49
Lower eccentric knee extension [294]	-0.44
Greater lateral deviation of the tibial tubercle (> 14.6mm) [296]	0.51
Higher grade of chondromalacia [296]	0.44
Less change in fear avoidance of physical activity [295]	0.46
Less change in fear avoidance of work [295]	0.34
Greater duration of symptoms (> 2 months) *[19]	-12.33
Worse baseline knee pain and function (AKPS < 70) [19]	0.33
Greater duration of symptoms (>12 months) * [298]	2.90
Worst pain (VAS) [298]	-0.52
Worst function (AKP score) [298]	0.48
Older age [299]	*r* = -0.25 (to VAS)
Faster reflex response time of VMO [300]	*r* = -0.33 (to AKP)
Greater duration of symptoms at 3 months [300]	*r* = -0.65 (to AKP)
Less knee strength (between affected and unaffected) [301]	*r* = -0.37 (to Lysholm)

**Note the same cohort used at different time points.*

AKP = anterior knee pain scale; VAS visual analogue scale' Lysholm = Lysholm knee scoring scale; CSA = cross-sectional area; VMO = vastus medialis oblique

2.9.3 Taping

2.9.3.1 Efficacy

In accordance with the prevailing theories around patellar maltracking, tape has been commonly applied in a medial direction as means of counteracting the natural, lateral movement of the patella and thus improving pain and function [215]. It has commonly been applied in combination with exercise or used in isolation [213]. A number of systematic reviews [2, 302-305] provide a clear state of the current evidence for the efficacy of tape. Consistently there is evidence for tape reducing pain in the immediate to short term [302, 304, 305]. All the earlier reviews highlight the need for studies to include longer follow-up periods, and show that a large variation exists in the taping application and techniques. This variation in tape techniques supports a recent systematic review by Barton *et al.* (2014) [303] who reviewed the literature in terms of tailored taping (individualised adjustment for patellar spin, rotation and/or tilt) versus untailored taping. They showed that tailored taping appeared to provide more pain reduction than the untailored (often medially directed) taping, however, concluded similarly to previous reviews that the long-term effects are inconclusive. Of note in this review is the inclusion of any study design that included a comparative group. A more stringent study selection criterion was applied by a recent Cochrane review. [2] They concluded that the current evidence for taping in PFP, based on five small RCTs, was of low quality and insufficient to support the effectiveness of tape.

2.9.3.2 Mechanism of effect

The actual mechanism of effect of taping is still widely debated. The use of taping to improve VMO activation has been explored. A number of studies [217, 218, 306-308] show that the application of tape in a medial direction will improve the VMO: VL timing, with VMO activating earlier than VL which was been noted prior to application. Interestingly, this change in ratio of activation showed an increase in VMO activation [217] whilst another study noted a decrease in activity but an earlier activation [306-308]. Collectively all these studies showing a decrease in activity used a more demanding activity such as single legged squats[306, 307] and exercising to fatigue [308], which may have accounted for the difference.

A traditional justification for using taping has been to counteract the malalignment of the patella. There is conflicting evidence around the effect of taping on the position of the patella [305], however much of the conflict appears to arise from comparison of different outcomes,

procedures and even populations. Under static XR [292] and CT [309] no change in position of the patella was found using a variety of malalignment radiographic outcomes after taping. In contrast there are several studies that have demonstrated a change in patellar position following tape [310-314]. These may have detected a change by using a larger variety of knee flexion angles and better representing the dynamic nature of the PFJ [310, 314]. It is also clear that all the studies that utilised MRI, rather than XR [315]and CT [309] detected a change. This explanation is unclear as many of the imaging features are applied in exactly the same way, regardless of imaging modality. Caution is also advised interpreting these findings because what constitutes a 'normal' patellar position is unknown [314].

Tape has also been shown to have an influence on both lower limb kinematics and kinetics [213]. It has been demonstrated [316, 317] that the application of patellar tape will increase the knee extensor moment during a step-up and stair ambulation task respectively. These studies have also shown [317] that tape leads to an increase in knee flexion angle during stair ascent and descent. These improvements in kinetics and kinematics could be the result of increased confidence during loading tasks in response to reduced pain or could be the result of alterations in cortical activity. A few authors who have questioned the importance of the direction of the applied taping [217] suggest that cutaneous stimulation and changes in proprioception could be the more probable mechanism of effect. Callaghan *et al.* (2012) [26] utilised functional magnetic resonance imaging (fMRI) of the brain and applied patella tape to eight healthy participants. A comparison between the tape and untaped conditions showed that application of the tape decreased the activity within the cingulated motor area cerebellum (the regions of the brain concerned with the unconscious aspects of proprioception). They interpreted this as the tape making the task easier to perform and thus leading to less activity in these regions of the brain [26]. At this stage these conclusion are only based on eight asymptomatic individuals so the generalisability of these findings is limited.

2.9.3.3 Predictors of Response

The predictors of a likely successful outcome following taping have been investigated in 150 participants published across two studies [318, 319]. The following factors have been identified: i) positive patellar tilt test; ii) tibial varum greater than 5° [319]; iii) lower BMI, smaller LPA and iv) larger Q angle [318]. Both studies use a similar testing approach with pain score given during a stepping task with and without tape. The consistency in testing techniques does allow comparison and synthesis of the data; however, caution is advised

over the generalisation of these findings. Both studies have a relatively high age range of 20 to 60 years compared to the rest of the literature within this field. It is also worth noting that Lesher *et al.* (2006) [319] shares the shame cohort with another study published [320], which looked at the predictive factors that affected a lumbopelvic manipulation intervention. These papers appear to share the same cohort and were likely conducted at a similar time. What is not known is whether there was wash-out period between study interventions to prevent a potential carry-over effect [321].

2.9.4 Knee orthoses

An expanded version of this review of the literature has been published as:
Smith TO, **Drew BT**, Meek TH, Clark AB. (2015). Knee orthoses for treating patellofemoral pain syndrome. *The Cochrane Library*[25]

2.9.4.1 Efficacy

Knee orthoses, which include knee, braces, sleeves etc. can be used to treat PFP. The typical orthosis often made of neoprene comprises of a patella hole with some additional straps or buttresses [25]. Despite being considered a viable option for PFP treatment, there is no consensus on the use of orthoses for patellofemoral and whether they should be used as an adjunct to exercise or in isolation [322]. Our systematic review of the literature [25], identified five trials [323-327] that have explored the efficacy of knee orthoses. Most of the trials incorporated the addition of a home therapeutic exercise programme, with the exception of Finestone *et al.* (1993) [324] whose participants continued with basic military training. All the studies compared knee orthoses and exercise to an exercise only control group showing that the addition of the orthoses did not provide any significant statistical or clinical difference in pain or function. Only one study compared knee orthoses to exercise alone [325] showing that both groups improved, however, there was no statistical or clinical difference between groups.

Despite efforts to synthesise and pool data, there is notable heterogeneity in the studies, which may limit the conclusions made. Five different orthoses were used across the five studies all with slightly different proposed mechanism of effect and the outcomes used varied greatly particularly for the measurement of function. Similar to the outcome of a previous review [328], the overall effect of knee orthoses in PFP appears limited, however,

the ‘very low’ quality of the current literature does not allow a definitive conclusion to be drawn.

2.9.4.2 Mechanism of effect

There is no consensus to the exact mechanism of the knee orthoses [329]. The design of each orthoses will also have different intended mechanistic effects [330]. A number of studies [148, 167, 314, 331] have shown that orthoses have a direct effect on the alignment and kinematics of the patellofemoral joint. Most of these studies showed that the application of a knee orthoses was able to change both the PTA and BSO although Powers *et al.* (2004) [167] found no difference in PTA but a small significant change in BSO. Worrell *et al.* (1998) [314] found significant effects only at 10° flexion. However, this study did not measure at full extension, in contrast to the other studies, which appears to be the optimal angle to show the most pronounced difference [148]. Powers *et al.* (2004) [167] also showed that application of orthoses had a significant effect on the patellofemoral joint contact area. They showed that both the ‘On Track’ brace and ‘Patella Tracking Orthosis’ demonstrated mean increases of 59.3 mm^2 and 52 mm^2 in patellofemoral contact area respectively, compared to no brace conditions. This would lend itself to reducing the underlying patellofemoral joint stress (as discussed in section *2.7.2*). These findings are also supported by work based on cadaveric studies showing significant reduction in peak and centre of pressure under brace conditions [332]..

Outside the potential biomechanical effects, it is presumed that the enclosing nature of the brace will provide a level of cutaneous and proprioceptive input [333]. This has been shown in a number of studies applying an knee orthoses to an asymptomatic population [334, 335] but never shown in PFP population. Selfe *et al.* (2011) [336] has probably shown the strongest link between knee orthoses and potential proprioceptive effects in PFP patients. They demonstrated that the application of a knee orthosis during a step descent procedure resulted in a significant reduction in the total range of knee movement in both frontal and transverse planes compared to both tape and no treatment condition. These authors attribute these findings to the likely stimulation of cutaneous receptors, which may enhance muscular activity leading to more effective limb control. However, as discussed in section *2.4.8* other mechanisms of effect have also been proposed for observed increases in proprioceptive function.

2.9.4.3 Predictors of response

There is paucity of data showing predictors of response to knee orthoses. Draper *et al.* (2009) [148] highlighted the association between abnormal patella kinematics and the effect of knee orthoses. They observed that a subset of patients with abnormal patellar kinematics including BSO, PTA displayed a greater effect from the application of the orthoses. It may be that the studies exploring the efficacy of knee orthoses may have unintentionally selected participants with 'normal' baseline patellar kinematics thus reducing the potential for effect. This provides some potential justification for subgrouping when applying orthoses.

2.9.5 Foot orthoses

2.9.5.1 Efficacy

The use of foot orthoses in the management of PFP is advocated by a systematic review of reviews incorporating level 1 evidence with expert opinion [16]. Based on the current evidence, two systematic reviews [337, 338] based predominantly on the same RCT [339] have recommended that prefabricated orthoses are more effective in providing a subjective global improvement score compared to flat inserts in the short term (six weeks). However, this effect is not carried on to 12 or 52 weeks. Since these reviews were published, a further RCT has shown that foot orthoses show greater improvements in a similar global improvement scale when compared against a wait-see policy [340]. This RCT was also only based on short-term follow up (6 weeks) thus the long-term effect of foot orthoses is uncertain.

Using foot orthoses in conjunction with physiotherapy would seem appropriate considering the evidence to support multimodal treatment. Nevertheless, conflicting evidence exists to support addition of physiotherapy based on the current evidence from RCTs. Eng and Pierrynowski (1993) [341] showed that an orthosis plus physiotherapy programme provided a greater reduction in pain compared to physiotherapy alone at eight-week follow up, whereas the greater-powered study by [339] found no difference at a short, moderate or long term follow up. This difference may be explained by the Eng and Pierrynowski (1993) [341] selecting only patients with pronated foot type (calcaneal or forefoot valgus >6 degrees). This application of orthoses, based on selection of participants with more than nine degrees calcaneal valgus, has been also been showed to be successful at three months [342]. This suggests that tailoring your prescription of orthoses is essential to the overall efficacy of using orthotics in combination with physiotherapy. Caution is advised, however, as to establish the efficacy of any intervention a control condition is required. Although unclear from most study reporting, Rodrigues *et al.* (2014) [263] highlights the point that some

'healthy controls' may be using specialist footwear that mimic a foot orthotic-type intervention thus impacting on the conclusion that can be derived.

2.9.5.2 Mechanism of effect

Despite the promising efficacy of orthoses in treating people with PFP, the mechanism of effect has not been demonstrated definitively. Authors suggest that the likely mechanism is either mechanical, neuromotor or a combination of both [337]. Mechanically, the application of an orthoses has been shown to control predominantly the frontal and transverse knee motion [343]. Early research focused on the foot with data showing that orthoses reduced the eversion of the foot [261, 343] and internal rotation of knee/ shank [343]. Further research has shown that orthoses were also able to significantly reduce the hip adduction movement during stair ascent [344]. These biomechanical alterations are likely to normalise the patellofemoral joint stress by ensuring better alignment and equalising the force distributions around the PFJ[341].

An abnormal change in neuromotor activity is another possible mechanistic effect [337]. Foot orthoses have been shown to reduce the effort and activity of important muscle groups, with one study showing a reduction in peak amplitude of gluteus medius during stair ascent [344]. Whilst in PFOA, the application of orthoses has been shown to cause a later onset of vastus lateralis and lateral hamstring [345]. It may be that a reduction in activity of some muscles such as quadriceps can reduce their potential fatigability. Alternatively, a reduction of other muscles like hamstrings may be advantageous due to their known over-activity in PFP [346] and their proposed impact on rotational tibial alignment and biomechanics [347].

A further consideration to both the mechanism and potential efficacy is simply the comfort of the orthoses. Mills *et al.* (2012) [348] showed that a less comfortable orthosis resulted in a more unfavourable relative increase in hip adduction and a significant increase in VL activity. Furthermore, any intervention like orthoses requires an element of compliance. McPoil *et al.* (2011) [349] found that both PFP and controls perceived a contoured orthoses to provide greater support and comfort than flat inserts suggesting these would be preferred by patients. No difference, however, was found in the number of hours each foot orthoses was worn between groups. A clear association between foot orthosis comfort and compliance has not been established in PFP.

2.9.5.3 Predictors of response

The predictive factors for a favourable outcome following the prescription of foot orthotics have been identified and are shown in Table 2.7.

Table 2.7: Predictors of response to foot orthoses

Type of feature	Features
Static	• Ankle dorsi flexion < 41.3 [350] • Midfoot difference from NWB to WB> 10.96 [351] • Midfoot difference from NWB to WB > 11.25mm [340] • > 2 degrees of forefoot valgus [352] • < 78 degrees passive toe extension [352] • < 3mm navicular drop [352]
Dynamic	• Greater rearfoot eversion [350] • Foot wear motion control < 5 [350]
Clinical	• Immediate reduction in pain with single leg squat [350] • Usual VAS < 22 [350] • Worst VAS < 53.25 [351] • Longer duration of symptoms [353] • Worse AKPS score [353]
Demographic	• Age > 25 [351] • Height > 165cm [351]

These results present a number of features that can be used clinically to determine whether an orthoses might be useful as an intervention. It is, however, worth noting that the post-hoc nature of many of these studies leads to a potential for over-fitting the model. Regardless of the varied sample sizes (n= from 26 to 179), the fit of model will be determined by a ratio of the sample size to the number of variables. There is also the suggestion that adult predictors cannot be extrapolated to an adolescent population. Pitman and Jack (2001) [354] showed, in a sample with over a third aged between 11 to 18 years that orthoses lead to 67% reduction in pain at 6 months. This may contradict the suggestion made by Vicenzino *et al.* (2010) [351] that being aged over 25 years is a predictor of success based on their cohort aged 18 to 40 years.

2.9.6 Link between PFP interventions and stratification

In summary, this section further supports the need for stratification by highlighting the multiple treatment options available for PFP. Strong evidence exists to support both knee

and hip strengthening alone and in combination for the management of PFP. However, there is conflicting evidence to support any difference in these strengthening regimes with some evidence suggesting hip strengthening may achieve desired outcomes earlier. Despite a paucity of evidence, the growing use of novel treatment options such as movement retraining might be important when it is considered that some PFP cohorts show normal strength at baseline and are thus unlikely to benefit from further strength training. Limited evidence is available to support the use of both taping and knee orthoses but with some evidence suggesting that tailored taping may be more effective than untailored taping. Taping and bracing have been shown on MRI studies to consistently alter patella malalignment features despite contrasting findings observed under different imaging modalities. The other potential mechanisms which include improved proprioception and cutaneous activity remain speculative at present due to being based on limited data. Moderate evidence exists to support the use of foot orthoses in the short term with no effect found at long term follow up. Foot orthoses also remains one intervention to have been used within stratified approaches already and demonstrates promising findings, with 79% of people with PFP reporting a favourable outcome. The predictors of response for all these interventions cover a diverse range of structural, biomechanical, clinical, psychosocial and demographic factors which could also explain the heterogeneous response to these interventions.

2.10 Stratification & subgrouping

The presentation of the literature in the preceding sections of this review demonstrates that PFP is a condition which: i) has a multifactorial aetiology; ii) likely demonstrates multiple relevant targets for intervention; and iii) provides multiple treatment options with heterogeneous responses. In this scenario the use of stratification is recommended [124]. The idea of stratified medicine was first proposed over 50 years ago [355] by American Psychologist, Lee Cronbach[140], who advocated that “we should design treatments not to fit the average person but to fit groups with particular aptitude patterns…on the assumption that aptitude-treatment interactions exist”. A variety of definitions of *stratified medicine* are shown in Table 2.8. The commons themes from these definitions are: the classification of individuals into subgroups/ subpopulations; based on response to treatment or biological characteristics; in order to target /tailor treatment; and to improve efficacy, safety and economic outcomes.

Table 2.8: Definitions for stratified medicine
Adapted from [356, 357]

Source	Definition
Prognosis Research Strategy (PROGRESS) Partnership	Stratification of treatment is the act of targeting treatments according to biological or risk characteristics shared by subgroups of patients
President's Council of Advisors on Science and Technology	The tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of medicine or medical devices that are unique to a patient but rather the ability to classify individuals into subpopulations that differ in their susceptibility to particular disease or their response to a specific treatment. Preventative or therapeutic interventions can then be concentrated on those who will benefit, sparring expense and side effect for those who will not
Academy of Medical Sciences	Stratified medicine is the grouping of patients based on risk of disease or response to therapy by using diagnostic test or techniques
Innovate UK	Stratified medicine is an effective therapy that requires: • A companion diagnostic test • A clearly identified group of patients defined by in vitro diagnostics, biomarkers, defined algorithms, clinical responses, imaging, pathology • A molecular level understanding of the disease • Availability of both tests and medicines to clinicians
International Society of Pharmacoeconomics and Outcome Research	Stratified/ personalised medicine is the used of genetic or other biomarker information to improve the safety, effectiveness and health outcomes of patient via more efficiently targeted risk stratification, prevention and tailored medication and treatment management approaches

The graph shown in Figure 2.8 demonstrates the distribution of effects in a typical clinical trial and how the treatment effect may be diluted by the inclusion of groups whom the treatment is not effective [358]. As Foster *et al.* (2011) [358] eloquently states in relation to musculoskeletal medicine:

> *"The analysis of trial data relies on average treatment effects which can mask a wide range of individual responses to treatment, including for example patients who benefit a great deal along with those who benefit little or not at all. This underpins the interest in identifying important subgroups"*

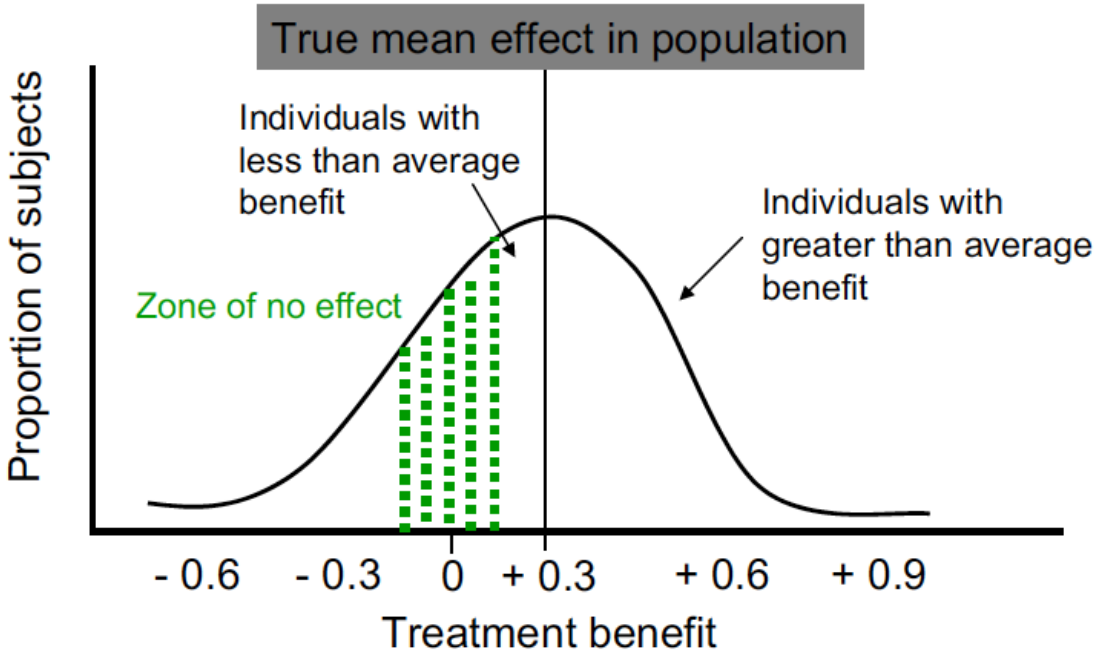


Figure 2.8: Distribution of the effects of treatment
Reprinted with permission from Elsevier; Manual Therapy [358]

Callaghan (2012) [22] conducted an analysis of all RCTs within the PFP literature up to 2009 showing that 61% (32/52) reported overall statistical significance when comparing different treatment regimes but found a limited attempt to stratify treatment. He found only two examples (2/52) [307, 359] that applied criteria to select treatment. However, in both these examples participants were excluded from the study, rather than treatment being stratified [22]. Analysing the most recent Cochrane review on patellofemoral and conservative interventions [24], none of the studies included appear to utilise any stratification or sub-classification. Outside the methodological rigour of an RCT, some other studies discussed below in section 2.10.2 have attempted stratified, targeted treatments without exclusion.

Foster *et al.* (2011) [358] provides alternative explanations for the lack of treatment efficacy and thus the need for stratification as applied to lower back pain. These explanations can also be applied in the context of PFP. Firstly, it may be that we just over estimate the effectiveness of our interventions. In PFP, intervention groups sample sizes vary from three to 65 participants [24] and collectively demonstrate wide confidence intervals suggesting studies are not adequately powered to detect a change. Secondly, the non-treatment effects of any intervention cannot be ignored. It is plausible that factors such as clinician empathy and support are more significant in pain-related conditions such as PFP that often presents

to a treating clinician in chronic state. Doménech *et al.* (2014) [118] have shown recently that individuals with PFP present with greater levels of catastrophization, which has been shown to be modulated better in other populations, by interventions providing emotional support and expectation management [360]. Finally, it has been postulated that those providing treatment in the RCTs are not competent or that the treatment itself is not appropriate for the desired outcome [361]. Lack *et al.* (2015) [198] highlight the inconsistencies within the programme used to train the hip and proximal components for PFP. They demonstrate the many studies employ inadequate treatment dosage in terms of the intensity and frequency of the prescribed exercises and that a great deal of variation exists in the literature. To address this discrepancy in exercise prescription parameters, Powers (2015) [281] recently presented a treatment paradigm that aimed to clinically stratify hip strength training. Three distinct phases have been identified anecdotally as: muscle activation, strengthening and movement training. This forms an algorithmic approach where each component must be considered and satisfied. This work, however, remains unpublished and is based purely on anecdotal evidence. It does raise the possibility though that other stratification approaches might be in use in current clinical practice without having been subject to the rigours of research.

In support of future stratification, the last three International Patellofemoral Retreat consensus statements [14, 20, 115] have highlighted the need for diagnostic sub-grouping and subsequent treatment stratification within the overall PFP population. The belief is that better sub-grouping will allow better targeting of interventions. Within musculoskeletal medicine a number of sub-grouping method and designs can be employed. A series of studies by Kent and colleagues [362-364] have highlighted the difference in approaches for subgrouping in musculoskeletal medicine. The different approaches are detailed below in the context of PFP.

2.10.1 Diagnostic subgroups

Diagnostic subgrouping aims to group individuals based on the pathoanatomical characteristics and underlying mechanisms. Over the last 30 years, attempts have been made to classify and subgroup the presentation of PFP. These diagnostic sub-groupings are detailed in Table 2.9. Historically, classification focused more on patellofemoral *disorders* i.e. any condition affecting the patellofemoral joint. These earlier classification systems were primarily designed to guide surgical decisions and are often associated with recipe-like prescriptive rehabilitation protocols [22]. It was not until 2005, that Witvrouw *et al.* (2005) [18]

began to consider variations in the associated soft tissue with particular consideration of quadriceps activity and activation. More recently, groups have begun to propose classifications based on a greater consideration of the multifactorial nature of PFP. Both Smith *et al.* (2013) [365] and Keays *et al.* (2015) [366] have proposed broad classifications which consider important features such age, abnormal kinematics, muscle flexibility and psychosocial issues; with the latter even including patellofemoral osteoarthritis which, although the link is unproven, is widely considered to form a continuum with PFP [5]. Four recent studies have also begun to consider heterogeneity within single imaging feature such as patella lateralisation and patella tilt [181, 367, 368] and kinematic factors [243].

Table 2.9: Classification systems of PFP

Study	Classification
Ficat 1979 [369]	• Chondromalacia of the lateral facet • Chondromalacia of the medial facet- • Central chondromalacia-characterized by a localization as a saddle straddling the median ridge with symmetrical extension onto the 2 facets • Bipolar chondromalacia-involving the central portion of the 2 facets separated by a normal median ridge. • Global or total chondromalacia-involving the totality of both facets

Merchant 1986 [370]	• Isolated trauma
	• Repetitive trauma
	• Patellofemoral dysplasia
	  ○ Lateral patella compression
	  ○ Chronic subluxation of patellae
	  ○ Recurrent dislocation of patellae
	• Chronic dislocation
	• Idiopathic chondromalacia patella
	• Osteochondritis dissecans
	• Synovial plicae

Merchant 1994 [371]	• Trauma
	  ○ Acute
	  ○ Repetitive
	  ○ Late effects
	  ○ Chronic dislocation
	• Patellofemoral dysplasia
	  ○ Lateral patella compression
	  ○ Chronic subluxation of patellae
	  ○ Recurrent dislocation of patellae
	• Idiopathic chondromalacia patella
	• Osteochondritis dissecans
	• Synovial plicae
	• Iatrogenic disorders

Wilk et al 1998 [372]	• Excessive lateral patellar syndrome • Global patellar pressure syndrome • Patellar instability • Chronic subluxation • Patellar dislocation • Acute patellar dislocation • Recurrent patella dislocation • Lower extremity biomechanical dysfunction • Direct patella trauma • Soft tissue lesion • Overuse syndrome • Apophysitis • Osteochondritis dissecans • CRPS • Combined pathologies

Holmes & Clancy 1998 [373]	• Patellofemoral instability • Patellofemoral pain with malalignment • Patellofemoral pain without malalignment

Witrouw et al 2005[18]	• Alignment
	  ○ Absence of malalignment
	  ○ Malalignment of the whole leg
	  ○ Malalignment of PFJ
	• Muscular dysfunction
	  ○ Quadriceps hypotrophy
	  ○ Selective VMO hypotrophy
	  ○ Altered VMO;VL reaction pattern
	  ○ Muscle flexibility

Naslund et al 2006 [71]	• Idiopathic AKP • Slow bone turnover • Diagnoses of pathology
Sheehan et al 2010 [181]; Harbaugh et al 2010 [367]	• MRI lateral maltrackers • MRI non-lateral maltrackers
Dierks 2011[243]	• Knee valgus group • Hip abduction/adduction group • PFP other
Pal et al 2012 2012 [368]	• MRI maltrackers • MRI Normal trackers
Smith et al 2013 [365]	• Underlying rotational profile • Central tibiofemoral-patellofemoral features • Psychosocial issues
Keays et al 2015 [366]	• Hypermobile group of young females group • Active older patients with muscle tightness group • Dynamic knee valgus group • PFOA group
Selhorst et al 2015 [374]	• Fear avoidance group • Flexibility group • Functional malalignment group • Strengthening/ Functional progression group
Selfe et al 2016 [254]	• Strong group (greatest hid abduction, greatest quadriceps strength and lowest patella mobility) • Weakest group (weakest quadriceps strength, weakest hip abductor and shortest quadriceps length) • Pronated feet group (highest FPI, highest patella mobility)

Probably the most comprehensive work on subgrouping to date, which has applied this diagnostic approach, has been undertaken by Selfe *et al.* (2016) [254]. In this multicentre feasibility study, 127 people with PFP were statistically sub-grouped using six clinically available tests which included quadriceps length, gastrocnemius length, isometric quadriceps strength, isometric hip abductor strength, total patellar mobility and foot posture

index. They identified three sub-groups: ‘strong’, ‘weak and tight’ and ‘weak and pronated’ (see
Figure 2.9). The identification of a ‘strong group’ is perhaps most surprising considering that quadriceps weakness is accepted as both an associated [194] and a risk factor [53] for PFP . This further justifies the need for subgrouping, as the concern is that current treatment paradigms may have meant these people would have still received quadriceps strengthening as this forms a core component of most multimodal treatment approaches. These diagnostic groups are of high clinical utility, only requiring six simple clinical tests without the need for expensive equipment. However, due to this intentional clinical utility these subgroups are unable to consider factors related to patellofemoral structure [181, 367, 368] and kinematics [243] which require expensive equipment such as MRI and 3D motion analysis systems. The addition of structural and kinematic outcomes, however, may inform subsequent treatments, improve the understanding of the mechanism within these groups and refine these existing groups further. The imaging outcomes may also allow the identification of a group with osteoarthritic changes. A group with these changes would be considered as having a risk of developing future osteoarthritis and may lead to a shift in the focus of future trials.

The Selfe *et al.* (2016) [254] study also uses unsupervised statistical tests e.g. cluster analysis and latent class analysis to identify their subgroups. Unsupervised tests, in contrast to supervised tests, do not work backwards from a outcome but instead explore relationship between characteristics using cross-sectional data [364]. This allows these subgroups to be later studied against a number of treatment targets, which is the proposed plan for Chapter 5. However, because subgroups identified by unsupervised techniques are not derived from a clinical outcome they have sometimes been criticised as having limited clinical relevance [363]. This is because clinical interpretation is made post-hoc. Novel statistical methods have been recently published [364] that use a two–stage clustering approach which aims to address this problem and improve the clinical applicability. More detail is provided in Chapter 5.

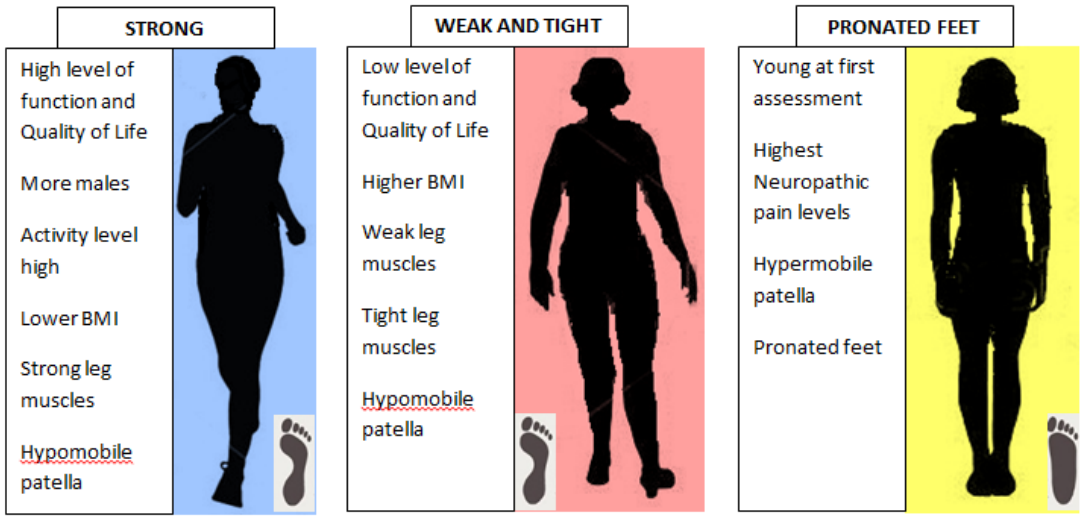


Figure 2.9: Clinical subgroups.
Reprinted with permission from author [375]

2.10.2 Treatment effect modifier subgroups

Treatment effect modifier subgroups aim to identify individuals most likely to respond positively to a particular intervention. A number of studies have used post hoc analysis to assess the response to treatment in PFP for tape [318], orthoses [350, 376] and to develop clinical predication rules for lumbopelvic manipulation [320] and taping [319]. These studies have yielded a number of viable factors that may predict likely response to treatment in PFP but only one study has used these findings to support the selection of suitable patients and to validate their use.

An RCT by Mills *et al.* (2012) [340] used predictors, reported in section 2.9.4.3, from Vicenzino *et al.* (2010) [351] to select a specific sub-group of patients who received prefabricated foot orthoses. Mills *et al.* (2012) [340] selected patients if they presented with greater than 2 of the following features: i) greater than 10.96mm change in midfoot width between WB to NWB; ii) pain severity less than 53/100mm; iii) older than 25 years; and shorter than 165cm. They compared this stratified PFP group (n=19) with a PFP group (n=20) who received no intervention (wait and see policy). Those in the stratified PFP group reported being 79% improved or much improved on a global rating of change scale (GROC). This showed a significant difference between groups (p=0.008). Along with their high success rate, no individuals in the stratified group reported being *worse*. This compares

positively to the unfavourable recovery (no improvement) of 40-62% reported from previous RCTs in PFP without stratification [19, 377]. It does, however, depend on how success is defined for a GROC scale.

Consideration of the interventional procedure in Mills *et al.* (2012) [340] does show, however, that stratification was not only based on the predictors. The procedure for selecting the orthoses was also determined by participants who based their decision on the level of comfort of the orthotic during running. This means that the outcome cannot be entirely attributed to stratifying based on predictors but may also be the result of self-stratifying for comfort. Furthermore, the study used greater than two predictors. Two predictors in the Vicenzino *et al.* (2010) [351] study was showed to have post-test probability of 60% (for reporting a 'marked improvement' on a five point Likert scale) whereas three predictors showed a post-test probability of 85%. No justification is provided to why the greater number of predictors (i.e. > 3) did not form the selection criteria and thus aiming for a better post-intervention outcome. One can assume that recruitment becomes more challenging when attempting to identify patients that satisfy at least three predictors.

Further evidence from two studies of one-group pre-test-post-test design have shown that stratifying patients for gait retraining may optimise treatment outcomes. Both Noehren *et al.* (2010) [204] and Willy and Davis (2013) [205] selected patients with PFP who demonstrated abnormal hip mechanics. Both showed that a targeted intervention aimed at addressing gait retraining resulted in a significant reduction in pain of 86.5% [204] and 90.5%[205] - considerably greater than previous reported studies [278]. Critically this was only based on total of 20 runners with PFP across both studies and only provides level 4 evidence, however, they do demonstrate some positive signal and thus support the need for further research into stratified PFP treatment.

Selhorst *et al.* (2015) [374] piloted a clinical-decision making algorithm within a similar one-group pre-test-post-test design for the treatment of PFP that subgroups patients sequentially based on fear avoidance, flexibility, functional malalignment and strengthening/ functional progression. In essence, the algorithmic approach helps to control for individuals who are classified into more than one subgroup. Their results show that all participants (n=21) reported a clinically significant change from baseline to six week follow up in both AKPS and GROC scales [374]. The concern is that the algorithmic approach is still fundamentally multimodal in nature and thus may require an individual to adhere to long treatment regimens and/or be prescribed extensive exercise programmes. This impacts on the

adoption of the approach into a real life clinical setting where patient adherence and departmental economic pressures are known to be barriers [11]. Specifically, this clinical algorithm places a large emphasis on flexibility and fear avoidance (1st and 2nd components) neither of which, although considered anecdotally important, have strong evidence to support their use over other factors. Furthermore the strengthening component is the last component of the algorithm and determined by the limb symmetry index which may inherently fail to capture weakness in those with bilateral symptoms, which is typically reported as the most common presentation in PFP [254].

2.10.3 Prognostic factor subgroups

Prognostic factors subgroups are symptoms, signs or other characteristics that indicate a subgroup outcome regardless of treatment [362, 363]. A number of prognostic analyses have been conducted within the PFP literature [19, 55, 301, 353]. They have demonstrated a number of factors that consistently influence future prognosis following predominantly multimodal treatment. To date, none of these studies or this subsequent information has been used to develop a classification system or to stratify treatment. This reason for this is unclear, however, it might be due to that fact that many of the features that have been identified e.g. duration of symptoms, baseline AKP etc. are non-modifiable so don't translate to known treatment interventions.

2.10.4 Which stratification approach?

The decision on which subgrouping approach to take is largely dependent on the desired output; however, some important considerations should be made. Treatment effect modifier and prognostic groups are typically based on the prediction of one single outcome often for one single treatment [364]. Data from these types of design can be limited as predictors of pain may not represent the same for function. Diagnostic sub-groups, on the other hand, are determined from cross-sectional, baseline data and thus not dependant on outcome [364]. This approach lends itself for a range of treatments and outcomes to be targeted in later studies [364]. Theoretically it can be considered a 'pre-phase' before a treatment modifier or prognostic effects are investigated [363]. One concern with diagnostic groups is that they don't link directly to clinical efficacy and derived groups may have little clinical relevance or clear treatment targets [364]. To ensure clinical relevance, it would appear appropriate that the selection of factors/ variables need to be determined by current evidence to be both

clinically modifiable and have a recognised treatment target e.g. quadriceps weakness will respond to strengthening regime etc.

2.10.5 Summary

Patellofemoral pain is a common musculoskeletal complaint in adolescents and young adults, and thought to be a precursor to future knee osteoarthritis. Despite a range of treatments being available, the current treatment paradigms appear limited, with over a third of people continuing with symptoms into later life**.** It has been proposed that positive treatment effects seen in some people with PFP are being cancelled out by negative effects observed in others, suggesting a need to identify subgroups within this population. This review shows that there is evidence to support a multitude of treatments for PFP and that stratifying these treatments appears the optimal way to achieve the best treatment outcomes for patients.

The concept of subgrouping and stratification has been hailed as the “holy grail” of PFP research, however, the concept remains under-investigated. This review highlights some potential approaches to PFP subgrouping although there remains a lack of understanding of how the patellofemoral joint structure and lower limb kinematics may contribute to these subgroups. Knowledge of the prognosis of these PFP subgroups is also not understood and would help guide future research priorities. By aligning all known modifiable features highlighted in this review to identify PFP subgroups it is hoped that it will inform the future stratified treatment for people with PFP.

The central hypothesis of this thesis can be summarised as follows:

Improved subgrouping of people with PFP based on modifiable features will enable stratification and targeting of interventions

Chapter 3 - Which patellofemoral joint imaging features are associated with patellofemoral pain? Systematic review and meta-analysis

This chapter describes a systematic review and meta-analysis of the imaging literature in patellofemoral pain. By controlling for confounding factors such as loading and knee flexion the chapter explores which imaging features are associated with patellofemoral pain. The results of this chapter have been published as:
Drew BT, Redmond AC, Smith TO, Penny F, Conaghan PG. (2015). Which patellofemoral joint imaging features are associated with patellofemoral pain? Systematic review and meta-analysis. Osteoarthritis and Cartilage. 24(2), 224-236 [378].

3.1 Introduction

In section 2.7, the reported importance of the structure and the function of the patellofemoral joint (PFJ) as an underlying cause of PFP has been described. PFP is believed to be caused by abnormal tracking and alignment of the patellofemoral joint (PFJ) leading to irritation of the subchondral bone, lateral retinaculum or synovium[34]. Recently, the PFJ was established as the most common compartment for knee OA [379, 380] and hence the structure of the PFJ has become the subject of increased interest.

The PFJ has historically been visualised using X-rays in a static, non-weight bearing position. Over the last 20 years, imaging has revolutionised the understanding of the knee as a whole [381] with advances in structural visualisation, kinematic applications and loading capabilities [382]. A variety of modern imaging modalities have been used to assess PFJ structure [151], but no consensus exists on which of these image modalities should be used or the key features to image.

3.2 Aims

This chapter aimed to establish which PFJ imaging features using a range of commonly available imaging modalities are associated with PFP compared to asymptomatic individuals.

3.3 Methods

3.3.1 Protocol and registration

This systematic review was performed using a predetermined protocol in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [383]. The study protocol was registered with PROSPERO, registration number CRD 42014009503.

3.3.2 Search strategy and study selection

A systematic literature search of AMED, CiNAHL, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, PEDro, EMBASE and SPORTDiscus was undertaken from their inception to September 2014. This search also included a secondary electronic search of unpublished and trial registry databases including OpenGrey, the WHO International Clinical Trials Registry Platform, Current Controlled Trials and the UK National Research Register Archive. The electronic search was complemented by hand searching the references of the retrieved articles. An example of the search terms used for Medline (also used for the other databases) are in Table 3.1. The search terms used were based on terms used by two recent Cochrane reviews [2, 24] with relevant terms added.

Table 3.1: An example search strategy from Medline

	Search Term	Results
1	Arthralgia/	42891
2	Patella/	16585
3	((patellofemoral or patello-femoral) adj joint).tw.	2795
4	1 and (or/2-3)	428
5	2 or 3	18392
6	1 and 5	428
7	Patellofemoral pain syndrome/	1198
8	((Patello-femoral or patellofemoral) adj (pain or syndrome or dysfunction)).tw.	2416
9	((lateral compression or lateral facet or lateral pressure or odd facet) adj syndrome).tw.	44
10	Chondromalacia patellae/	814
11	((chondromal$ or chondropath$) adj (knee or patell$ or femoropatell$ or femoro-patell$ or retropatell$ or retro-patell$)).tw.	849
12	or/5-10	20745
13	"anterior knee pain".tw.	2231
14	12 or 13	21904
15	(radiograph* or radiogram* or radiology or roentgen* or x-ray* or x ray* or xray*).tw.	982319
16	Magnetic Resonance Imaging/	744267
17	(MR imag* or magnetic resonance imag* or MRI).tw.	573363
18	Computed tomography/	495319
19	(CT or computed tomogr* or CTA).tw.	713372
20	Ultrasonography/	262969
21	(USS or ultrasound or ultraso* or sonogra*).tw.	629242
22	15 or 16 or 17 or 18 or 19 or 20 or 21	3019543
23	14 and 22	6013
24	limit 23 to english language	5182
25	limit 24 to humans	4670
26	remove duplicates from 25	3231

3.3.3 Eligibility criteria

Studies were selected using the titles and abstracts, independently screened by two reviewers (BD, FP). All potential studies had the full text retrieved and were screened against the eligibility criteria. Studies were eligible if: 1) they included human participants under 45 years diagnosed with PFP; 2) magnetic resonance imaging (MRI), computed tomography (CT), ultrasound (US) or x-ray (XR) was used to image the patellofemoral joint and local structures; 3) a comparison of PFP cases and a healthy control group was provided; 4) they were published in English.

As discussed in section 2.2, the nomenclature around PFP remains ambiguous. PFP was determined using published clinical criteria taken from a recent Cochrane review [24]. Studies that included participants diagnosed with, but not restricted to, PFP, anterior knee pain or chondromalacia patellae were all considered. Despite efforts to standardise the terminology [14], chondromalacia patellae is still used interchangeably with PFP. If a study included participants with arthroscopically confirmed chondromalacia patellae outside the currently accepted clinical presentation of PFP [24] then these studies were excluded. Studies that may come under the umbrella term of *anterior knee pain* including conditions such patella tendinopathy and patella dislocation were also excluded if the PFP could not be analysed separately.

The extraction of data was initially piloted by two reviewers before the formal extraction was undertaken. Two reviewers then used a standardised, piloted form to extract data which included: a) study design and methodology; b) patient demographics; c) imaging procedure; d) imaging outcomes; e) patient reported outcomes; f) outcome date results. Discordance in opinion, regarding eligibility, data extraction or quality assessment, was resolved by a third reviewer.

3.3.4 Quality assessment

The methodological quality of the included studies was assessed by the same two reviewers. The Downs & Black Checklist [384] was selected as the preferred quality assessment tool. The Downs & Black checklist has been highlighted as one of the most comprehensive quality assessment tools for non-randomised studies [385].The

tool has established high reliability and validity [384] and is considered relatively user-friendly [385]. An alternative choice of tool, would have been the Newcastle-Ottawa Scale (NOS) [386] which was recommended for cohort and case control studies in a recent systematic review of all quality assessment tools [387]. However, at the time of the conception of the review, there were concerns about the inter-rater reliability of the NOS based on Hartling *et al.* (2013) [388] who reported only low agreement between raters (k=0.29, 95% CI0.10, 0.47) .

The Downs & Black checklist was modified for this chapter in response to its criticism that it is time consuming and that not all the criteria are applicable to case-control studies [389]. The original 27 items were reduced to 17 items as described previously [390] (Table 3.2). Items not applicable for non-interventional studies were removed. During assessment, if it was unclear whether an item was satisfied then UTD (unable to detect) was added to the form and that item was given a score of zero. All included studies were classified using the following quality rating bandings which have been used previously in conjunction with Downs & Black checklist [391]: low (< 33.3%), moderate (33.4 -66.7%) and high (≥66.8%)[392].

Table 3.2: Modified Downs & Black Checklist

	Reporting	Yes	Partial	No	Score
1	Is the hypothesis /aim / objective of the study clearly described?	1		0	
2	Are the main outcomes to be measured clearly described in the Introduction or Methods section?	1		0	
3	Are the characteristics of the patients included in the study clearly described?	1		0	
4	Are the interventions of interest clearly described?	1		0	
5	Are the distributions of principal confounders in each group to be compared clearly described?	2	1	0	
6	Are the main findings of the study clearly described?	1		0	
7	Does the study provide estimates of the random variability in the data for the main outcomes?	1		0	
8	Have the actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	1		0	
	External validity				
9	Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	1		0	
10	Were the subjects who were prepared to participate representative of the entire population from which they were recruited?	1		0	
	Internal validity				
11	Was an attempt to blind those measuring the main outcome?	1		0	
12	If any of the results of the study were based on “data dredging” was this made clear?	1		0	
13	Were the statistical tests used for the main outcomes appropriate?	1		0	
14	Were the main outcome measures used accurate (valid and reliable)?	1		0	
15	Were the case and controls recruited from the same population?	1		0	
16	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	1		0	
17	Did the study have sufficient power to detect a clinically important effect?	1		0	
		Total		/18	

3.3.5 Data analysis

Using the extraction tables the heterogeneity of the included studies was assessed. A pooled meta-analysis was conducted if there were no heterogeneity between studies in relation to population, assessment procedure or outcome measurement method. Meta-analyses compared case and control groups for each PFJ feature calculating the standardised mean difference (SMD). SMD was categorised as small (SMD ≥ 0.2), medium (SMD ≥ 0.5) and large (SMD ≥ 0.8) [139]. Statistical heterogeneity was assessed using I-squared (I^2) and Chi-squared tests (X^2). When I^2 was greater than 20% and X^2 less than p=0.10, a random-effects model was used. When I^2 was less than 20% and X^2 was greater than p=0.10, a fixed-effect model was adopted. When substantial heterogeneity was present, a narrative synthesis of the literature was presented. Both the narrative synthesis and the meta-analysis were interpreted using a best evidence synthesis [393] (Table 3.3) determined by the results of the risk-of-bias assessment and the methodological quality of the included studies [394, 395].

Table 3.3: Best Evidence Synthesis [396]

1	Strong evidence is provided by generally consistent findings in multiple high-quality cohort studies.
2	Moderate evidence is provided by general consistent findings in one high-quality cohort study and two or more high quality case–control studies or in three or more high-quality case–control studies.
3	Limited evidence is provided by (general consistent) findings in a single cohort study, in one or two case–control studies or in multiple cross-sectional studies.
4	Conflicting evidence is provided by conflicting findings (i.e. <75% of the studies reported consistent findings).
5	No evidence is provided when no studies could be found.

3.4 Results

3.4.1 Study selection

Figure 3.1 summarises the results of the search strategy. The search identified 5,290 papers, with 3,852 after duplications were removed. Following screening of the title and abstract, 3,702 of these were excluded. Subsequent full text assessment identified 46 papers describing 40 studies. Five studies [159, 163] [65, 170] [397-399] [66, 68] [294, 400] reported the same study population in more than one paper. These papers described different outcomes so were analysed independently, although the risk of bias assessment was conducted on only 40 studies to prevent the overestimation of effects [401].

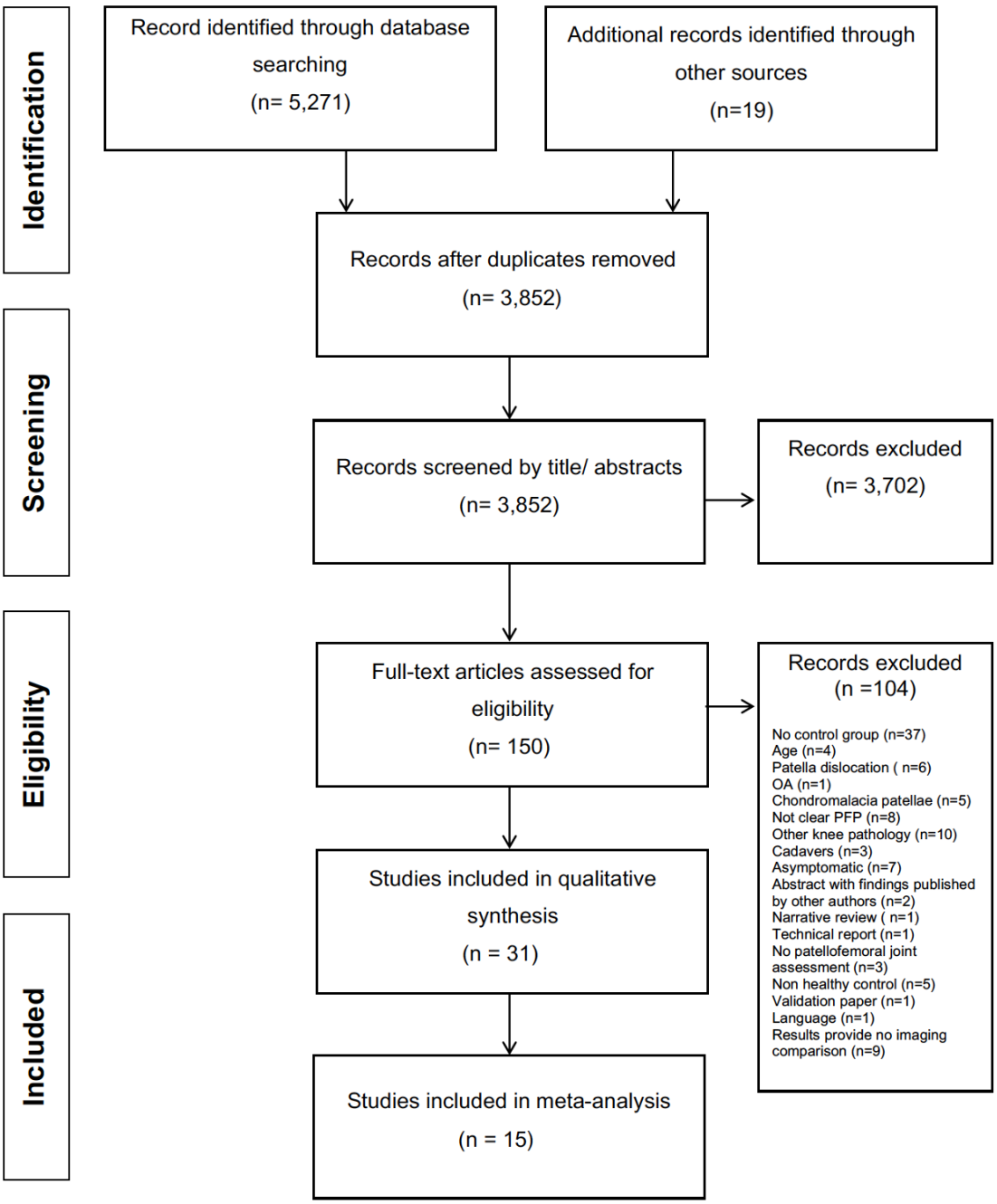


Figure 3.1: Study selection flow diagram

3.4.2 Study characteristics

Study characteristics are presented in Table 3.4. Of the 40 studies included, 22 used MRI [65, 66, 68, 148, 159, 160, 163, 165, 166, 168-170, 173, 179, 256, 294, 397-400, 402-409], of which five included kinematic MRI [148, 179, 404, 408, 409] , eight used CT [410-417], six used US [82, 216, 228, 359, 418, 419] and five used XR [413, 420-423]. The review included 1,043 PFP subjects and 839 control subjects. The mean age was 27.0 years (range: 14 -40.7 years), with 74.3% women in the case group and 69.0% in the control group. The duration of symptoms was reported in only 10 of the 40 studies [65, 82, 160, 170, 294, 359, 400, 402, 408, 413, 416, 422] and ranged from two [160] to 168 months [416]. All except two studies presented cross-sectional data [148, 166]. Pain was established in the PFP cohort most commonly from reproducible pain in greater than two functional activities [65, 148, 159, 160, 163, 165, 168, 170, 179, 216, 256, 359, 397-400, 402, 404, 418, 419, 424]. This was further quantified by five studies that only recruited participants with a Visual Analogue Scale (VAS) score greater than 3/10 on these provocation activities [65, 160, 165, 170, 179, 256]. A further four studies used the Anterior Knee Pain (also known as Kujala scale) score to quantify pain and dysfunction of their PFP cohort [148, 169, 400, 402]. In ten studies it was unclear how pain was measured [82, 173, 403, 407, 410, 411, 413, 415, 416, 421]. Imaging reliability data was presented in 43% (20/46) of the included studies [68, 160, 165, 169, 170, 179, 359, 398-400, 402, 404, 406, 412, 418, 423-425] (Table 3.5) and most of these studies used a single observer. Pooling of reported intraclass correlation coefficients (ICC) data was available for MRI bisect offset, patella tilt, patellofemoral contact area, Insall-Salvati ratio and sulcus angle showing mean ICCs of 0.92, 0.85, 0.90, 0.96, 0.82 respectively. Inter -observer reliability data was only presented in seven studies [148, 166, 169, 400, 412, 420, 423].

At the time of writing this review (up to September 2014) the selection of studies predominantly focused on malalignment. The update of the literature in section 7.2.1, however, shows how semi-quantitative MRI outcomes are becoming more commonly investigated.

Table 3.4: Sample sizes and population characteristics for each paper

Study	Study Design	Follow up	Country of origin e.g. UK, USA	Population e.g. students, athletes	Sample size	Age (years)	Female %	Mean Duration of symptoms (months)
Aglietti et al 1983[421]	Case-control	No	USA	UTD	Case = 53 Control = 150	22	Case = 60.3 Control = 50	UTD
Bretcher & Powers 2002a[159] **Bretcher & Powers 2002b[163]**	Case-control	No	USA	Orthopaedic referrals	Case = 10 Control = 10	34.6	Case = 50 Control = 50	UTD
Botanlioglu et al 2013[216]	Case-control	No	Turkey	UTD	Case = 11 Control = 22	29.5	Case = 100 Control = 50	UTD
Callaghan & Oldham 2004[359]	Case-control	No	UK	Orthopaedic & Rheumatology referrals	Case = 57 Control = 10	32.6	Case = 61 Control = 60	34
Chen & Powers 2014 [256]	Case-control	No	USA	Orthopaedic referrals & University students	Case = 20 Control = 20	27	Case =100 Control = 100	UTD
Chen *et al* 2012[418]	Case-control	No	Taiwan	Orthopaedic referrals	Case = 26 Control = 26	27.8	Case = 81 Control = 81	UTD
Chiu *et al* 2012[166]	Case-control	8 weeks	Hong Kong	UTD	Case = 9 Control = 6	33.1	Case = 55.6 Control = 50	UTD
Connolly *et al* 2009[168]	Case-control	No	Canada	Sports Medicine Physician referrals	Case = 10 Control = 10	27	Case = 100 Control = 100	UTD
Draper *et al* 2006[169]	Case-control	No	USA	UTD	Case = 34 Control = 16	28.8	Case = 64.7 Control = 50	UTD
Draper *et al* 2009[148]	Case-control	No	USA	Orthopaedic & Sports Medicine referrals	Case = 23 Control = 13	29.4	Case = 100 Control = 100	UTD
Eckhoff et al 1994[415]	Case-control	No	USA	Failed conservative management	Case = 20 Control = 20	UTD	UTD	UTD

Farrokhi *et al* 2011a[170] **Farrokhi *et al* 2011b[65]**	Case-control s	No	USA	UTD	Case = 10 Control = 10	27.4	Case = 100 Control = 100	87.6
Felicio *et al* 2011a[397] **Felicio *et al* 2012b[399]** **Felicio *et al* 2014c[398]**	Case-control	No	Brazil	UTD	Case = 19 Control = 20	22.5	Case = 100 Control = 100	UTD
Guzzanti *et al* 1994[410]	Case-control	No	Italy	Adolescents	Case = 27 Control = 20	14	Case = 77.8 Control = 50	UTD
Haim et al 2006 [422]	Case-control	No	Israel	Military soldiers	Case = 61 Control = 25	21.8	Case = 0% Control = 0%	19
Harman *et al* 2002[409]	Case-control	No	Turkey	UTD	Case = 17 Control = 10	29.4	Case 0% Controls 0%	UTD
Ho et al 2014[68] **Ho et al 2014b[66]**	Case-control	No	USA	UTD	Case = 10 Control= 10	25.5	Case = 100 Control = 100	UTD
Joensen *et al* 2001[403]	Case-control	No	Denmark	Athletes	Case = 24 Control = 17	21.6	Case =37.5 Control =35.3	UTD
Jones *et al* 1995[414]	Case-control	No	USA	Failed conservative management	Case = 40 Control = 10	UTD	Case = UTD Control = 50	UTD
Kim *et al* 2014[423]	Case-control	No	South Korea	Orthopaedic referrals	Case =51 Control =44	27.4	Case = 47 Control = 50	UTD
Laprade & Culham 2003[420]	Case - control	No	Canada	Military	Case =33 Control = 33	30.9	Case = 33.3 Control = 33.3	UTD
Jan *et al* 2009[424]	Case-control	No	Taiwan	Orthopaedic referrals	Case = 54 Control = 54	40.7	Case = 75.9 Control = 75.9	UTD
Metin Cubuk *et al* 2000[413]	Case-control	No	Turkey	Orthopaedic referrals	Case = 42 Control = 40	27	Case = 100 Control = 100	11
Muneta *et al* 1994[412]	Case-control	No	Japan	UTD	Case = 60 Control = 19	21	Case = 100 Control = 100	UTD

Pal *et al* 2013 [402]	Case-control	No	USA	University Orthopaedic and Sport Medicine referrals	Case = 37 Control = 15	29.7	Case = 54.1 Control =53.3	3 - 132
Pattyn *et al* 2011[230] **Pattyn *et al* 2013c[294]**	Case-control	No	Belgium	Hospital Orthopaedic Surgeon referrals	Case = 46 Control = 30	23.3	Case = 54.3 Control = 56.7	17.37
Pinar et al 1994[417]	Case-Control	N/A	Turkey	UTD	Case = 26 Control = 14	29	Case = 78.5	UTD
Powers 2000b[404]	Case-control	NAD	USA	Orthopaedics referrals & university students	Case = 23 Control = 12	27.9	Control = UTD	UTD
Ribeiro *et al* 2010[405]	Case-control	NAD	Brazil	UTD	Case = 12 Control = 12	22.5	Case = 100 Control = 100	UTD
Salsich & Perman 2007[165]	Case-control	No	USA	UTD	Case = 21 Control = 21	25	Case = 76.2 Control = 66.7	UTD
Salsich & Perman 2013[160]	Case-control	No	USA	Multiple sources – including community dwelling population	Case = 27 Control = 29	25.6	Case = 77.8 Control = 65.5	> 2
Schoots *et al* 2013 [82]	Case-control	No	Netherlands	Sports medicine & Orthopaedic referrals	Case = 10 Control = 10	29.3	Case =60 Control = 60	> 6
Schutzer *et al* 1986 [416]	Case-control	No	USA	UTD	Case = 24 Control = 10	19	Case = 91.7 Control = 70	3 - 168
Souza et al 2010 [179]	Case-control	No	USA	Orthopaedic referrals & community dwelling population	Case = 15 Control = 15	29.9	Case = 100 Control = 100	UTD
Taskiran et al 1998 [411]	Case- control	No	Turkey	UTD	Case = 10 Controls = 9	27	Case= 100 Control = 88.9	UTD
Teng *et al* 2014 [406]	Case-control	No	USA	UTD	Case = 18 Control = 18	27.3	Case = 100 Control = 100	UTD
Thuiller *et al* 2013 [173]	Case-control	No	USA	Sports Medicine referrals	Case = 20 Control = 10	31.3	Case = 60 Control = 50	UTD
Tuncyurek et al 2010 [407]	Case-control	No	Turkey	Orthopaedics referrals	Case = 23 Control = 9	31.3	Case = 52 Control = 78	UTD

Wilson et al 2009 [419]	Case-control	No	USA	UTD	Case= 7 Control = 7	30.6	Case = 71.4 Control = 57.1	UTD
Witzonzi & Goraj 1999 [408]	Case - control	No	Poland	UTD	Case = 10 Control = 10	19.1	Case = 100 Control = 80	8 to 60

UTD = unable to detect

Table 3.5: Imaging methods, outcome measures and results

Study	Imaging procedure	Imaging position & knee angle	Imaging outcome	Reliability	Baseline Results	Post-intervention results
Aglietti et al 1983[421]	XR A/P & lateral	Supine 30-45	•Patella height (Insall-Salvati method) • Patella height (Blackburne & Peel method) • Sulcus angle •Congruence angle	UTD	**Insall-Salvati** Female PFP 1.08 (0.09) vs. Controls 1.06 (0.12) Male PFP 1.11 (0.08) vs. Controls 1.01 (0.09); * All PFP 1.08 (0.09) vs. Controls 1.04 (0.11); * **Blackburne & Peel** Female PFP 0.90 (0.12) vs. Controls 0.97 (0.12) Male PFP 0.93 (0.08) vs. Controls 0.94 (0.15) All PFP 0.91 (0.11) vs. Controls 0.95 (0.13) **SA (°)** Female PFP 139 (5) vs. Controls Males PFP 140 (3) vs. Controls; P<0.005 ** All PFP 139 (4) vs. Controls 137 (6); p<0.01* **CA (°)** Female PFP 2 (11) vs. Controls -10 (6) * Male PFP 1 (4) vs. Controls -6 (6); ** All PFP -2 (9) vs. Controls -8 (6); * *p<0.001 **p<0.005	N/A
Bretcher & Powers 2002a[159]	MRI 1.5T 3D SPGR	Supine •0° •20° •40° •60°	•Peak PFJ stress •PFJ stress time integral •peak PFJRF •PFJRF time integral •mean utilised contact area	UTD	**PFJ stress integral (MPa % stance)** ascent PFP 88.6% vs. Controls 100% descent PFP 159.3% vs. Controls 140.6 **peak PFJRF (N/kg)** ascent PFP 25.0 vs. Control 37.3* descent PFP 11.9 vs. Controls 14.675; p >0.05 **PFJRF time integral (N/kg % stance phase)** ascent PFP 288.2 vs. Controls 501.9; * descent PFP 464.4 vs. Controls 605.9 **Mean utilised contact area ($mm^{2)}$** ascent PFP 250.16 vs. Controls 275.53	N/A

					descent PFP 261.46 vs. Controls 276.73 *p<0.05 NB. Data extrapolated from graphics	
Bretcher & Powers 2002b[163]			•Peak stress •PFJ stress time integral •PFJRF time integral •Mean area		**Peak PFJ stress (Mpa)** PFP 5.57 (3.56 vs. Controls 1.97 (0.40) **PFJ stress time integral (Mpa % GC)** PFP 51.42 (21.94) vs. Controls 22.36 (3.87); * **PFJRF peak force (N/kg -^{1}%GC)** PFP 7.46 (1.25) vs. Controls 9.51 (1.24); * **PFJRF force-time integral (N/kg -^{1}%GC)** PFP 84.58 (13.83) vs. Controls 107.21 (14.97); **Mean contact area (mm^{2})** PFP 138.31 (60.38) vs. Controls 225.53 (24.25) * *p<0.05	N/A
Botanlioglu et al 2013[216]	US Shear Wave Elastography 4-15MHz	Long sitting 0°	Contraction capacity and Contraction ratio of -VL -VL at 30 hip abduction -VMO -VMO at 30 hip abduction	UTD	**Contraction capacity (kPa)** VL(Neutral) Right Rest - PFP 13.8 ± 4.2 vs. Controls 16.5± 2.6; Cont- PFP 80.6± 26.0 vs. Controls 113.7± 53.2 Left Rest - PFP 15.8± 3.3 vs. Controls 13.9 ± 3.7 Cont - PFP 98.2±34.3 vs. Controls 122.6±58.1 **VL (30° hip abduction) (kPa)** Right Rest PFP 13.7 ± 6.1 vs. Controls 16.9±4.5; Cont PFP 98.5 ± 34.6 vs. Controls 125.5 ± 51.6; Left Rest PFP 13.3 ± 4.1 vs. Controls 14.6 ± 3.8; p Cont PFP 92.2 ± 38.5 vs. Controls 113.7± 42.0; **VMO (Neutral) (kPa)** Right- Rest PFP14.2 ± 4.0 vs. Controls 11.4 ± 3.7; Cont PFP 116.2± 45.2 vs. Controls 139.1±47.6; Left PFP 13.0±3.3 vs. Controls 12.1±3.5; Cont PFP 103.9±39.3 vs. Controls 157.6±31*	N/A

					VMO (30°) (kPa) Right Rest PFP 12.1±3.6 vs. Controls 12.4±5.1; Cont PFP101.8±28.3 vs. Controls 160.6 ± 46.1 * Left Rest PFP 11.6±3.7 vs. Controls 9.6 ±2.3; Cont PFP 102.9 ±41.1 vs. Controls 168.3± 37.3* **Contraction ratio (VL & VMO) (kPa)** VL (Neutral) PFP 5.32± 2.48 vs Controls 7.30 ± 4.93; VL (30) PFP 7.41 ± 5.45 vs Controls 7.03 ± 3.08 VMO (Neutral) PFP 7.60±3.78 vs Controls 12.52 ±4.94; * VMO (30) PFP 8.72 ±5.35 vs Controls 15.91 ± 7.54; * *p<0.05	
Callaghan & Oldham 2004[359]	US Static B Compound	Mid way between lateral joint line & greater trochanter 0°	CSA of quadriceps	**Intra-observer** ICC 0.99; SEM 0.29cm^2	**CSA of quadriceps (cm^2)** Female PFP 16.82 (4.6) vs. 18.07 (5.5) Male PFP 20.03 (3.8) vs. 23.07 (2.3) Total PFP 18.06 (4.6) vs. 20.08 (5.1)	N/A
Chen & Powers 2014[256]	MRI 1.5T Sagittal, frontal & axial	Supine – unloaded &loaded 20,40, 60°	• Resultant PFJR • Peak anterior/posterior force • Peak medial/lateral force • Peak superior/inferior force	UTD	**Resultant PFJRF** Walking = PFP 7.8 (1.2) vs. Control 9.8 (1.3) Stair descent = PFP 21.9 (2.9) vs. Controls 28.4 (3.2) Stair ascent =PFP 29.8 (3.0) vs. Controls 35.7 (3.1) Running= PFP 44.2 (5.0) vs. Controls 54.8 (5.3) **Posterior force** Walking = PFP 6.4 (1.8) vs. Controls 8.0 (2.1) Stair descent = PFP 20.9 (2.3) vs. Controls 27.7 (2.9) Stair ascent = PFP 28.2 (3.1) vs. Controls 34.5 (4.1) Running = PFP 41.2 (4.2) vs. Controls 51.6 (4.7) **Superior force** Walking = PFP 5.1 (1.0) vs. Controls 6.7 (1.4) Stair descent = PFP 5.1 (1.3) vs. Controls 6.9 (1.1) Stair ascent = PFP 6.5 (1.7) vs. Controls 8.9 (2.1) Running = PFP 15.0 (2.4) vs. Controls 18.9 (3.0) **Lateral force**	N/A

					Walking = PFP 1.8 (0.6) vs. Controls 1.6 (0.8) Stair descent = 7.2 (1.5) vs. Controls 3.3 (1.2) Stair ascent= 7.8 (1.6) vs. Controls 4.1 (1.3) Running = 8.0 (1.4) vs. Controls 3.8 (1.2)	
Chen *et al* 2012[418]	US M-mode 200Hz	Supine Intersection of M line and the upper margin of the patella	• Electrical mechanical delay (EMD)	**Intra-observer** VMO EMD (ICC 0.81) VL EMB (ICC 0,92)	**EMD (ms)** VMO PFP (37.3 +/- 0.7) vs. Control (25.9 +/- 0.7) * VL PFP (18.4 +/- 0.5) vs. Control (25.1 +/- 0.5) * p<0.001*	N/A
Chiu *et al* 2012[166]	MRI 1.5T (axial T1 weighted) Or 3.0T (fast supplied gradient echo)	Supine 20°	• PFJ contact area • Patellar tilt angle	**Intra-observer** PFJ contact area (ICC 0.91) Patella tilt (0.85) **Inter-observer** ICC 0.78	**PFJ Contact area (cm^2)** PFP (187,43 ± 51.96) vs Controls (217,65 ± 75.24) **Patella tilt angle (°)** PFP (16.61± 7.52) vs Controls (16.17 ± 6.52)	**PFJ Contact area pre/post difference (cm^2)** • PFP (58.89 ± 17.53) vs. Controls (17.30 ± 26.77); p< 0.001 **Patella tilt angle pre/post difference (°)** • PFP (0.94 ± 7.41) vs. Controls (3.16 ± 3.22); p= 0.5 **Kujala Patellofemoral Score** • PFP baseline (70.6 ± 5.46) vs. PFP post-training (83.8 ± 7.01); p <0.001 **Numeric pain rating scale** • PFP baseline (6.8 ± 0.67) vs. PFP post-training (2.8 ± 1.64); p< 0.001
Connolly *et al* 2009[168]	MRI 3.0T Sagittal	Supine Loaded 0,15,30 & 45°	•Contact area magnitude •Tracking •Medial/lateral contact area •Patella Cartilage thickness •Congruence index •Shape	UTD	**Mean total contact area (mm^2)** 15 - PFP 231.3 (49.6) vs. Control 187.2 (31) 30 - PFP 230.6 (40.3) vs. Controls 236.8 (43.4) 45 - PFP 334.5 (58.9) vs. Controls 350 (49.6) **Mean medial contact area (mm^2)** 15- PFP 56.2 (40.3) vs. Controls 25 (27.9) 30- PFP 62.4 (40.3) vs. Controls 65.5 (31.1) 45- PFP 115 (18.7) vs. Controls 115.5(21.7) *Mean lateral contact area - not available*	N/A

					Proximal/distal migration (mm) 15 - PFP -7.92 (1.6) vs. Controls -8.56 (2.0) 30- PFP -7.04 (0.88) vs. Controls -6.96 (2.8) 45- PFP -2.16 (0.96) vs. Controls -2.24 (2.4) **Congruence index (mm^{-1})** 15 - PFP 0.105 vs. Controls 0.122 30- PFP 0.115 vs. Controls 0.114 45 - PFP 0.094 vs. Controls 0.091 **Patella Cartilage thickness (mm)** 15 - PFP 2.87 (7.29) vs. Controls 2.608 (4.3) 30 - PFP 2.84 (4.86) vs. Controls 3.0 (5.4) 45 - PFP 3.5 (6.75) vs. Controls 3.5 (3.51) ***NB. Data extrapolated from graphics***	
Draper *et al* 2006[169]	MRI 1.5T 3D SPGR	Supine 0°	•Patella mean cartilage thickness • Femoral mean cartilage thickness • Patella peak cartilage thickness • Femoral peak cartilage thickness	**Intra-observer** Patella cartilage (CV 2.8%) Femoral cartilage (CV 2.4%) **Inter-observer** Patella cartilage (CV 0.2%) Femoral cartilage (CV 5.9%)	**Peak patella cartilage thickness (mm)** Male PFP (n=12) vs. Male controls (n=8) Superior - PFP 4.21 (3.61-4.93) vs. Controls 5.15 (3.91-6.39); p<0.01* Middle - PFP 5.18 (4.24-6.00) vs. Controls 6.06 (4.70-7.51): p<0.01* Inferior - PFP 4.30 (3.39 -5.26) vs. Controls 4.33 (3.24-5.30) **Mean patella cartilage thickness (mm)** Female PFP vs. Female Controls Superior - PFP 3.00 (2.51 -3.51) vs. Controls 2.8 (2.19 -3.34) Middle - PFP 3.97 (3.05-4.72) vs. Controls 3.83 (2.97 - 4.66) Inferior- PFP 2.80 (2.03-3.51) vs. Controls 2.52 (1.89 - 3.29) **Mean femoral cartilage thickness (mm)s** Male PFP (n=12) vs. Male Control (n=8) Superior- PFP 1.58 (1.08 - 2.05) vs. Controls 1.72 (1.25 -2.13) Middle- PFP 2.63 (2.10-3.03) vs. Controls 2.32 (1.92-2.85) Inferior- PFP 3.18 (2.75-3.69) vs. Controls 3.05 (2.56-3.58) Female PFP (n=22) vs. Female Control (n=8) Superior - PFP 1.36 (0.93 - 1.85) vs. Controls 1.39 (1.06 - 1.84) Middle- PFP 2.00 (1.65-2.59) vs. Controls 1.97 (1.62 -2.49) Inferior PFP 2.46 (2.06-3.03) vs. Controls 2.36 (1.60 -3.06) ***NB. Data extrapolated from graphics***	N/A

Draper *et al* 2009[148]	Kinematic MRI 0.5T Open	90% WB 0 to 60°	•Bisect offset •Patella tilt angle	**Intra-observer** Bisect offset (CV 3%; RMS 4%) Patella tilt (2%' RMS 3%)	**PTA (°)** 0° PFP 9.75 (7.0) vs. Controls 4.25 (2.8) 20° PFP 8.75 (6.9) vs. Controls 4.875 (2.0) 40° PFP 5.0 vs. Controls 4.75 60° PFP 3.75 vs. Controls 4.0 **BO (%)** 0° PFP 70% (10.1) vs. Control 54.5% (4.8) 20° PFP 66.3% (10.8) vs. Controls 55% (3.1) 40° PFP 64.5% (9.5) vs. Controls 55.5% (3.5) 60°PFP 62.5% (9.8) vs. Controls 57.6% (5.3) ***NB. Data extrapolated from graphics***	**Patellofemoral stabilising brace** **PTA (°)** 0° PFP 6.1 (6.7 20° PFP 6.1 (6.4) 40° PFP 5.0 (5.8) 60°- PFP 3.8 (5.6) **BO (%)** 0° PFP 63.7 (9.4) 20° PFP 62.7 (7.7) 40° PFP 59.7 (7.4) 60°- PFP 60.6 (6.9) **Patellofemoral sleeve** **PTA (°)** 0° PFP 8.9 (6.1) 20° PFP 8.9 (4.9) 40° PFP 5.5 (4.4) 60°- PFP 3.6 (3.6) **BO (%)** 0° PFP 66.3 (8.9) 20° PFP 65.6 (7.9) 40° PFP 61.7 (5.9) 60°- PFP 61.7 (5.3) ***NB. Data extrapolated from graphics***
Eckhoff et al 1994[415]	CT	Proximal to intercondylar notch	•Femoral anteversion •Lateral patellofemoral angle •Sulcus angle •Congruence angle		**Femoral anteversion** PFP 23° (±12) vs Controls 18° (±7); p<0.01 * NS difference between PFP and controls in femoral anteversion and correlation with patella orientation [no data available]	N/A
Farrokhi *et al* 2011a[170]	MRI 3.0T 3D SPGR	25% WB 0,15 & 45°	•Hydrostatic pressure • Octahedral shear stress	UTD	**Peak patella hydrostatic pressure** Stress @ 15°- PFP 2.0 (0.5) vs. Control 1.3 (0.5) * Stress @ 45°- PFP 3.2 (0.8) vs. Control 2.7 (0.7) All angles - PFP 2.6 (2.2-2.9) vs. Control 2.0 (1.7-2.3) * **Mean patella hydrostatic pressure** Stress @ 15° - PFP 0.8 (0.2) vs. Control 0.6 (0.2) * Stress @ 45° PFP 1.2 (0.3) vs. Control 0.9 (0.2)*	N/A

					All angles - PFP 1.0 (0.9 - 1.1) vs. Control 0.8 (0.6-0.9); * **Peak femur hydrostatic pressure** Stress @ 15° - PFP 2.1 (0.5) vs. Control 1.4 (0.4); * Stress @ 45° - PFP 3.7 (1.2) vs. Control 3.0 (0.6); All angles - PFP 2.9 (2.5-3.3) vs. Control 2.2 (1.8-2.6)* **Mean femur hydrostatic pressure** Stress @ 15° - PFP 0.8 (0.1) vs. Control 0.6 (0.1)* Stress @ 45° - PFP 1.3 (0.3) vs. Control 1.1 (0.2) All angles - PFP 1.1 (0.9-1.2) vs. Control 0.9 (0.7-1.0) * **Peak patella octahedral shear stress** Stress @ 15° - PFP 0.6 (0.2) vs. Control 0.3 (0.1)* Stress @ 45° - PFP 1.3 (0.7) vs. Control 0.9 (0.3) All angles - PFP 1.0 (0.8-1.1) vs Control 0.6 (0.4-0.8); p<0.05* **Mean patella octahedral shear stress** Stress @ 15° - PFP 0.4 (0.1) vs. Control 0.2 (0.2); p<0.05* Stress @ 45° - PFP 0.6(0.1) vs. Control 0.5 (0.1); p>0.05 All angles - PFP 0.5 (0.4-0.5) vs. Control 0.3 (0.3 -0.4); p<0.05* **Peak femur octahedral shear stress** Stress @ 15° - PFP 0.6 (0.2) vs. Control 0.4 (0.1)* Stress @ 45° - PFP 1.2 (0.4) vs. Control 1.0 (0.2) All angles - PFP 0.9 (0.8 -1.0) vs. Control 0.7 (0.6-0.8)* **Mean femur octahedral stress** Stress @ 15° - 0.4(0.1) vs. Controls 0.2 (0.2); * Stress @ 45° - 0.6 (0.1) vs. Controls 0.5 (0.1); All angles - PFP 0.5 (0.4-0.5) vs. Controls 0.4 (0.3-0.4)* p<0.05*	

Farrokhi *et al* 2011b[65]	MRI 3.0T Axial	Supine 0°	• Patella cartilage thickness • T2 Relaxation time	**Intra-observer** Patella cartilage thickness (CV 0.018; SEM 0.018) Patella cartilage T2 (CV 0.013; SEM 0.294)	**Patella cartilage thickness (mm)** Lateral facet- PFP 2.4± 0.32 vs. Controls 2.79 ± 0.36* Medial facet - PFP 2.33 ± 0.39 vs. Controls 2.72± 0.57 Total - PFP 2.37 ± 0.33 vs. 2.76± 0.43* **Patella cartilage T2 relaxation time (ms)** Lateral facet - PFP 32.81 ± 1.33 vs. Controls 32.46 ± 2.70 Medial facet - PFP 31.59 ± 1.96 vs. Controls 30.80 ± 1.80 Total - PFP 32.50 ± 1.37 vs. Controls 31.78± 2.22	**<u>Post exercise percentage change</u>** **Patella cartilage thickness** Lateral facet- PFP -2.10 ± 3.99 vs. -8.91 ± 4.14* Medial facet - PFP -6.65± 5.41 vs. -10.97± 7.33 Total - PFP -4.44± 3.27 vs. Controls -10.00 ± 4.18* **Patella cartilage T2 relaxation time** Lateral facet - PFP -1.92±6.25 vs. Controls -0.38±4.75 Medial facet - PFP 1.25 ±6.25 vs. Controls 1.50±5.75 Total - PFP -2.25±5.50 vs. Controls 0.25±4.02 p<0.05*
Felicio *et al* 2011a[397]	MRI 1.5T Axial	Supine 0,15,30,45°	•Patella tilt angle • Bisect offset		**PTA (°)** OKC 15 - PFP 8.5 (7.4) vs Controls 7.0 (5.6) OKC 30 - 6.9 (4.5) vs Controls 6.0 (4.8) OKC 45 - 7.7 (4.9) vs Controls 7.4 (4.7) CKC 15 - PFP 7.8 (7.5) vs Controls 7.8(6.3) CKC 30- PFP 5.1 (4.7) vs Controls 6.0 (4.3) CKC 45 - PFP 7.0 (3.5) vs Controls 6.8 (4.6) **BO (%)** OKC 15 - PFP 59.8 (8.9) vs Controls 56.3 (8.5) OKC 30 - PFP 54.3 (4.5) vs Controls 52.8 (4.5) OKC 45 - PFP 56.8 (8.8) vs Controls 53.1 (5.5) CKC 15 - PFP 61.0 (11.2) vs Controls 56.7 (10.0) CKC 30 - PFP 53.1 (4.8) vs Controls 52.8 (4.5) CKC 45 - PFP 54.6 (5.0) vs Controls 53.0 (5.6)	N/A
Felicio *et al* 2012b[399]	MRI 1.5T Axial	Supine 0,15,30,45°	• Patella tilt angle • Bisect offset • Sulcus angle	SA (ICC >0.75) PTA (ICC >0.75) BO (ICC >0.75)	**15° of knee flexion** SA Rest - PFP 140.71 (10.97) vs. Control 140.11 (11.09) OKC - PFP 145.07 (11.14) vs. Controls 147.29 (12.21) CKC – PFP 148.92 (9.71) vs. Controls 147.82 (12.14) PTA	N/A

					Rest – PFP 7.475 (6.24) vs. Controls 8.07 (6.79) OKC - PFP 8.35 (7.38) vs. Controls 7.02 (6.05) CKC - PFP 7.86 (7.23) vs. Controls 7.38 (6.97) BO Rest - PFP 55.18 (10.05) vs. Controls 50.61 (7.82) OKC - PFP 57.84 (8.17) vs. Controls 56.51 (7.99) CKC - PFP 60.64 (10.27) vs. Controls 56.33 (9.76) **30° of knee flexion** SA Rest - PFP 129.58 (10.3) vs. Controls 129.465 (8.03) OKC - PFP 133.44 (8.95) vs. Controls 134.23 (9.49) CKC - PFP 135.46 (9.01) vs. Controls 136.31 (8.37) PTA Rest - PFP 8.2 (4.29) vs. Controls 6.91 (5.83) OKC - PFP 6.58 (4.68) vs. Controls 5.29 (5.69) CKC - PFP 5.42 (4.42) vs. Controls 6.14 (5.32 BO Rest - PFP 53.64 (5.78) vs. Controls 52.15 (5.195) OKC - PFP 54.55 (5.48) vs. Controls 52 (4.51) CKC – PFP 52.56 (4.69) vs. Controls 52.99 (4.56) **45° of knee flexion** SA Rest –PFP 123.97 (8.84) vs. Controls 125.9 (7.01) OKC - PFP 126.57 (6.86) vs. Controls 129.39 (6.96) CKC - PFP 127.83 (8.03) vs. Controls 130.3 (8.96) PTA Rest - PFP 9.045 (3.78) vs. Controls 8.07 (4.75) OKC - PFP 7.21 (5.02) vs. Controls 6.6 (5.11) CKC- PFP 6.49 (3.27) vs. Controls 6.0 (5.33) BO Rest – PFP 54.94 (5.68) vs. Controls 53.45 (4.59) OKC- PFP 55.55 (8.22) vs. Controls 52.47 (5.02) CKC- PFP 53.51 (4.49) vs. Controls 52.77 (4.79	

Felicio *et al* 2014c[398]	MRI 1.5T Axial & Sagittal	Supine 15°,30°,45°	Insall-Salvati index	Insall-Salvati (ICC>0.75)	**Insall-Salvati index** Rest 15 - PFP 1.07 (0.14) vs Controls 1.08 (0.11) 30 - PFP 1.09 (0.13) vs Controls 1.07 (0.15) 45- PFP 1.10 (0.19) vs Controls 1.13 (0.17) OKC 15 - PFP 1.19 (0.15) vs Controls 1.19 (0.16) 30- PFP 1.21 (0.17) vs Controls 1.21 (0.15) 45 - PFP 1.19 (0.14) vs Controls 1.24 (0.19) CKC 15- PFP 1.22 (0.15) vs Controls 1.18 (0.15) 30- PFP 1.21 (0.17) vs Controls 1.19 (0.18) 45- PFP 1.19 (0.16) vs Controls 1.25 (0.21)	N/A
Guzzanti *et al* 1994[410]	CT	Supine 15°	•Congruence angle (CA) •Congruence angle with quadriceps contraction (CAc), •Patellar tilt angle (PTA) •Patellar tilt angle with quadriceps contraction (PTAc), •Sulcus angle (SA) ,•Trochlear depth (TD)	UTD	**CA** Males PFP 20.0 (16) vs. Controls -11.6(8) Females PFP 13.8 (21) vs. Controls -13.5 (8) Total - PFP 15.4 (21) vs. Controls -12.5(8) **PTA** Males PFP 10.3 (7) vs. Controls 13.5 (5) Females PFP 3.2 (10) vs. Controls 15.6 (5) Total PFP 5.0 (10) vs. Controls 14.5 (5) **CAc** Males 26.0 (20) vs. Controls -10.7(8) Females 25.1 (23) vs. Controls -12.3 (8) Total 25.3 (22) vs. Controls -11.5(8) **PTAc** Males 9.9 (8) vs. Controls 13.4 (5) Females 2.5 (11) vs. Controls 14.5 (5) Total 4.4 (11) vs. Controls 13.9 (5) **SA** Males PFP 146(6) vs. Controls 124 (8) Females - PFP 148 (12) vs. Controls 130 (7) Total PFP 147 (10) vs. Controls 127 (8) **TD** Males PFP 7.3 (2) vs. Controls 12.9 (2) Females PFP 6.6 (3) vs. Controls 11.3 (2) Total PFP 6.8 (3) vs. Controls 12.1 (2)	N/A
Haim et al 2006[422]	XR	Supine 30°	• Insall-Salvati index • Sulcus angle	UTD	**Patellar subluxation** PFP15 (25%) vs. Controls 1 (4%); p= 0.032	N/A

	Lateral & axial		• Merchant angle • Laurin angle • Patella subluxation • Subcondral sclerosis		**Subchondral sclerosis** PFP 2 (3%) vs. Controls 0 **SA (°)** PFP 139 ± 5.1 vs. Controls 138 ± 5.8 **Laurin angle (°)** PFP 9.9 ± 4.1 vs. Controls 10.8 ± 5.6 **Merchant angle (°)** PFP −4.2 ± 9.9 vs. Controls −5.4 ± 14 **Insall-Salvati index** PFP 1.03 ± 0.15 vs. Controls 1.02 ± 0.11;	
Harman *et al* 2002[409]	Kinematic MRI 0.3T Open MRF with spoiled gradient echo	Prone 0-45°	•PTA •CA •SA •Patella height	UTD	**Case group** 2 normal 10 Lateralisation 2 Patella tilt 2 Lateralisation & patella tilt 4 medialisation of patella **Control group** All normal (i.e. median ridges of the patella were in a centralised position relative to the femoral trochlear grooves through active flexion)	N/A
Ho et al 2014[68]	MRI 3.0T 1. 3D IDEAL pulse sequence2.3D SPGR 3. sagittal 3D SPGR 4. axial D SPGR	1. Supine 2. 25 % WB (45°) 3. Supine 4. Supine	•Patella cartilage thickness • Peak maximum strain • Peak minimum strain	**Intra-observer** Patella cartilage (ICC 0.99; SEM 0.18mm)	**Cartilage thickness** PFP 2.54 ± 0.38 vs. Control 3.07 ± 0.44; p =0.008 * **Minimum principal strain** **Peak** PFP -2635.5 ± 1755.7 vs. Controls -1236.9 ± 734.2; 0.038 * **Average** -247.4 ± 125.6 vs. Controls -142.9 ± 60.2; p =0.029 * **Maximum principal strain** **Peak** 2617.2 ± 1815.3 vs. Controls 1201.6 ± 796.1; p =0.036 * **Average** 251.9± 117.4 vs. Controls 150.5 ± 62.3; p =0.027	N/A
Ho et al 2014b[66]	MRI 3.0T	Supine 0°	• Total water content • Lateral patella content	UTD	**Total patella water content (%)** PFP 15.4 ± 3.5 vs Controls 10.3 ± 2.1%; p=0.001*	N/A

	3D SPGR with IDEAL and single relaxation (e.g. 1,T2)		• Medial patella water content		**Lateral patella water content (%)** PFP 17.2 ± 4.2 vs Controls 11.5 ± 2.4%; p =0.002* **Medial patella water content (%)** PFP 13.2 ± 2.7 vs Controls 8.4 ± 2.3%; p<0.001 *	
Joensen *et al* 2001[403]	MRI 1.0T 3D SPGR	Supine 0°	Articular cartilage lesion grade 1-4	UTD	**Articular cartilage lesions** **None** - PFP 7 (29.2%) vs Controls 13 (76.6%); OR 1.0 **Grade 1** - PFP 11 (45.8%) vs Controls 1 (5.9%); OR 20.4 (2.2 - 193) **Grade 2** - PFP 4 (16.7%) vs Controls 2 (11.8%); OR 3.7 (0.5 - 25.6) **Grade 3** - PFP 1 (4.2%) vs Controls 1 (5.9%); OR 1.9 (0.1 - 34.4) **Grade 4** - PFP 1 (4.2%) vs Controls 0 (0%);	N/A
Jones *et al* 1995[414]	CT Transaxial	Supine 20	Tibial tubercle lateralisation	UTD	**Tibial tubercle lateralisation (mm)** PFP 11 (11.9 ± 0.5) vs Controls 6 (6.5 ± 0.4); p<0.05*	N/A
Kim *et al* 2014[423]	XR Merchant view	Supine 100% WB 45°	•Patella tilt angle •patellofemoral angle •congruence angle •subluxation distance •lateral patella displacement	Intra-observer (k 0.87) Inter-observer (k 0.85)	**PTA (°)** PFP WB 1.67 (6.71) vs Controls WB 3.66 (2.00) ; p<0.0001 PFP NWB 10.27 (9.00) vs Controls NWB 5.33 (2.46) **Lateral patellofemoral angle (°)** PFP WB 14.60 (4.65) vs Controls WB 11.30 (4.73); p =0.0035 PFP NWB 7.20 (3.72) vs Controsl NWB 6.82 (3.81) **Subluxation distance** PFP WB -2.79 (2.13) vs Controls WB -1.96 (1.80); 0.0150 PFP NWB -0.21 (3.72) vs Controls NWB -1.04 (2.75) **Lateral patella displacement** PFP WB -3.67 (2.38) vs Controls WB -3.45 (3.65); p < 0.0001 PFP NWB 1.40 (5.46) vs Controls -3.45 (3.65) **CA (°)** PFP WB -14.29 (11.33) vs Controls -8.70 (2.39); p<0.0001 PFP NWB 3.59 (13.73) vs Controls -3.53 (4.51)	N/A
Laprade & Culham 2003[420]	XR Merchant view	Supine & sitting 35°	• Lateral patella angle •Laurins angle • Congruence angle • Patella height (Catons ratio) • Femoral sulcus anlge •patella anlgle	**Intra-observer** ICC 0.43 to 0.89 **Intra-observer** ICC 0.83 to 0.96	**SA (°)** PFP 139.6 ± 9.1 vs. Controls 141.3 ± 6.2 ; p **PTA (°)** PFP 124 ± 6.8 vs. Controls 125.5 ± 5.6 **Lateral patella angle (°)** Unloaded - PFP 12.5 ± 6.6 vs. Controls 10.6 ± 4.4; Loaded - PFP 13.1 ± 7.5 vs. Controls 11.2 ± 4.2; **CA (°)**	N/A

					Unloaded = - 21.2 ± 11.1 vs. Controls -19.6 ± 7.4; Loaded = -18.1 ± 18.3 vs. Controls -23.7 ± 9.8; **Caton's ratio** PFP 1.00 ± 0.18 vs. Controls 1.03 ± .19 ; p=0.59	
Jan *et al* 2009[424]	US 5 to 12MHz linear array	Supine Distal insertion of medial border of the patella to the most proximal insertion of the upper margin	• VMO Insertion level • VMO Fibre angle • VMO Volume	**Intra-observer** VMO insertion level (ICC 0.87; SEM 0.22) VMO Fibre angle (ICC 0.86; SEM 3.38) VMO Volume (ICC 0.87; SEM 0.57)	**VMO Morphological Characteristics** **Insertion level (cm)** PFP 2.0 ± 0.7 (1.8-2.2) vs. Controls 2.4 ± 0.5 (2.3-2.6); p=0.006* **Fibre angle (°)** PFP 51.6 ± 9.0 (49.5-54.5) vs. Controls 56.7± 6.4 (53.3 -57.8); p=0.016* **Volume (cm^3)** PFP 1.8 ± 1.5 (1.6-2.4) vs. Controls 3.0 ± 2.2 (2.3-3.5); p=0.024*	N/A
Metin Cubuk *et al* 2000[413]	CT XR Lateral	CT- Supine 0° XR -Supine 30°	• Tibial tubercle rotation angle •Patellar height	UTD	**Insall-Salvati** PFP 1.10 vs. Control 1.09; p > 0.01 **Modified Insall-Salvati** PFP 1.75 vs. Control 1.75 **Caton** PFP 0.89 vs. Control 0.92 **Blackburne** PFP 0.75 vs. Control 0.81	N/A
Muneta *et al* 1994[412]	CT Between patella centre and tibial tubercle	Supine Unloaded	• Relationship between tibial tubercle & patella tilt • Relationship between tibial tubercle & external rotation	UTD	**Tibial tubercle rotation angle** 67.5° (± 4°) vs. Control 70° (± 3.8°); p<0.01* **Tibial rotation angle** PFP 34.1° (± 8.7°) vs. Control 33° (± 7.3°); P >0.01	N/A
Pal *et al* 2013c[402]	MRI 0.5T open 3D fast spoiled gradient echo sagittal sequence	90% bodyweight 5°	•Caton-Deschamps •Blackburne-Peel •Insall-Salvati •Modified Insall-Salvati •Patellotrochlear •Bisect offset index •Patella tilt angle		**Caton-Deschamps** PFP 1.10 vs. Controls 0.90; P<0.01* **Blackburne-Peel** PFP 1.00 vs. Controls 0.75; P<0.01* **Insall-Salvati** PFP 1.25 vs. Controls 1.00; P<0.01 * **Modified Insall-Salvati**	N/A

					PFP 1.35 vs. Controls 1.10; P<0.01 * **Patellotrochelar** PFP 0.25 vs. Controls 0.30 **PFP with patella alta vs. PFP with normal patella height** AKP - PFP 72 ± 12 vs. Controls 74 ± 15; p 0.782 **PFP with patella maltracking vs. PFP with normal tracking** AKP - PFP 70 ± 11 vs. Controls 75 ± 15; p =0.406	
Pattyn *et al* 2011[400]	MRI 3.0T Axial	Supine 0°	Cross sectional area of VMO, VL and Total Quadriceps at: -mid thigh - patella level	**Intra-observer** CSA (ICC 0 976 - 0.998) **Inter-observer** CSA (ICC 0 672 - 0.989)	**Patella level (cm²)** **VMO** - PFP 16.67 (4.97) vs Controls 18.36 (5.25); p=0.040* **VL** - PFP 5.90 (3.30) vs Controls 6.5 (2.66); p=0.0192 **VMO:VL** - 3.53 (1.99) vs Controls 3.02 (0.86) **Midthigh level (cm²)** **VM:VI** - PFP 31.47 (8.28) vs Controls 33.26 (8.92) **VL** - PFP 24.83 (5.43) vs Controls 27.19 **RF** - PFP 11.23 (2.59) vs Controls 12.11 (3.18); p=0.006* **Total Quadriceps** - PFP 66.99 (15.06) vs Controls 70.83 (15.30)	N/A
Pattyn *et al* 2013c[294]	mfMRI 3.0T Axial	Supine 0°	T2 rest & shift for: • VMO, • VM: VI • VL	UTD	**T2 rest** **VMO** Male PFP 45.57 ± 4.59 vs Controls 43.52 ± 3.03 Female PFP 46.11 ± 2.88 vs Controls 47.42 ± 3.24 Total PFP 45.86 ± 3.73 vs Controls 45.69 ± 3.67 **VM:VI** Male PFP 43.39 ± 2.17 vs Controls 43.74 ± 2.34 Female PFP 43.09 ± 1.61 vs Controls 44.75 ± 2.17; p=0.007* Total PFP 43.23 ± 1.87 vs Controls 44.32 ± 2.25; p =0.025* **VL** Male PFP 42.18 ± 2.38 vs Controls 41.66 ± 1.58; Female PFP 42.91 ± 2.12 vs Controls 43.73 ± 1.64 **T2 shift** **VMO** Male PFP 6.04 ± 4.12 vs Controls 6.22 ± 2.47; Female PFP 4.09 ± 3.13 vs Controls 4.29 ± 2.51 **VM:VI** Male PFP 5.85 ± 2.61 vs Controls 7.16 ± 2.90; p	N/A

					Female PFP 4.68 ± 1.98 vs Controls 5.60 ± 1.92 Total PFP 5.21 ± 2.34 vs Controls 6.28 ± 2.48; **VL** Male PFP 5.59 ± 2.84 vs Controls 5.59 ± 2.20; Female PFP 3.94 ± 2.27 vs Controls 5.16 ± 2.42; Total PFP 4.69 ± 2.65 vs Controls 5.35 ± 2.30;	
Pinar et al 1994[417]	CT Mid patella position	Supine 0,20,30,40 & 60°	•Patella tilt angle •Sulcus angle •Congruence angle	UTD	Based on 38 symptomatic knees) Tilt & lateralisation = 12 knees Lateralisation = 4 knees Medialisation = 5 knees Lateral to medial instability = 1 Tilt = 1 Normal = 15	N/A
Powers 2000b[404]	Kinematic MRI 1.5T Fast spoiled GRASS axial	Prone 0-45°	•Bisect offset •Medial patella tilt •Lateral patella tilt •Sulcus angle	**Intra-observer** Patell tilt (ICC 0.66 -0.82; SEM 2.9° Bisect offset (ICC 0.66 -0.82; SEM 3.4%) Sulcus angle (ICC 0.66 -0.82; SEM 2.0°)	**PTA** 0° = PFP 10.0 (10.) vs Controls 3.6 (4.0) 9° = PFP 11.0 (9.8) vs Controls 4.0 (3.2) 18° = PFP 10.0 (7.2) vs Controls 3.6 (3.8) 27°= PFP 11.6 (6.0) vs Controls 4.2 (3.4) 36° = PFP 11.0 (5.2) vs Controls 7.2 (2.8) 45° = PFP 11.4 (5.2) vs Controls 9.6 (4.6) Mean PFP 10.7° vs Control 5.5°; p<0.02* **BO** 0° = PFP 62.0 (18.0) vs Controls 52.9 (10.5) 9° = PFP 60.5 (16.75) vs Controls 52.9 (11.25) 18°= PFP 55.35 (12.0) vs Controls 53.2 (7.5) 27°= PFP 54.9 (6.4) vs Controls 52.5 (7.3) 36° = PFP 55.6 (6.2) vs Controls 53.2 (4.2) 45° = PFP 56.3 (7.8) vs Controls 56.3 (7.8) Mean PFP 57.9% vs Control 53.8% **SA** 0° = PFP 153.6 (11.2) vs Controls 146.0 (5.2) 9° = PFP 153.4 (10.6) vs Controls 145.6 (4.0) 18°= PFP 152.6 (10.2) vs Controls 144.0 (4.0)	N/A

					27°= PFP 146.2 (4.6) vs Controls 143.2 (4.4) 36° = PFP 143.6 (4.6) vs Conrols 142.6 (4.0) 45° = PFP 138.6 (6.0) vs Controls 138.6 (6.0) Mean PFP 149.4° vs Controls 144.6° ***NB. Data was extrapolated from graphics***	
Ribeiro *et al* 2010[405]	MRI 0.5`T Sagittal & axial	Supine 30°	•Sulcus angle •Patella tilt angle •Patella displacement •Congruence angle	UTD	**SA** PFP 140.23 (7.74) vs Controls 133.58 (5.62); p = 0.02* **CA** PFP -8.51 (8.30) Controls -20.35 (9.26); p=0.01 * **PTA** PFP 12.85 (3.97) vs Controls 11.73 (4.19); **PD** PFP 1.93 (4.46) vs Controls 4.38 (3.48)	N/A
Salsich & Perman 2007[165]	MRI 1.5T 1. Sagittal T1-weighted 3-D FSPGR series 2. Fat-suppressed 3D FSPGR - axial images perpendicular to PFJ	Supine 0°	•Contact area •Tibiofemoral rotation angle •Bisect offset index •Patella tilt angle •Patella width	**Intra-observer** Patellofemoral contact area (ICC 0.90) Bisect offset (ICC 0.93) Patella tilt (ICC 0.86) Patella width (ICC 0.99)	**Contact area (mm^2)** PFP 191.6 (38.3) vs. Controls 220.3 (44.5) **BO (%)** PFP 0.69 (0.12) vs. Controls 0.62 (0.07) **PTA (°)** PFP 12.4 (7.7) vs. Controls 9.0(6.1) **Tibiofemoral rotation angle (°)** PFP 5.2 (5.7) vs. Controls 3.5 (5.6) **Patella width (mm^2)** PFP 39.4 (2.7) vs. Controls 42.3 (3.5)	N/A
Salsich & Perman 2013[160]	MRI 1.5T • Sagittal T1 weighted 3D FSPGR • axial fat suppressed 3D FSPGR	Supine 0,20 & 40°	•Contact area •Tibiofemoral rotation angle •Bisect offset index •Patella tilt angle	**Intra-observer** Contact area (ICC 0.90; SEM 15.46mm$^{2)}$ Bisect offset (ICC 0.93; SEM 0.02%) Patella tilt angle (ICC 0.86; SEM 1.39°)	**Contact area (mm²)** 0 - PFP 203.8 (45.5) vs. Controls 224.1 (46.6); p = 0.05* 20 - PFP 276.8(56.2) vs. Controls 316.7 (82.8) ; p=0.02* 40 - PFP 388.5 (99.3) vs. Controls 427.3 (113.7) ; p =0.24 **Tibiofemoral rotation angle (°)** 0° - PFP 5.2(5.6) vs. Controls 4.0 (4.6) 20° - PFP -1.2 (4.2) vs. Controls -2.5 (5.2) 40°- PFP -4.9 (5.1) vs. Controls -5.3 **BO (%)**	N/A

				Tibiofemoral rotation angle (ICC 0.93; SEM 1.17°)	0° - PFP 0.69 (0.13) vs. Controls 0.64 (0.09); p =0.04 * 20°- PFP 0.56 (0.07) vs. Controls 0.53 (0.06) 40°- PFP 0.54 (0.05) vs. Controls 0.54 (0.05) **PTA (°)** 0° - PFP 12.5 (7.6) vs. Controls 9.22 (5.8); p =0.04* 20° - PFP 6.7 (5.2) vs. Controls 6.0 (4.1) 40° - PFP 4.4 (3.9) vs. Controls 5.3 (4.1) **PFP sub group (medial collapse movement pattern) vs. Controls** Contact area (mm²) 0° PFP sub 191.3(46.3) vs. Controls 224.1(46.6); p =0.02* 20° - PFP sub 261.5 (61.8) vs. Controls 316.7 (82.8); p= 0.01 * 40°- PFP sub 370.8 (112.1) vs. Controls 427.3 (113.7) **Tibiofemoral rotation angle (°)** 0° - PFP 6.4 (5.9) vs. Controls 4.0 (4.6); p = 0.07 20°- PFP -1.1 (4.5) vs. Controls -2.5 (5.2); p=0.20 40°- PFP -5.6 (5.4) vs. Controls -5.3 (4.9); p= 0.89 **BO (%)** 0° - PFP 0.67 (0.14) vs. Controls 0.64 (0.09) 20°- PFP 0.56 (0.08) vs. Controls 0.53 (0.06) 40° - PFP 0.54 (0.05) vs. Controls 0.54 (0.05) **PTA (°)** 0° - PFP 12.6° (8.3) vs. Controls 9.22° (5.8); p= 0.06 20°- PFP 7.7° (6.0) vs. Controls 6.0° (4.1) 40°- PFP 5.3° (3.9) vs. Controls 5.3° (4.1)	
Schoots *et al* 2013[82]	US 5cm 13 MHz linear Transvers plane	Supine 10°	Thickness of lateral retinaculum (from edge of patella) at: •0.5cm •1.0 cm •1.5cm	UTD	**Thickness of lateral retinaculum** 0.5cm - PFP 4.0 (1.3) vs. Control 3.0 (0.25) 1.0cm - PFP 3.9 (1.2) vs. Control 1.0 (0.15) 1.5cm - PFP 4.0 (1.5) vs. Controls 3.0 (0.3) Total - PFP 4.0 (1.4) vs. Controls 3.0 (0.1)	N/A
Schutzer *et al* 1986[416]	CT Transaxial mid-patellar	Supine 0-30°	•Femoral trochlear angle •Femoral trochlear depth •Patella tilt angle •Congruence angle	UTD	PFP lat (n=11) vs. PFP non lat (n = 13) vs. Controls (n=10) **CA** 0° PFP lat 32° vs. PFP non lat 0° vs. Control 5° 5° PFP lat 22° vs. PFP non lat 2° vs. Control -2° 10° PFP lat 18° vs. PFP non lat -5° vs. Control 2° 20° PFP lat 9° vs. PFP non lat -5° vs. Control 2°	N/A

					30° PFP lat 4° vs. PFP non lat -4° vs. Control -2° **Femoral trochlear angle** 0° PFP lat 159 vs. PFP non lat 142° vs. Control 146° 5° PFP lat 147° vs. PFP non lat 132° vs. Controls 144° 10°PFP lat 143° vs. PFP non lat 130° vs. Controls 139° 20°PFP lat 139 vs. PFP non lat 128 vs. Controls 133° 30°PFP lat 131° vs. PFP non lat 126° vs. Controls 128° **PTA** 0°PFP lat 8 °vs. PFP non lat 15° vs. Control 18° 5°PFP lat 9° vs. PFP non lat 12° vs. Control 18° 10° PFP lat 11° vs. PFP non lat 9 vs. Controls 18° 20°PFP lat 13 vs. PFP non lat 7 vs. Controls 17 30°PFP lat 10° vs. PFP non lat 7 vs. Controls 17	
Souza et al 2010[179]	Kinematic MRI 0.5T open Axial-oblique	100% WB 0-45°	•Lateral patella •displacement (%) •Lateral patella tilt (°) •Femoral rotation (°) •Patella rotation (°)	**Intra-observer** Bisect offset (ICC 0.91; SEM 3.6%) Patella tilt (ICC 0.95; 1.3°) Femoral rotation (ICC 0.96; SEM 1.0°) Patella rotation (ICC 0.99; SEM 0.7°)	**Lateral patella displacement (Bisect offset (%)** 0 - PFP 75.2 (8.4) vs Controls 58.2 (7.2) 15-PFP 64 (4.4) vs Controls 53.2 (4.8) 30-PFP 57.6 (7.6) vs Controls 51.2 (2.4) 45 - PFP 57.6 (6.0) vs Controls 53.2 (2.0) **UTD** 0- PFP 12.8 (5.4) vs Controls 7.5 (4.0) 15- PFP 8.8 (4.0) vs Controls 5.6 (2.0) 30 - PFP 7.8 (4.4) vs Controls 5.4 (2.4) 45 - PFP 6 (3.8) vs Controls 5.8 (3.7) **Femoral rotation (°)** 0 - PFP 12.1 (5.1) vs Controls 6.0 (5.4) 15- PFP 6.0 (2.1) vs Controls 0.9 (6.0) 30- PFP 3.0 (5.1) vs Controls 0.3 (4.5) 45 - PFP 2.4 (3.3) vs Controls -0.3 (5.1) **Patella rotation (°)** 0- PFP -2.1 (6.3) vs Controls -0.9 (7.2) 15 - PFP - 3.7 (5.4) vs Controls -3.0 (6.0) 30 - PFP -4.0 (6.0) vs Control -4.0 (5.4) 45- PFP -3.6 (5.7) vs Controls -6.0 (6.6)	N/A
Taskiran et al 1998[411]	CT	Supine 0,15,30 &45°	•Congruence angle •Sulcus angle `	UTD	**C**A 0° QU = PFP 24.7 (11.7) vs. Controls 14.9 (13.9)	N/A

	Mid-patellar axial		•Patella tilt angle		0° QC = PFP 37.2 (9.1) vs. `Controls 25.3 (17) 15° QU = PFP 23.8 (10) vs. Controls 8.1 (13.2) 15° QC = PFP 28.2 (12.9) vs. Controls 18 (15.9) 30° QU = PFP 8.9 (7.8) vs. Controls 1.0 (10.8) 30° QC = PFP 7.7 (9.6) vs. Controls 0.5 (11.7) 45° QU = PFP -6.2 (9.9) vs. Controls -5.8 (9.4) 45° QC = -10.3 (5.4) vs. Controls -8.9 (5.8) **PTA** 0° QU = 11.7 (5.1) vs. Controls 13.3 (5.3) 0° QC = 13.7 (6.3) vs. Controls 10.9 (5.1) 15° QU = 10.7 (4.7) vs. Controls 9.9 (4.1) 15° QC = 12.3 (7.2) vs. Controls 9.2 (4.1) 30° QU = 7.0 (3.9) vs. Controls 9.0 (5.7) 30° QC = 6.0 (4.3) vs. Controls 6.8 (3.9) 45° QU = 7.2 (4.4) vs. Controls 9.1 (5.2) 45° QC = 5.9 (3.6) vs. Controls 7.2 (3.4) QC - quadriceps contracted; QU = quadriceps uncontracted) **Sulcus angle - not reported**	
Teng *et al* 2014[406]	MRI 1.5T FSPGR-axial	Supine 25%WB 0,20,40,60°	•Bisect offset •Patella tilt angle •Sulcus Angle •Lateral trochlear inclination •Insall-Salvati Ratio	**Intra-observer** Bisect offset (ICC 0.95-0.99) Patella tilt angle (ICC 0.95-0.99) Sulcus Angle (ICC 0.95-0.99) Lateral trochlear inclination (ICC 0.95-0.99) Insall-Salvati Ratio (ICC 0.95-0.99)	**BO (%)** 0 - PFP 71.7 (12) vs Controls 62.7 (10.9) 20- PFP 62.1 (11.3) vs Controls 55.9 (6.4) 40- PFP 60.9 (11.2) vs Controls 52.8 (6.9) 60- PFP 58.9 (10.0) vs Controls 55.3(4.8) **PTA (°)** 0- PFP 15.5 (7.0) vs Controls 12.9 (6.2) 20- PFP 15.1 (7.8) vs Controls 11.6 (5.0) 40- PFP 12.1 (7.1) vs Controls 8.9 (4.5) 60- PFP 8.5 (6.1) vs Controls 8.5 (4.1) **SA (°)** 0- PFP 168.5 (13.5) vs Controls 166.4 (13.7) 20- PFP 149.0 (6.5) vs Controls 149.8 (7.1) 40- PFP 138.4 (8.8) vs Controls 136.4 (8.8) 60-PFP 132.4 (7.1) vs Controls 129.9 (6.2) **LTI** 0 - PFP 14.9 (5.4) vs Controls 17.9 (8.3) 20- PFP 19.5 (6.2) vs Controls 22.9 (3.4) 40- PFP 22.6 (5.4) vs Controls 25.2 (4.7) 60-PFP 22.9 (3.7) vs Controls 24.1 (4.8)	N/A

					Insall Salvati Ratio 0- PFP 1.16 (0.16) vs Controls 1.14 (0.15) 20- PFP 1.09 (0.16) vs Controls 1.06 (0.13) 40-PFP 1.11 (0.18) vs Controls 1.06 (0.14) 60- PFP 1.10 (0.17) vs Controls 1.06 (0.14)	
Thuiller *et al* 2013[173]	MRI 3.0T •T2 weighted fat suppressed FSE - sagittal & axial • T1 weighted FSE	Supine 0°	•Mean T1 value total patellofemoral cartilage •Mean T1 value medial facet •Mean T1 value lateral facet •Mean T2 value total patellofemoral cartilage •Mean T2 value medial facet •Mean T2 value lateral facet	UTD	**T1 value** **Total** - PFP 44.6 ± 4.6ms vs. Controls 41.99 ± 3.21 ms; p=0.14 **Medial** - PFP 42.2 ± 5.4ms vs. Controls 41.42 ± 4.09ms; p=0.69 **Lateral** - PFP 46.3 ± 4.9ms vs. Controls 42.32 ± 3.67ms; p =0.031* **T2 value** **Total** - PFP 36.8 ± 7.9ms vs. Controls 37.28 ± 4.12ms; p =0.87 **Medial** - PFP 36.8 ± 7.9 vs. Controls 38.04 ± 3.45ms; p=0.39 **Lateral** - PFP 37.4± 7.7 vs. Controls 36.86 ± 5.21ms; p=0.37 **T1 medial: lateral ratio** PFP 0.92 ± 0.05 vs. 0.98 ± 0.03; p =0.01*	N/A
Tuncyurek et al 2010[407]	MRI 0.23T T1 weighted non fat saturated conventional spin-echo - sagittal & coronal	Supine 30°	•Patella tendon surface area •Patella tendon length •Patella tendon thickness	UTD	**Surface area (mm^2)** PFP 1393.6 ± 300.7 vs. Controls 1287.5 ± 293.1; p =0.2 **Thickness (mm)** PFP 4.53 ± 0.90 vs. Controls 4.58 ± 0.99; p=0.2 **Length (mm)** PFP 53.2 ± 7.5 vs. Controls 52.9 ± 8.3; p=0.2	N/A
Wilson et al 2009 [419]	US 14Mhz B Mode Sagittal & axial	Siting 60	•VMO resting tendon length •VMO cross-sectional area •VL resting tendon length •VL cross sectional area		**Tendon resting length (mm)** VMO - PFP 18.69 (2.66) vs. Control 18.66 (3.4) ; p = 0.985 VL - PFP 52.32 (5.71) vs. Controls 55.17 (5.46); p = 0.360 **Cross-sectional area (mm^2)** VMO - PFP 56.14 (16.87) vs. Controls 59.14 (11.81); p=0.707 VL - PFP 48.71 (20.25) vs. Controls 52.57 (14.95); p=0.692	N/A
Witzonzi & Goraj 1999 [408]	Supine Kinematic MRI	0°, 10°, 20°, 30° loaded &	• Patella tilt angle • Sulcus angle • Congruence angle	UTD	**Congruence angle (°)** **With contraction** 0° - PFP -1.3 ± 15.5 vs. Control -8.4 ± 15.2;	

	1.5T	19 unloaded			10° PFP -0.5 ± 17.0 vs. Controls -10.2 ± 13.3 20 °- PFP 0.5 ± 18.6 vs. Controls -13.9± 10.6 30°- PFP 1.5 ± 20.5 vs. Controls -16.3 ± 10.8; **Without contraction** 0° -PFP 0.5 ± 15.9 vs. Controls -7.8 ± 11.3 10° -PFP 0.4 ± 16.3 vs. Controls -9.3 ± 9.5 20 °- PFP 0.1 ± 16.6 vs. Controls -12.1 ± 7.8; 30° - PFP -0.5 ± 18.7 vs. Controls -13.3 ± 8.0 **Patella tilt (°)** **With contraction** 0°- PFP 8.3 ± 6.5 vs. Controls 15.9 ± 4.8 10° - PFP 8.3 ± 6.5 vs. Controls 16.5 ± 5.8 20 °- PFP 9.5 ± 7.9 vs. Controls 16.9 ± 6.9 30° -PFP 10.5 ± 9.0 vs. Controls 16.8 ± 7.7 **Without contraction** 0° - PFP 5.6 ± 9.8 vs. Controls 12.7 ± 4.6 10° - PFP 5.3 ± 9.3 vs. Controls 13.1 ± 5.8 20 ° - PFP 5.9 ± 9.8 vs. Controls 13.7 ± 6.9 30° - PFP 6.0 ± 10.6 vs. Controls 14.1 ± 7.0 **Sulcus angle (°)** 0° - PFP 150.8 ± 5.7 vs. Controls 149.2 ± 5.3 10° - PFP 148.4 ± 6.3 vs. Controls 148.7 ± 3.3 20 ° - PFP 144.3 ± 7.4 vs. Controls 146.6 ± 3.6 30° - PFP 140.8 ± 8.2 vs. Controls 144.5 ± 3.4	

US = ultrasound; CT =computed tomography; MRI=magnetic resonance imaging; XR =x-‐ ray; SA = sulcus angle; CA = congruence angle; A/P = anterior -posterior; VMO = vastus medialis oblique; VL =vastus lateralis; PFJRF =patellofemoral joint reaction force; PFJ = patellofemoral joint; EMD = electrical mechanical delay; OKC = open kinetic chain; CKC = closed kinetic chain; BO = bisect offset; Cont = contraction; Lat = lateral

3.4.3 Quality assessment

The results of the quality assessment are presented in Table 3.6. Based on the categorisations used [392], 23 studies were judged as high quality [65, 66, 68, 82, 148, 160, 165, 166, 168-170, 173, 179, 228, 256, 294, 359, 397-400, 402-404, 418, 420, 422, 423], with the remaining 17 studies considered of moderate quality [159, 163, 216, 405-417, 419, 421]. The criteria of best performance using the modified Downs & Black checklist were 1,2,3 and 4, which were satisfied by all the included studies. The criteria that the included studies performed most poorly were 9, 10, 11, 15 and 17 (Table 3.2). Criteria 9, 10 and 15 pertained to the documentation of population in which participants are recruited. Only half the studies clearly documented from where their participants were recruited e.g. hospital, military etc. Criterion 11 posed: *was an attempt made to blind those measuring the outcome.* Only 17.5% (7/40) of the studies we were able to determine whether the person/s interpreting the images were blinded to group allocation. Criterion 17 posed: *did the study have sufficient power to detect clinically important effect*. Only 17.5% (7/40) of studies [160, 173, 228, 256, 359, 402, 420] clearly documented how they calculated their sample size.

Table 3.6: Quality assessment

Study	Q1 (/1)	Q2 (/1)	Q3. (/1)	Q4. (/1)	Q5. (/2)	Q6. (/1)	Q7. (/1)	Q8. (/1)	Q9 (/1)	Q10. (/1)	Q11. (/1)	Q12. (/1)	Q13. (/1)	Q14. (/1)	Q15. (/1)	Q16. (/1)	Q17. (/1)	Total (/18)	% Score
Aglietti et al 1983[421]	1	1	1	1	1	1	1	0	UTD	UTD	UTD	1	1	1	UTD	1	0	**11**	**61.1**
Botanlioglu et al 2013[216]	1	1	1	1	1	1	1	1	UTD	UTD	UTD	1	1	UTD	UTD	1	0	**11**	**61.1**
Bretcher & Powers 2002[159]	1	1	1	1	1	0	1	1	1	1	UTD	1	1	0	1	0	0	**12**	**66.7**
Bretcher & Powers 2002b[163]																			
Callaghan & Oldham 2004[359]	1	1	1	1	2	1	1	1	1	1	UTD	1	1	1	1	1	1	**17**	**94.4**
Chen & Powers 2014[256]	1	1	1	1	1	1	1	1	1	1	UTD	1	1	1	UTD	1	1	**15**	**83.3**
Chen *et al* 2012[418]	1	1	1	1	1	1	1	1	1	1	UTD	1	1	1	UTD	0	0	**13**	**72.2**
Chiu *et al* 2012[166]	1	1	1	1	1	1	1	1	UTD	UTD	1	1	1	1	1	0	0	**13**	**72.2**
Connolly *et al* 2009[168]	1	1	1	1	1	1	1	0	1	1	UTD	1	1	1	1	1	0	**14**	**77.8**
Draper *et al* 2006[169]	1	1	1	1	2	1	1	1	UTD	UTD	UTD	1	1	1	1	1	0	**14**	**77.8**
Draper *et al* 2009[148]	1	1	1	1	2	1	1	1	1	1	UTD	1	1	1	1	1	0	**16**	**88.9**
Eckhoff et al 1994[415]	1	1	1	1	0	0	1	0	0	0	UTD	UTD	1	1	UTD	0	0	**7**	**38.9**

Farrokhi *et al* 2011a[170]	1	1	1	1	2	1	1	1	UTD	UTD	UTD	1	1	1	1	1	0	**14**	**77.8**
Farrokhi *et al* 2011b [65]																			
Felicio *et al* 2011a[397]	1	1	1	1	2	1	1	1	UTD	UTD	UTD	1	1	1	1	1	0	**14**	**77.8**
Felicio *et al* 2012b [399]																			
Felicio *et al* 2014c [398]																			
Guzzanti *et al* 1994 [410]	1	1	1	1	1	1	1	0	UTD	UTD	UTD	1	1	1	UTD	1	0	**11**	**61.1**
Haim et al 2006 [422]	1	1	1	1	2	1	1	1	1	1	0	1	1	1	1	1	0	**16**	**88.9**
Harman *et al* 2002 [409]	1	1	1	1	0	1	0	0	UTD	UTD	UTD	1	0	1	UTD	0	0	**7**	**38.9**
Ho *et al* 2014 [68]	1	1	1	1	2	1	1	1	UTD	UTD	UTD	1	1	1	1	1	0	**14**	**77.8**
Ho et al 2014b [66]																			
Joensen *et al* 2011 [403]	1	1	1	1	2	0	1	0	1	1	1	1	1	1	1	1	0	**15**	**83.3**
Jones *et al* 1995 [414]	1	1	1	1	0	1	1	0	UTD	UTD	UTD	1	1	UTD	1	0	0	**9**	**50**
Kim *et al* 2014 [423]	1	1	1	1	1	1	1	1	1	1	UTD	1	1	UTD	1	0	0	**13**	**72.2**
Laprade & Culham 2003 [420]	1	1	1	1	2	1	1	1	1	1	1	1	1	1	1	0	1	**17**	**94.4**
Jan *et al* 2009 [424]	1	1	1	1	2	1	1	1	1	1	0	1	1	1	0	1	1	**16**	**88.9**
Metin Cubuk *et al* 2000 [413]	1	1	1	1	1	1	1	0	UTD	UTD	UTD	1	1	UTD	UTD	0	0	**9**	**50**
Muneta *et al* 1994 [412]	1	1	1	1	1	1	1	0	UTD	UTD	UTD	1	1	1	UTD	0	0	**10**	**55.6**
Pal *et al* 2013c [402]	1	1	1	1	2	1	1	1	1	1	UTD	1	1	1	1	1	1	**17**	**94.4**
Pattyn *et al* 2012a[400]	1	1	1	1	2	1	1	1	1	1	1	1	1	1	1	1	0	**17**	**94.4**

Pattyn *et al* 2013c [294]																		
Pinar 1994 [417]	1	1	1	1	1	1	0	0	UTD	UTD	UTD	1	0	1	UTD	1	o	**9**	**50**
Powers 2000 [404]	1	1	1	1	1	1	1	0	1	1	UTD	1	1	1	1	1	0	**14**	**77.8**
Ribeiro *et al* 2010 [405]	1	1	1	1	1	1	1	1	UTD	UTD	UTD	1	1	1	1	0	0	**12**	**66.7**
Salsich & Perman 2007[165]	1	1	1	1	1	1	1	1	UTD	UTD	1	1	1	1	UTD	1	0	**13**	**72.2**
Salsich & Perman 2013[160]	1	1	1	1	1	1	1	1	UTD	UTD	1	1	1	1	UTD	1	1	**14**	**77.8**
Schoots *et al* 2013[82]	1	1	1	1	1	1	1	1	1	1	1	1	1	UTD	0	0	0	**13**	**72.2**
Shultzer *et al* 1986[416]	1	1	1	1	1	1	0	0	UTD	UTD	UTD	0	1	UTD	UTD	0	0	**7**	**38.9**
Souza *et* al 2010[179]	1	1	1	1	2	1	1	1	1	1	0	1	1	1	UTD	1	0	**15**	**83.3**
Taskiran et al 1998 [411]	1	1	1	1	1	1	1	0	UTD	UTD	UTD	1	1	1	UTD	1	0	**11**	**61.1**
Teng *et al* 2014 [406]	1	1	1	1	1	1	1	0	UTD	UTD	1	1	1	1	UTD	0	0	**11**	**61.1**
Thuiller *et al* 2013 [173]	1	1	1	1	1	1	1	1	1	1	UTD	1	1	1	0	0	1	**14**	**77.8**
Tuncyurek et al 2010 [407]	1	1	1	1	1	1	1	1	UTD	UTD	UTD	1	1	UTD	UTD	1	0	**11**	**61.1**
Wilson et al 2009 [419]	1	1	1	1	1	1	1	1	UTD	UTD	UTD	1	1	1	UTD	0	0	**11**	**61.1**
Witzonzi & Goraj 1999 [408]	1	1	1	1	1	1	1	0	UTD	UTD	UTD	1	1	UTD	UTD	1	0	**10**	**55.6**
No. of studies scoring Yes	**40**	**40**	**40**	**40**	**50**	**37**	**37**	**25**	**17**	**17**	**7**	**38**	**38**	**31**	**18**	**24**	**7**		
% of studies scoring Yes	**100**	**100**	**100**	**100**	**62.3**	**92.5**	**92.5**	**62.5**	**42.5**	**42.5**	**17.5**	**95**	**95**	**77.5**	**45**	**60**	**17.5**		

UTD = Unable to detect; **Q1:** Is the hypothesis/aim/objective of the study clearly described?; **Q2:** Are the main outcomes to be measured clearly described in the Introduction or Methods section?; **Q3**: Are the characteristics of the patients included in the study clearly described?; **Q4**: Are the interventions of interest clearly described?; **Q5**: Are the distributions of principal confounders in each group to be compared clearly described?; **Q6**: Are the

main findings of the study clearly described?; **Q7**: Does the study provide estimates of the random variability in the data for the main outcomes?; **Q8**: Have the actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001: **Q9**: Were the subjects asked to participate in the study representative of the entire population from which they were recruited?; **Q10**: Were the subjects who were prepared to participate representative of the entire population from which they were recruited; **Q11**: Was an attempt to blind those measuring the main outcome?; **Q12**: If any of the results of the study were based on “data dredging” was this made clear?; **Q13**: Were the statistical tests used for the main outcomes appropriate?; **Q14**: Were the main outcome measures used accurate (valid and reliable)?; **Q15**: Were the case and controls recruited from the same population?; Q16: Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?; **Q17**: Did the study have sufficient power to detect a clinically important effect?

3.4.4 Synthesis of results

MRI features (patellofemoral contact area, patellar tilt, patellar bisect offset, patellar cartilage T2 relaxation times and sulcus angle) and CT features (congruence angle) were the only imaging features that yielded homogenous data appropriate for meta-analysis. These features are demonstrated schematically in Figure 3.2. If discrepancies were noted in either the knee loading status, assessments of the imaging feature or knee flexion angle, then features were not considered for meta-analysis. The results of the meta-analyses are displayed in Table 3.7.

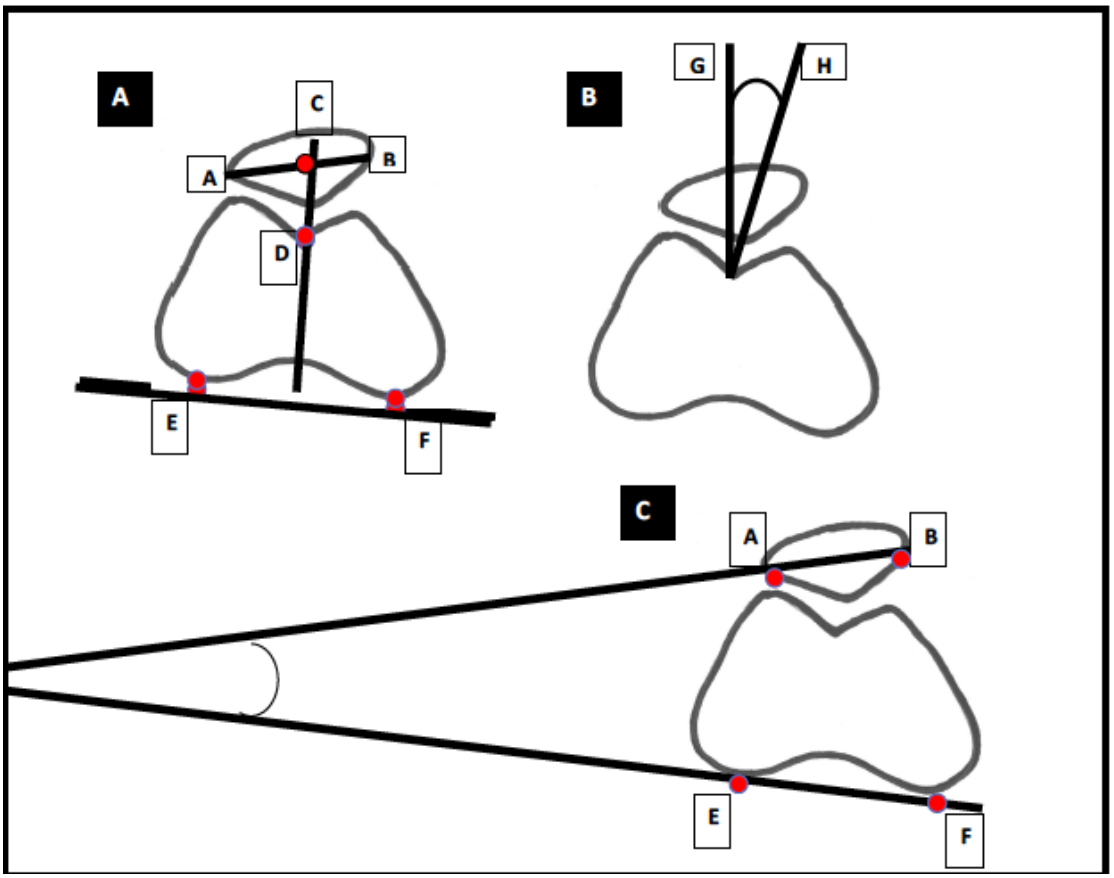


Figure 3.2. Measurement of patella alignment
Line A to B forms the patella width. Line E to F forms a line along the most posterior femoral condyles. Point D is located at the deepest point of the trochlear groove. Point C is the bisecting point of the perpendicular line through the AB line. Line G bisects the sulcus angle to form a zero reference and line H is the projected from the apex of the sulcus angle through the most dorsal part of the patella. A) Bisect offset = (length of AC / length of BC) X 100%; B) Congruence angle = angle formed between G line and H line; C) Patella tilt = the angle formed by line between AB and EF [406]

Funnel plots were considered to examine the bias in meta-analyses. A funnel plot is a scatter plot of the treatment effects against the study precision. In the absence of any bias the plot should resemble an inverted symmetrical funnel [426]. Typically bias identified by funnel plots is attributed to publication bias, however, other sources of biases including selective reporting and poor methodological design may be the cause of funnel asymmetry [426]. Based on published guidelines [427], funnel plots were not indicated as none of the meta-analyse conducted in this chapter included more than 10 studies. Fewer than 10 studies reduces the power of identifying real asymmetry [426] and increases the likelihood of a spurious result.

Table 3.7: Result of the meta-analysis

Imaging feature	Outcome	Studies	Total Participants	Statistical Method	Effect Estimate
MRI Patellofemoral Contact area (mm^2)	Patellofemoral Contact Area at 20° under load	2	71	Std. Mean Difference (IV, Fixed, 95% CI)	-0.53 [-1.01, -0.06]
MRI Patella Tilt (°)	Patella tilt at 0° under load	6	235	Std. Mean Difference (IV, Fixed, 95% CI)	0.63 [0.37, 0.90]
	Patella tilt at 20° under load	4	143	Std. Mean Difference (IV, Fixed, 95% CI)	0.35 [0.02, 0.69]
	Patella tilt at 30° without load	2	63	Std. Mean Difference (IV, Fixed, 95% CI)	0.25 [-0.24, 0.75]
	Patella tilt at 45° under load	3	104	Std. Mean Difference (IV, Fixed, 95% CI)	0.14 [-0.25, 0.54]
	Patella tilt at 0°under full weight bearing	2	66	Std. Mean Difference (IV, Fixed, 95% CI)	0.99 [0.47, 1.52]
MRI Bisect Offset (%)	Bisect offset at 0 ° under load	6	235	Std. Mean Difference (IV, Random, 95% CI)	0.99 [0.49, 1.49]
	Bisect offset at 20 ° under load	3	128	Std. Mean Difference (IV, Random, 95% CI)	0.73 [0.29, 1.17]
	Bisect offset 40° under load	3	127	Std. Mean Difference (IV, Random, 95% CI)	0.61 [-0.09, 1.31]
	Bisect offset at 45° under load	3	104	Std. Mean Difference (IV, Random, 95% CI)	0.39 [-0.13, 0.92]
	Bisect offset at 60 ° under load	2	72	Std. Mean Difference (IV, Fixed, 95% CI)	0.50 [0.02, 0.98]
	Bisect offset 0° under full weight bearing	2	66	Std. Mean Difference (IV, Fixed, 95% CI)	1.91 [1.31, 2.52]
MRI T2 Relaxation Times (ms)	T2 Relaxation times at 0° without load	2	130	Std. Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.35, 0.34]
MRI Sulcus angle (°)	Sulcus angle at 0° under load	2	71	Std. Mean Difference (IV, Random, 95% CI)	0.44 [-0.17, 1.05]

	Sulcus angle at 30° without load	2	63	Std. Mean Difference (IV, Random, 95% CI)	0.43 [-0.48, 1.35]
CT Congruence angle (°)	Congruence angle at 15 ° under load	2	66	Std. Mean Difference (IV, Random, 95% CI)	1.40 [0.04, 2.76]
	CT Congruence angle at 15 ° without load	2	66	Std. Mean Difference (IV, Random, 95% CI)	1.24 [0.37, 2.12]

3.4.5 Magnetic Resonance Imaging

Of the twenty-two studies that used MRI, sixteen studies [65, 66, 68, 148, 160, 165, 166, 168-170, 173, 179, 256, 294, 397-400, 402-404, 428] were judged as high quality. Controlling for the knee loading status, assessment of the imaging feature and knee flexion angle, patella bisect offset at 0 degrees with load demonstrated the largest SMD (0.99; 95% CI: 0.49, 1.49; moderate evidence) based on five high quality and one moderate quality study (Figure 3.3).This was the only MRI feature which presented with a large SMD [139]. Five other features demonstrated a medium SMD [139].These included: patella bisect offset at 20 degrees with load (0.73; 95% CI: 0.29, 1.17; limited evidence), patella tilt at 0 degrees with load (0.63: 95% CI: 0.37, 0.90; moderate evidence), patella bisect offset at 40 degrees with load (0.61; 95% CI:-0.09, 1.31; limited evidence), patellofemoral contact area at 20 degrees with load (-0.53; 95% CI: -1.01,-0.06; limited evidence) and patella bisect offset at 60 degrees with load (0.50; 95% CI 0.02, 0.98; limited evidence).

A small SMD was found for the pooling of sulcus angle at 0° with load (0.44; 95% CI: -0.17, 1.05; limited evidence), sulcus angle at 30° without load (0.43; 95% CI: -0.48, 1.35; limited evidence), patella tilt at 20° with load (0.35; 95% CI: 0.02,0.69; moderate evidence), patella tilt at 30° without load (0.25; 95% CI: -0.24, 0.75; limited evidence), T2 Relaxation time at 0° with without load (-0.01; 95% CI: -0.35,0.34; limited evidence). The data for patellofemoral joint reaction force (PFJRF) was considered inappropriate for pooling as its outputs were produced via computational modelling, with imaging as only one component. For the data not amenable to pooling, there was limited evidence to support a difference between PFP and a control group with regards to: congruence angle at 20° [408]and 30° [405]without load; T1 value of the lateral patellofemoral cartilage without load [173]; articular lesions of the patella [403]; peak PFJRF; and patella cartilage thickness in males [169]. There was conflicting evidence to support a difference in patella cartilage thickness in women [66, 168-170] and no evidence to support differences in patella tendon morphology [407].

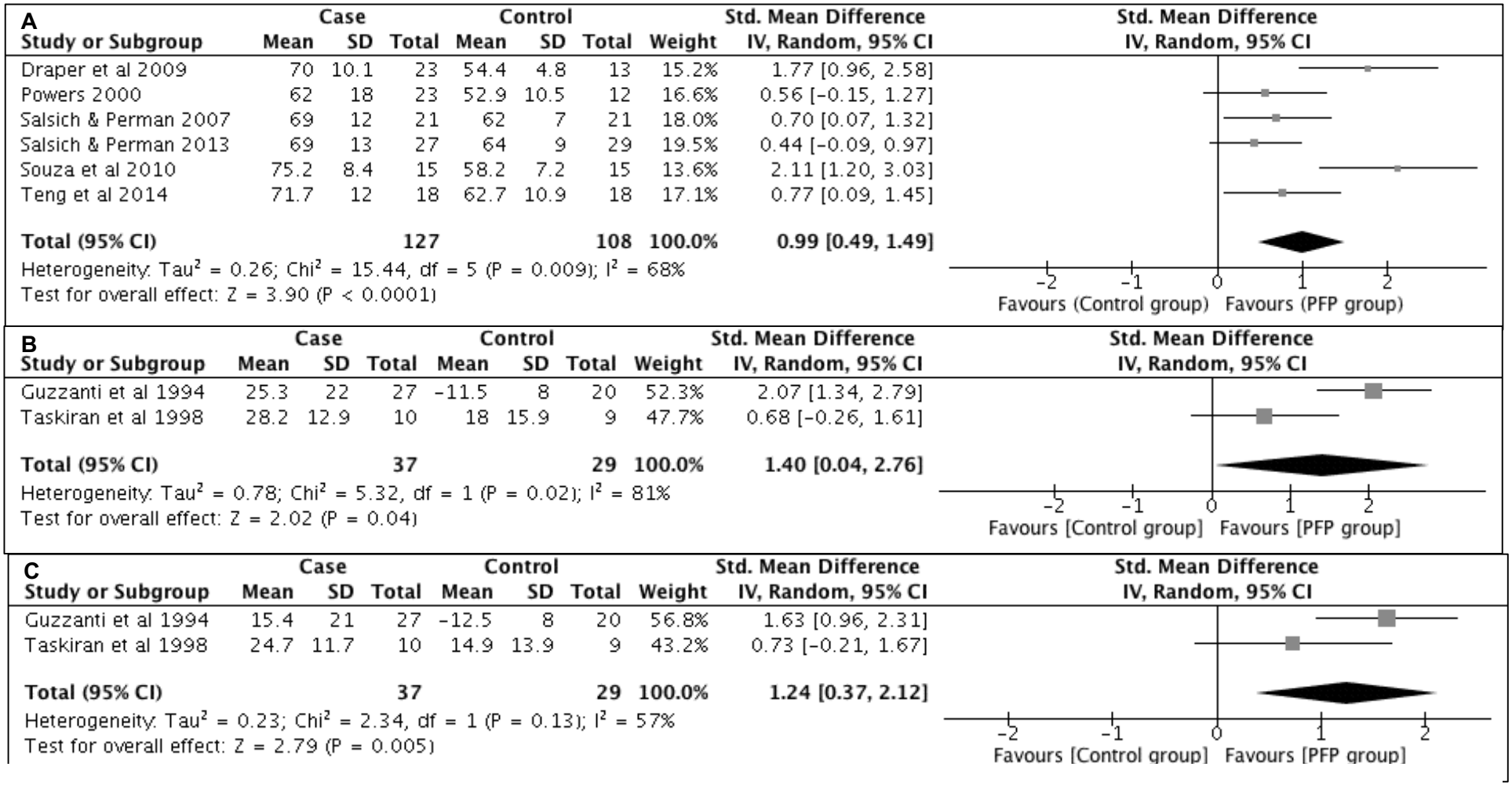


Figure 3.3: Forest plots

A) MRI bisect offset at 0° under load; B) CT congruence angle at 15° under load; C) CT congruence angle at 15° without load

3.4.6 Ultrasound

US was used to assess PFP imaging features in four studies [82, 228, 359, 418]. These were all judged as high quality. Pooling of data was not appropriate due to the variety of outcome features analysed and the different assessment techniques used. For the data not amenable to pooling, there was limited evidence, from single studies, to support a difference between PFP and control group in terms of: a reduction in vastus medialis oblique (VMO) contraction ratio and capacity [216]; an increase in VMO electrical mechanical delay and a reduction in vastus lateralis (VL) delay[418]; and a difference in VMO fibre angle, insertion level and volume [228].

3.4.7 Computed Tomography

CT was employed in eight studies, all of which were judged as moderate quality. Pooling of data was limited for congruence angle [410, 411, 416, 417]; patella tilt angle [410, 411, 416, 417]; sulcus angle [410, 417] since studies either: did not provide adequate data [417]; it was unclear whether their participants' knee was loaded or unloaded [416]; or they adopted different measurement techniques for patella tilt angle [410]. Pooling was appropriate for congruence angle at 15 degrees without load and congruence angle at 15 degrees under load. Both features demonstrated a large SMD (1.24; 95% CI 0.37, 2.12; limited evidence) and (1.40 95% CI: 0.04, 2.76; limited evidence) respectively, based on two studies [410, 416] (Figure 3.4). For the data not amenable to pooling there is limited evidence to support a difference between PFP and a control group with regards to: congruence angle at 15° without load [411]; tibial tubercle rotation angle at 0° without load [412, 413]; trochlear depth at 15° without load [410]. Conflicting evidence exists for patella tilt at 15° with load [410, 411].

3.4.8 X-ray

XR features were assessed in five studies. Of these, three were judged as high quality [420, 422, 423] and two as moderate quality [413, 421]. The following features were considered for meta-analysis: sulcus angle [420-422], congruence angle [420-422], Insall-Salvati index [421, 422] and lateral patellofemoral angle [420, 423]. It was not possible to pool data for any of these XR features however, due to variations in the knee flexion angle. For the data not amenable to pooling there was limited evidence to support a difference between PFP and a control group with regards to:

congruence angle at 45° with load [421, 423] but no evidence at 35° [420]. There was limited evidence to support sulcus angle at 45° without load [421, 423] but no evidence to support it at 30°[422] and 35° [420] .There was conflicting evidence for Insall-Salvati index at 30° without load [413, 421, 422] and no evidence for lateral patellofemoral angle at 35° [420] and 45° [423] without load.

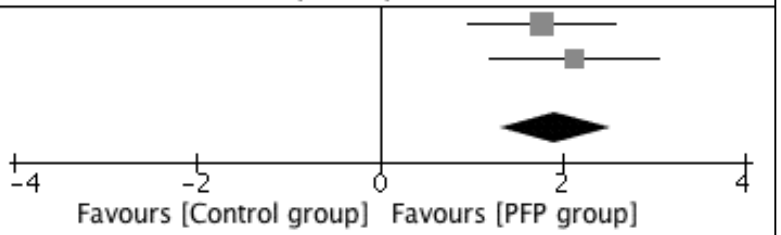
3.4.9 Sensitivity analysis

Two studies included in the meta-analysis [148, 179] used a full weight-bearing procedure to load the PFJ during imaging. Analysing appropriate features under full weight bearing separately demonstrated a marked increase in the SMD (Figure 3.4) of MRI patella bisect offset at 0 degrees with load (1.91; 95% CI: 1.31,2.52; limited evidence) and MRI patella tilt at 0 degrees with load (0.99; 95% CI: 0.47,1.52; limited evidence).

A

Study or Subgroup	Case Mean	Case SD	Case Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Draper et al 2009	70	10.1	23	54.5	4.8	13	56.5%	1.76 [0.96, 2.57]
Souza et al 2010	75.2	8.4	15	58.2	7.2	15	43.5%	2.11 [1.20, 3.03]
Total (95% CI)			**38**			**28**	**100.0%**	**1.91 [1.31, 2.52]**

Heterogeneity: Chi² = 0.32, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 6.20 (P < 0.00001)



B

Study or Subgroup	Case Mean	Case SD	Case Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Draper et al 2009	9.75	7	23	4.25	2.8	13	53.9%	0.92 [0.20, 1.63]
Souza et al 2010	12.8	5.4	15	7.5	4	15	46.1%	1.09 [0.31, 1.86]
Total (95% CI)			**38**			**28**	**100.0%**	**0.99 [0.47, 1.52]**

Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%
Test for overall effect: Z = 3.71 (P = 0.0002)

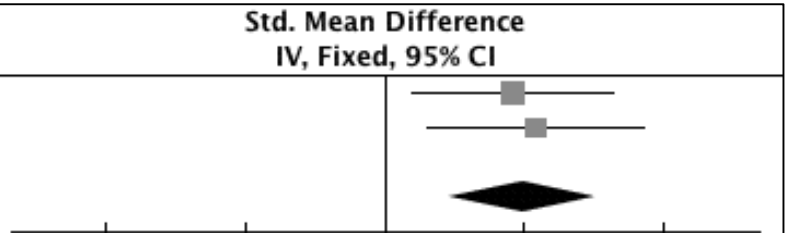


Figure 3.4: Forest plots for full weight bearing studies.
A) MRI bisect offset at 0° under full weight bearing B) MRI patella tilt at 0° under full weight bearing

3.5 Discussion

This systematic review suggests that an increased MRI bisect offset at 0° knee flexion under load and CT-derived congruence angle at 15° knee flexion with and without load are both associated with PFP. This is based on a large SMD as determined from moderate and limited evidence respectively. A medium SMD was identified for the association between PFP and the following MRI features: patella tilt and patellofemoral contact area. Limited evidence existed to support the association of PFP with other features of MRI, US, CT and XR.

As highlighted in Chapter 2, Lankhorst *et al.* (2013) [194] provides a comprehensive review into a broad range of factors associated with PFP (searched up to November 2010). Unlike Lankhorst *et al.* (2013) [194], the current analysis did not restrict inclusion by sample size to improve inclusivity [429] and together with inclusion of more recent studies, this resulted in over 70% of the current review studies being different from Lankhorst *et al.* (2013) [194]. The present review also controlled for variables such as imaging modality, knee flexion angle, and knee loading, known to influence the homogeneity of the imaging outcomes [154].

Sufficient homogeneity was only demonstrated by MRI and CT studies and thus deemed appropriate for meta-analysis. Bisect offset measured with MRI was most amenable to pooling across a variety of knee flexion angles demonstrating medium to large SMDs. This is notable as bisect offset has been shown to be the most statistically significant feature in the progression of PFJ joint space narrowing over a five-year period in adults with symptomatic knee pain aged 70-79 years [430]. Considerable clinical heterogeneity was present in the studies utilising XR and US. Studies using XR reported outcomes with subtle variations in knee flexion angle or assessment techniques that limited the pooling of data. The imaging features used in US were distinctly different and so offered no potential for pooling.

The sensitivity analysis demonstrated an increase in SMD for both patella tilt and bisect offset when MR images were acquired under upright full weight bearing. This is in contrast to previous studies that have shown that bisect offset is more pronounced in the supine position when investigating people with PFP under both

supine-loaded and upright full weight bearing conditions [164, 425]. The reason for this disparity is unclear, however, it may be explained by the fact that the previous studies selected people with excessive patella lateralisation, whereas the studies included in the current review likely contained a range of patella alignments. Another possibility is that the control group in the current review demonstrated an average *reduction* in bisect offset under full weight bearing, which may also explain the increased SMD.

An on-going debate surrounds imaging under load [367]. The concept of 'weight bearing' has been challenged by Harbaugh *et al.* (2010) [367] who suggest that quadriceps activity is the primary determinant of patella position in PFP rather than the axial loading. Studies that use full weight bearing in this chapter employed a 0.5 Tesla (T) open, upright scanner and the field strength of 0.5T may have affected image quality [431, 432]. Full weight bearing conditions also have the potential to elicit pain during the procedure [185]. In PFP, pain is recognised as having an inhibitory effect on quadriceps [433]. Altering quadriceps activity may influence the validity of the results by affecting patellar orientation [367].

A number of limitations in the literature were identified based on participant selection. Firstly, a number of the included studies [65, 66, 68, 148, 168, 170, 179, 256, 397-399, 404-406, 413] used all female cohorts, and of these studies only a few selected a matched cohort. Controlling for gender, knee flexion angle and loading of the knee has been advocated because these factors have been reported to influence the PFJ mechanics and the comparisons made [154]. Furthermore, only half the studies clearly stated the recruitment source of participants e.g. hospital, military etc. Extrapolating results taken from a military or very physically active group and applying them to a more sedentary community dwelling population is likely to affect the external validity. Secondly, the quantification of pain in the PFP cohort was inconsistent. Over two thirds of the included studies selected participants based on reproducible pain with functional activities, however the number of provocative activities required for diagnosis and inclusion varied from one [169, 406, 412, 417, 422, 423] to five [166, 408, 409]. The use of the VAS to quantify pain on provocation activities was used in six studies [65, 160, 165, 170, 179, 256, 406] . The duration of symptoms was also poorly reported, with fewer than a quarter of the included studies documenting the duration of PFP, and in these studies the data was presented differently (e.g. mean duration, range of duration). The duration of symptoms is important, as this has been shown in PFP to be a predictor of poor long-term

outcomes [19]. The effect of the duration of symptoms in relation to structural imaging findings is unknown. It is known however, that long term pain will lead to muscle inhibition [433] and thus there is a probability that a reduction in quadriceps strength and activity could influence the PFJ structural features observed.

A number of limitations were identified in terms of the imaging assessment and outcomes for the included studies. Fewer than a quarter of included studies clearly recorded who interpreted the images [82, 160, 165, 166, 294, 400, 403, 406, 420]. A person's level of experience interpreting imaging has been demonstrated to affect the accuracy of the analysis [434] and the level of confidence drawn from their findings. Furthermore, only a few studies documented whether the person analysing the images was blinded to group allocation. Blinding of allocation in this type of study design should be achievable [435] and lack of blinding raises the concern of confirmation bias [435]. The reliability of the imaging assessment was reported in fewer than half the included studies. Generally, the ICCs showed a moderate to high reliability for the MRI variables: bisect offset, patella tilt angle, patellofemoral contact area, Insall-Salvati index and sulcus angle, supporting the use of these features in future studies.

A recent international expert consensus group highlight the need for sub-grouping of the PFP population [20]. The current review demonstrated a number of PFJ imaging features associated with PFP suggesting that these features should be considered as important components of future stratification. In addition, although most of the included studies employed cross sectional analyses, two studies did employ an interventional pre-post study design [148, 166]. These studies detected a significant change in patellofemoral contact area following strengthening exercise [166] and patellofemoral bisect offset and patella tilt following patella bracing [148]. As these imaging features have been shown to be modifiable it highlights the opportunity of using imaging features clinically as a treatment target

3.6 Limitations of the current review

Study selection remains challenging in terms of the PFP nomenclature and the fact that historically, the condition has been referred to by a variety of other names [436]. In the present review, over 20% of the studies used terms differing from

patellofemoral pain or *patellofemoral pain syndrome*. This makes study selection challenging with selection of the studies based on the description of the condition when more ambiguous terms are used. We attempted to minimise the potential bias in this process by using two reviewers to select studies and a third independent mediator.

From a study design perspective, the cross-sectional nature of the studies means the results from the current review cannot imply causality. Furthermore, the small sample sizes used in many of the included studies may influence the validity of the results. However, meta-analyses were possible for a number of imaging features thus increasing the overall sample size and improving statistical power [437].

With consideration of the methodology, determining whether an image was captured under load was based on a dichotomised value (loaded/ unloaded) rather than quantifying the exact load which may be important [367]. Only a few studies reported the quantity of loading so a comparison between studies was not possible. It was also apparent that some potential data for the review was the outcome of complex modelling such as finite element modelling. Where possible these imaging features were isolated and reported, however, the features that could not be isolated should be considered for a separate, future review.

3.7 Conclusion

The analyses within this chapter suggests that PFP is associated with a number of imaging features, in particular MRI bisect offset and CT congruence angle analysed at 0° knee flexion and 15° knee flexion respectively. A degree of caution in interpretation of this data is advised, however, due to the role of both features being derived from only moderate and limited evidence respectively. The results of this systematic review suggest that future studies need to clearly document the specific population in which participants are recruited and to improve reporting of imaging-related issues. The inclusion of two interventional studies demonstrates that imaging features are potentially modifiable [148, 166] supporting their use in clinical subgrouping as shown in Chapter 5 and the presence of twenty- two studies reporting MRI features informs the investigation in Chapter 3. Limitations identified in terms of participant selection and imaging assessment will be further addressed in the following chapters.

Chapter 4 - Patellofemoral joint morphology in middle-aged people with patellofemoral pain measured using 3D quantitative analysis: data from the Osteoarthritis Initiative

This chapter describes a retrospective study which employed novel technology to create 3D equivalents of commonly used patellofemoral joint imaging features and overall 3D bone shape to investigate whether these features differed between people with and without patellofemoral pain and between genders. The results from this chapter have been published as: Drew BT, Bowes MA, Redmond AC, Dube B, Kingsbury S, Conaghan PG. (2017). Patellofemoral morphology is not related to pain when using 3D quantitative analysis: data from the Osteoarthritis Initiative. Rheumatology. 56 (12), 2135-2144. [438].

4.1 Introduction

The findings of Chapter 3 show a number of MRI features associated with PFP [378]. Features such as patella medial-lateral position and patella tilt were shown to be associated with PFP in small cohorts [378] (section 3.4.4). However, these findings were predominantly based on radiographic methods that have inherent limitations arising from their 2D methodology [439]. These studies typically used methods originally designed for radiographs and applied them to single MRI slices [439]. This type of '2D' measurement is not optimal, as it does not control for the position of the leg within the image. For example, a difference in patella alignment or shape may be genuine or may be caused by the object's pose, the combined relative position and rotation of the bones [440, 441] (see Figure 4.1). From a practical perspective, these manual assessment methods are also user-dependent and time-consuming, making it difficult to analyse features for large datasets [442].

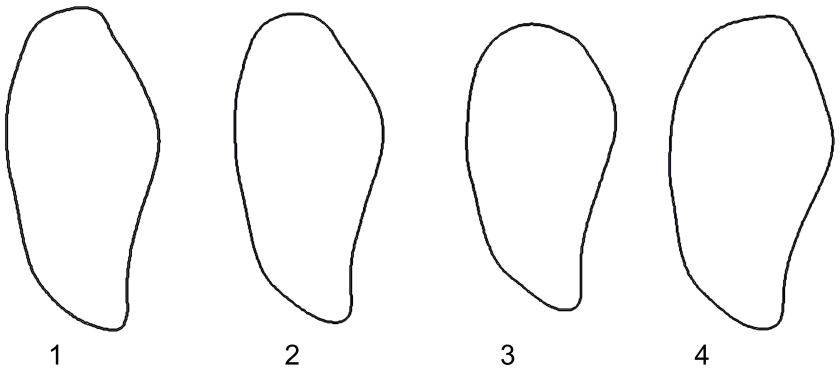


Figure 4.1: The apparent shape of the patella after small translations and rotations

1) Shows the outline of the mean patella in the coronal plane; 2) outline at the same height in the coronal plane but with patella rotated by 10° around the medial-lateral axis; 3) outline at the same height but with the patella rotated by 10° around the anterior-posterior axis; 4) patella translated 10mm superiorly, plus both rotations (2) and (3). The overall outline of the patella varies despite being the same 3D shape and object.

The utilisation of supervised machine learning with Active Appearance Models (AAMs) [443], provides a solution to these recognised imaging shortfalls. This 3D quantitative analysis uses the statistics of shape and image information, calculated from a training set of images, and uses the resulting model to match to new images [444] (see 4.3.4.). This automated segmentation is capable of accurate identification of the shape and appearance of bone, providing an accurate, faster and highly reliable solution for analysing large imaging datasets [443, 445]. A major benefit is that the 3D imaging measures are not influenced by the pose of the object [446].

Previous studies have considered the shape of the patellofemoral joint (PFJ) using statistical shape models [447, 448] but these have included only asymptomatic individuals in small cohorts and have failed to consider the differences in the PFJ anatomy that exist between gender [449, 450].

4.2 Aims

The primary aim of this study was to use modern image analysis technology to investigate the differences between 3D imaging features (based on existing

radiographic measures) and overall bone shape for people with and without PFP in a large cohort; and to investigate whether any single 3D imaging feature, or combination of features, was associated with the presence of pain. As evidence suggests there are differences in PFJ morphology between genders [449-451], the secondary aim was to validate the measures used by exploring whether these features could significantly discriminate men and women.

4.3 Methods

The data used in this chapter was taken from the publically available Osteoarthritis Initiative (OAI) database.

4.3.1 Summary of the Osteoarthritis Initiative (OAI)

The Osteoarthritis Initiative (OAI) is a multicentre longitudinal, observational study [452] comprising of those with knee osteoarthritis (OA) and those at risk of knee OA aged between 45-79 years. The study database includes 4796 participants with an extensive range of patient reported, clinical and imaging data publically available. The overall recruitment aim of the OAI was to enrol equal numbers of males and females of which at least 23% were from ethnic minorities with or at risk of symptomatic tibiofemoral OA [452]. Scans were performed bilaterally using 3.0 T MRI and the following MRI sequences were employed (see Table 4.1). Bilateral radiographs were used to determine the Kellgren & Lawrence (KL) grade using posterior-anterior views in a fixed flexion standing position.

Table 4.1: MRI sequences used in the OAI

MRI Sequences
Sagittal 3D DESS WE
Coronal MPR 3D DESS WE
Axial MPR 3D DESS WE
Coronal IW TSE FS 3200 29
Sagittal IW TSE FS 3200 30
Coronal T1 3D FLASH WE
Sagittal T2 MAP 120 mm FOV

DESS: double-echo steady state; Multiplanar reconstruction; IW: intermediate weighted; WE: water excitation; TSE: turbo spin echo; FOV: field of view.

4.3.2 Setting

Data was retrieved at the 24-month time point from the OAI. This time point was chosen because this was the only time point when pain location (one of our selection criteria) was recorded. A Knee Pain Map was recorded asking the patient to use their fingertip to point to the locations of pain. Only pain located to the patella was included in this study. The full OAI database can be found at: https://oai.epi-ucsf.org/

4.3.3 Participants

All patients at each Institutional Review Board (IRB) approved study site provided informed consent. The OAI study and the public use of all data used in the study were approved by the committee on Human Research, University of California, San Francisco (IRB approval number 10-00532). This chapter has been reported here in accordance to the Strengthening the Reporting of Observation Studies in Epidemiology (STROBE) guidelines [453]

Our PFP group was selected based on fulfilling all the following criteria: the presence of pain reported in the patella region by the participant (using a Knee Pain Map); knee pain when using stairs - taken from the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale question; and a tibiofemoral joint KL grade of 0. Participants with any history of knee surgery in either knee, including replacement surgery, were excluded from the analysis. When bilateral knee pain was identified, the knee with the highest pain score on stair use was selected. If both knees had the same severity of pain, the right leg was chosen. One knee was selected for the control group based on fulfilling all the following: no pain in the patella region indicated by the participant; overall WOMAC score of 0; a

numerical rating scale (NRS) score of 0; KL grade of 0; and no history of surgery. Matching was considered but not applied in order to optimise the sample size for this high dimensional data set i.e. a large number of potential correspondences are required to specify a specific point (see 4.4.2 for further details). The MRI data and associated clinical data was gathered from the selected participants and the MRIs then analysed using AAMs (see 4.3.5)

4.3.4 An overview of Active Appearance Modelling

The 3D quantitative analysis used is based on the Active Appearance Models developed by Cootes *et al.* (2001) [443]. Modern applications of AAMs include treatment planning in cardiology [454], neurology[455] as well as its recognised use in facial recognition [456]. Active appearance modelling is a specific form of statistical shape modelling (SSM). SSM can provide 3D morphological data that could be used to understand pathophysiology, non-invasively *in vivo* [457]. Historically, joint shape is reliant on manual segmentation, the process of dividing an image into different regions and performed on individual MRI slices. This is particularly used for quantitative imaging measures as described in Chapter 3. Clearly these measures are labour intensive and not feasible for large datasets without many months of manual segmentation [444, 445]. If the geometrical shape is manually segmented enough from a representative population then a segmented region of interest can be analysed by statistics in order to allow the application of SSM. The process involves identifying a large number of anatomical equivalent landmarks (correspondences) on a mean shape, which allows for automated recognition in a target image - similar to face recognition software. The statistics behind this SSM uses principal component analysis (PCA) in which the correspondences are data points. These data points are constructed into eigenvalues (how much variance of data in a particular direction) and eigenvectors (the direction the line of data). The PCA finds the line that explains the most variation with the fewest axes possible –often the eigenvector with the highest eigenvalue. PCA is also able to reduce the dimensionality of the data by stripping the data down to its basic components, which is essential for analysing complex 3D data. This ‘trained SSM’ is then able to recognise the same object or part of an object in any target image it encounters allowing for accurate, automated segmentation [457]

The second generation SSM is the active shape model (ASM), which advances this approach to control for the natural variation that exists within the same tissue. This statistical algorithm fits the data to the target image to ensure the best fit. Advancing the ASM further, the third generation of this approach and the technology used in this chapter is the active appearance modelling (AAM). The AAM utilises the grey scale texture, which considers the gradient, corners and any other points of interest [444] to more accurately define the shape. In the training set, a 5-6 rim is applied to ensure that the model learns the grey scale texture allowing this to be identified and matched to target images in encounters. This is depicted schematically in Figure 4.2.

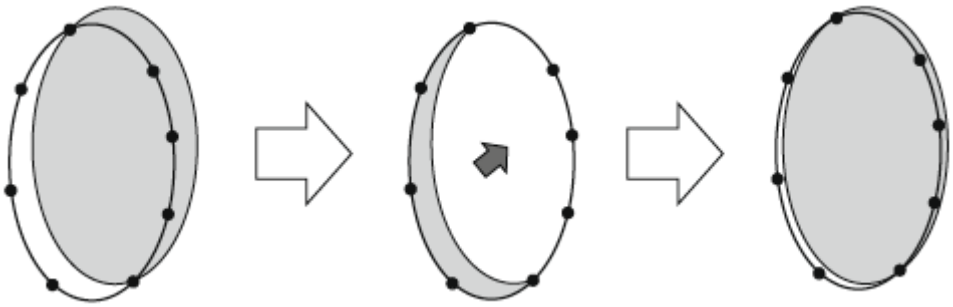


Figure 4.2: A schematic diagram of Active Appearance Modelling

To start with, the model is located in the lower left of the true position (solid grey). The texture is then sampled and compared to appearance model. The corresponding residuals are shown in the next image, which suggests move to the upper right. The final image brings model closer to true position and appearance. Reprinted with permission from Elsevier, Medical Image Analysis [458].

4.3.4.1 How does AAM address previous imaging shortfalls?

The 3D quantitative imaging analysis utilises the centroid of the feature. The centroid can be thought of as the geometrical centre of gravity representing the average position between the x, y and z axes [459]. The centroid is a more robust descriptor of an imaging feature's location rather than relying on the midpoint of points in single slice 2D image. The 2D midpoint points are thought to be influenced by the errors in peripheral single pixels that may occur due to problems with acquisition or noise [460] as well as the highlighted inconsistencies in testing procedures. The centroid also represents an accepted, consistent reference location rather than relying on different reference locations for difference features. For example, the reference

location for congruence angle is the deepest part of sulcus (see Figure 3.2) whereas the patella tilt uses the posterior condyles (see Table 2.5.).

4.3.5 Data sources

In this chapter, the bone surfaces for the trochlear femur and the subchondral patella were obtained by automatic segmenting using AAMs of the selected participant MRIs. The AAMs for the femur and patella joint surfaces (Figure 4.3) were built from an independent training set of 96 examples acquired using the DESS-we MRI sequence chosen so as to contain examples from each stage of OA. Anatomical regions of subchondral bone were outlined on the mean patella and femur shapes using the correspondence points of the model, as previously described [445]. In this case, the PFJ surfaces were identified (Figure 4.3). An advantage of this method is that each automatic segmentation of an individual PFJ surface is automatically fitted with a dense set of anatomically corresponded landmarks, which can be used for measurements or for registration of examples.

This study relies on the ability of the AAM to accurately represent the 3D shape of the trochlear femur and the patella. Accuracy was assessed using 96 leave-one-out models, which were then fitted to the missing example. Distances from the known 3D surface to the AAM-searched surfaces were calculated as point-to-surface distance (mm) at each point in the model. Mean error (calculated using the root-mean-square method [RMS]), and 95^{th} percentile errors were calculated.

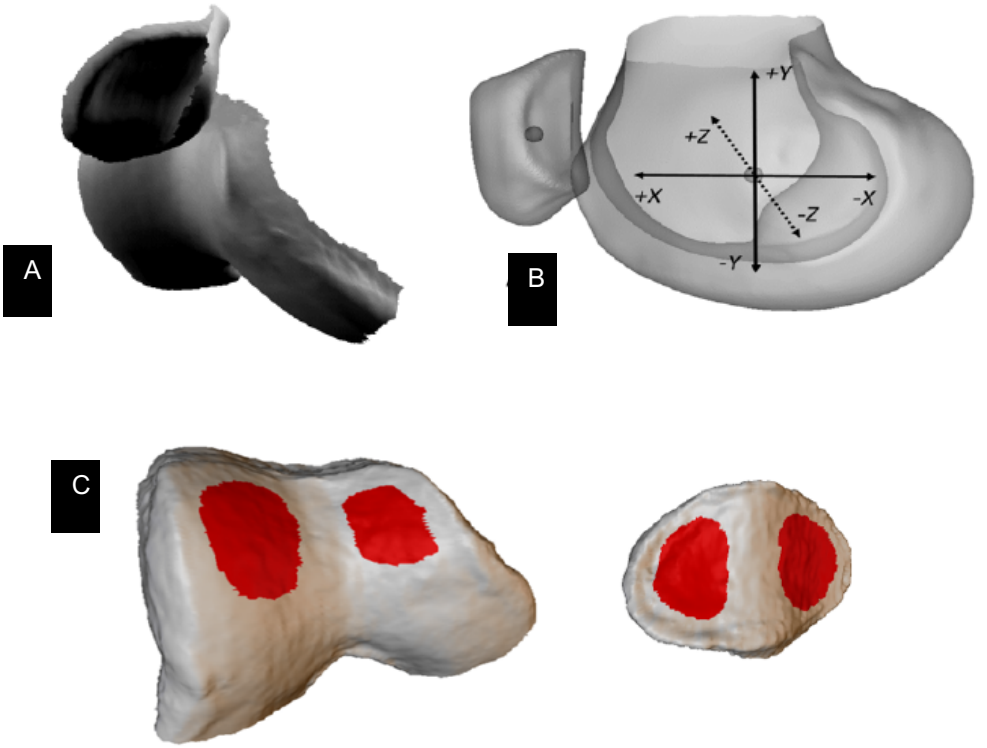


Figure 4.3: Coordinate frame and model extent, facet regions

A) Model extent – articulating surfaces plus small amount of bone surface beyond the articulating surface. Inferior boundary of trochlear femur is defined as the anterior edge of the menisci in the mean model

B) Axes are taken from the mean model: X axis – anterior-posterior (anterior +ve); Y axis – superior-inferior (superior +ve); Z axis – medial-lateral (lateral +ve); Coronal plane – looking along the x axis (in the +ve direction); Axial plane – looking along the y axis (in the +ve direction); Sagittal plane – looking along the z axis (in the +ve direction)

C) Facet regions of medial and lateral trochlear femur, and medial and lateral patella

The patella sub-region was defined as the subchondral area of the patella, together with a 'halo' of approximately 10mm around the subchondral plate. The femoral sub-region was defined as the trochlear subchondral region of the femur, using the anterior edge of the menisci as the boundary of this region, plus a similar halo around the region. These two regions were combined into a single shape model, describing 95% of the variance in the shape, and the principal components for each individual PFJ surface were recorded.

4.3.6 Variables

We evaluated whether there were between-group differences in terms of the following thirteen 3D imaging features: patella medial-lateral position (mm), patella inferior-superior position (mm), patella anterior-posterior position (mm), medial patella facet area (mm^2), lateral patella facet area (mm^2), medial to lateral patella facet area (ratio), sulcus angle (°) [461], congruence angle (°) [461], medial trochlear inclination (°) [406], lateral trochlear inclination (°) [406], patella medial-lateral tilt (°), patella rotational alignment (°) and patellofemoral contact area (ratio). These 3D imaging features were converted from a range of standard MRI features derived from the systematic review in Chapter 3.

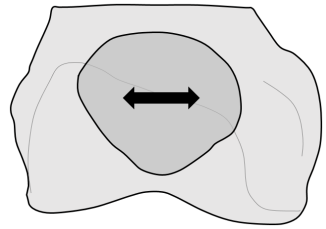
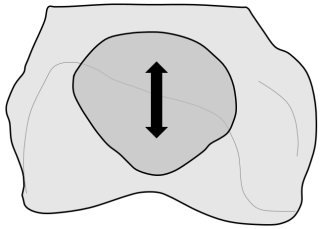
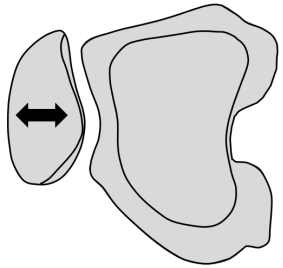
An outline of the methods used to assess the imaging features, using the surfaces shown in Figure 4.3 are shown in Table 4.2. All PFJ surfaces were rigidly aligned with the mean shape, using a least squares fitting method, which fitted only the femur region. The x, y and z-axes were defined as anterior-posterior, superior-inferior and medial-lateral respectively (coordinate frame Figure 4.3). The geometrical centre of gravity (COG) was calculated for patella and femur surfaces of each knee separately.

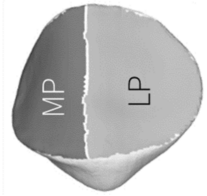
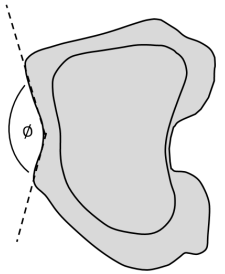
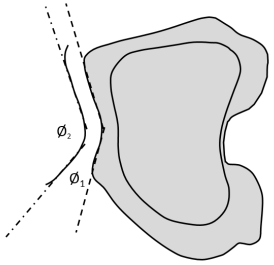
To determine the translation of the patella relative to the femur position, differences between the patella and femoral COGs were calculated along the x, y and z-axes. Angles between the medial and lateral facets of the patella and femur were calculated as follows: correspondence points within the facets were identified in the model as previously described (Figure 4.3) [445], and these masks were used to consistently identify these facets in each knee. For each knee bone surface, a plane was fitted to each of the medial patella, lateral patella, medial trochlea and lateral

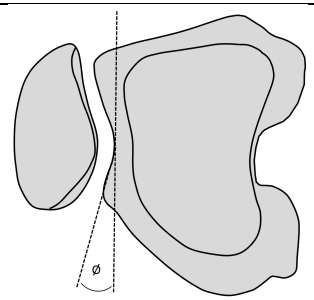
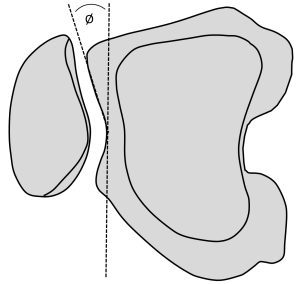
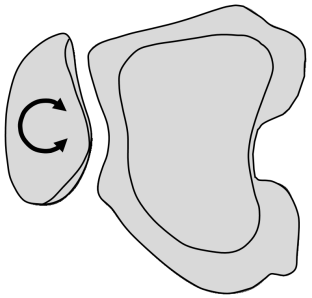
trochlea facets, and the angle calculated between the pairs of planes projected onto the x, y and z-axes.

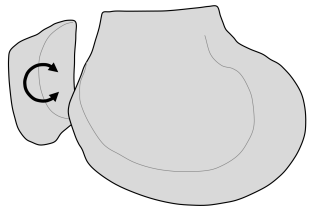
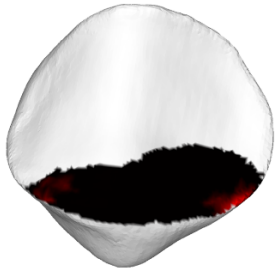
Patella contact area was defined as the area of patella surface, which intersects with vectors normal to the trochlear femur at each correspondence point (based on the mean model Figure 4.3), and expressed as a ratio of the total patella surface area. The sulcus angle, congruence angle and both the medial and lateral trochlear inclination angles were measured using planes established in the mean model (Table 4.2). The relationship between the area of the medial and lateral facets was expressed as a ratio (MP: LP ratio). Patella tilt and rotational alignment was established by rigidly aligning each individual patella with the mean patella, and recording the rotation from the mean patella. For the direction of patella tilt and rotational alignment see Table 1.

Table 4.2: 3D imaging features

PFJ Feature	Description	3D assessment method	Graphical representation
Patella medial-lateral position (mm)	Position of the ***patella*** with respect to the ***femur*** in the medial-lateral direction (lateral = +ve)	Distance between the centre of gravity of the femur and the patella in the coronal plane when projected onto the z (medial-lateral) axis	
Patella inferior superior position (mm)	Position of the ***patella*** with respect to the ***femur*** in the superior-inferior direction (superior = +ve)	Distance between the centre of gravity of the femur and the patella when projected onto the y (superior-inferior) axis.	
Patella anterior-posterior position (mm)	Position of the ***patella*** with respect to the ***femur*** in the anterior-posterior direction (anterior = +ve)	Distance between the centre of gravity of the femur and the patella when projected onto the x (anterior-posterior) axis.	

Medial patella facet area (mm^2)	3D surface area of the medial facet	tAB area of the region shown as MP	
Lateral patella facet area (mm^2)	3D surface area of the lateral facet	tAB area of the region shown as LP	See figure for medial patella facet
Medial patella facet to lateral patella facet ratio	The ratio of the medial and lateral facet area	The ratio of the medial and lateral facet area	See figure for medial patella facet
Sulcus angle (°)	The angle between the medial and lateral trochlear facets in the axial plane (viewed along the y-axis)	The angle between planes fitted to the medial and lateral trochlear facets, viewed along the y axis (degrees)	
Congruence angle (°)	The difference in the sulcus angle and the angle between the patellar facets in the axial plane (viewed along the y axis)	Calculate the patellar facet angle as per the sulcus angle, but using the patellar facets. Congruence angle is sulcus angle minus the patellar facet angle	

Medial trochlear inclination (°)	The angle between the medial trochlear femur and the medial-lateral axis in the axial plane	The angle between a plane fitted to the ***medial*** trochlear of the femur (see Fig 1) and the medial-lateral axis (x axis), when viewed along the y axis	
Lateral trochlear inclination (°)	The angle between the lateral trochlear femur and the medial-lateral axis in the axial plane	The angle between a plane fitted to the ***lateral*** trochlear of the femur (see Fig 1) and the medial-lateral axis (x axis), when viewed along the y axis	
Patella medial-lateral tilt (°)	Rotation of the patella with respect to the femur in the axial plane	Following rigid alignment of the combined femur/patella surfaces using only the femur points, rotation of the patella around the y axis (+ve – rotated laterally, -ve rotated medially) compared to the mean position of the patella;	

Patella rotational alignment (°)	Rotation of the patella with respect to the femur in the sagittal plane	Following rigid alignment of the combined femur/patella surfaces using only the femur points, rotation of the patella around the x axis (+ve – rotated superiorly, -ve rotated inferiorly) compared to the mean position of the patella;	
Patellofemoral contact area (ratio)	The percentage of patella coverage in relation to the femur	The percentage of patella surface which intersects with normal from the trochlear femur	

+ve = postive direction; -ve = negative direction; tAB = total area of subchondral bone

4.4 Statistical analysis

Statistical analysis was carried out in SPSS software, version 21.0 (Armonk, NY: IBM Corp). Descriptive statistics were used to describe the main characteristics of the study population and were presented as mean (SD) where appropriate for continuous variables, and frequency and percentages for categorical variables. For simple comparison between groups, independent sample t-tests were used to compare the mean differences for all the thirteen 3D imaging features. Graphical exploration of the data was performed to ensure that assumptions of normality were valid prior to performing the t-tests.

4.4.1 Multiple testing

Repeated statistical testing leads to multiple testing and thus increases the chances of a type 1 error [462]. As a rule, adjusting the significance level is recommended and commonly a Bonferroni correction is applied, however, there are situations when the Bonferroni is too conservative [463]. Armstrong (2014) [463] suggests that Bonferroni corrections are not indicated when multiple t-tests are applied and the *individual* tests are important. This could be considered the case with this chapter. In contrast, they also suggest Bonferroni should be applied when a large number of tests are carried out without a pre-planned hypotheses in an attempt to find any results that are significant [463]. Although a clear aim was stated (see 4.2), no specific features were hypothesised and thirteen different features were investigated. A decision was made to apply a Bonferroni correction to minimise the effect of an experiment wise error and the level of significance set at $\alpha = 0.004$ (0.05/13).

4.4.2 Controlling for confounders

Gender has been highlighted as an important confounder in PFJ structure [12]. There are number of data-analytical techniques that can be applied to control for confounders. These can be broadly classified into: non-model based techniques (stratification and matching) and model based techniques (regressional analyses)

4.4.2.1.1 Non-model based techniques

Non-model based adjustment techniques are conducted without underlying model assumptions. Stratification involves the dividing participants into categories based on a confounding factor [464]. Matching involves the selection of patients with similar values of a confounding factor in both groups [464]. The advantages and limitations of the stratification and matching are typically similar [465]. The advantages of both these methods is that they allow clear interpretation of the results and do not have to comply to any model assumptions about the outcome and covariates [465]. The major limitation is that multiple covariates are difficult to deal with leading to potential empty strata or mismatches of cases during matching. Furthermore, in the context of Chapter 3, both these approaches also reduce the available sample size. For example, stratifying by gender reduces the size of the PFP group to 67 female and 48 males.

4.4.2.1.2 Model based techniques

Multivariable statistical techniques offer the ability to reduce bias by including a number of covariate factors in order to adjust the effect. Multivariable techniques have the advantage of optimising sample size and retaining the original sample. One of the recognised drawbacks of adjustment through modelling occurs if there is a lack of covariate overlap between groups that can lead to increased bias and variance [466]. Matching provides warnings of this problem, whereas this is not highlighted during multivariable modelling. In the context of Chapter 3, however, the gender covariate is equally distributed across both groups thus the problem does not apply in this scenario.

4.4.2.1.3 Preferred method for controlling for confounders

As only one covariate (gender) was considered for this analysis then stratification or matching would appear to be viable approaches. However, as a result of the high dimensionality of data in 3D shape there was a need to optimise the sample size as much as possible. So, in order to retain the sample size, a decision was made to use a gender-adjusted multivariable regression model.

4.4.3 Logistic regression models

Logistic regression models were used to identify whether any of the 3D imaging features, or a combination of features, were associated with PFP. Firstly, univariable

models were performed on all thirteen features to establish their individual association with PFP. For the two ratio variables (medial patella facet area to lateral patella facet and patellofemoral contact area) values were categorised based on the median value into lower than median and higher than median. This was then followed by multivariable models adjusted for gender.

4.4.3.1 Directed acyclic graph (DAGs)

To achieve parsimony and also mitigate the effects of collinearity, the relationship of a selected number of 3D imaging features was considered for the multiple logistic models. As recommended by Zuur *et al.* (2010) [467], biological knowledge and clinical understanding was used for variable selection to ensure a pragmatic model. The variable selection was based on the directed acyclic graph approach [468], which has been employed in other studies [442] to allow appropriate model specification. A DAG is graphical representation of causal effects and an approach for understanding relationships of variables [468]. Effectively, the DAG aims to identify the ancestor (a direct cause or indirect cause of a particular variable) and the descendent (a direct effect or indirect effect of a particular variable). Figure 4.4 and Figure 4.5 show a simplified version of the DAGs used for the trochlear variables (medial trochlear inclination, lateral trochlear inclination, sulcus angle and congruence angle) and cartilage variables (lateral patella facet area, medial patella facet area, patellofemoral contact area and medial patella facet and lateral patella facet ratio). In the scenario when an ancestor and descendant are identified then the ancestor is retained and the descendant omitted [468].

This approach results in parsimonious models being chosen without the risk of over adjustment; although causality was not explicitly assumed from our models. An imaging feature was thus excluded from the model if one or more of the other imaging features were required for its formation and thus highly correlated. Accordingly, the medial patella facet to lateral patella facet ratio and patellofemoral contact area were omitted, as they are derived using both the medial and lateral patella facet area. The congruence angle and sulcus angle were omitted, as they are both built from the medial and lateral trochlear inclination.

In addition to the DAG, a correlation matrix was computed to investigate the dependence between the variables retained and to ratify my clinical decisions. Both

lateral patella facet area and medial patella facet area (r=0.99) (Table 4.3) and medial trochlear inclination and lateral trochlear inclination (r =-0.49) (Table 4.4) demonstrate significant association, however, in the absence of any clinical hierarchy for these variables neither could be removed based on clinical grounds. Based on guidance from Field (2013) [469], as there are no statistical grounds for omitting one variable over another then its suggested that the only solution is to acknowledge these background interactions in the eventual model

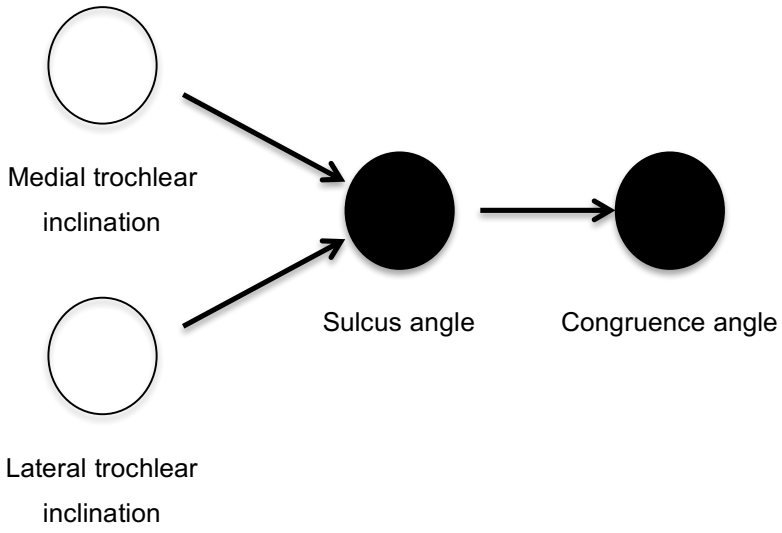


Figure 4.4: Directed acyclic graph to illustrate the relationship between trochlear morphological variables
Black circles indicates variables removed from the eventual model

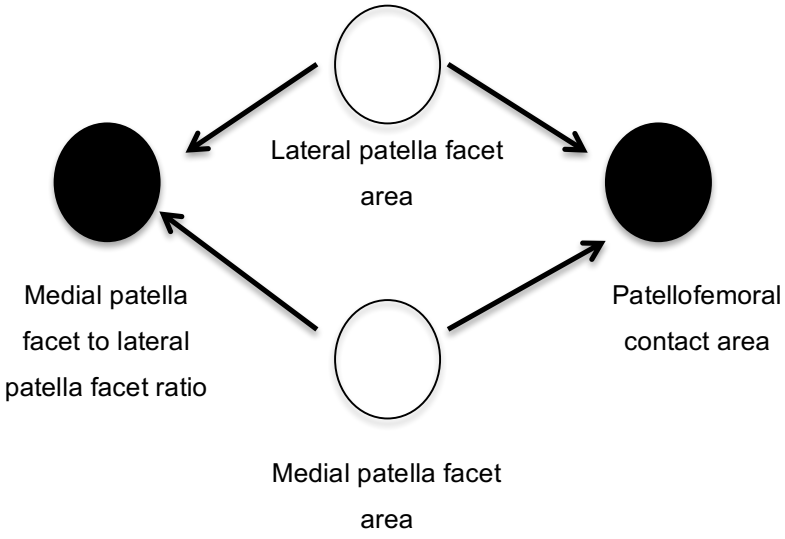


Figure 4.5: Directed acyclic graph to illustrate the relationship between patella cartilage variables
Black circles indicates variables removed from the eventual model

Table 4.3: Correlation of retained variables medial and lateral patella facet area

	Medial patella facet area	Lateral patella facet area
Medial patella facet area	1	0.99*
Lateral patella facet area	0.99*	1

*Significant at p = < 0.01

Table 4.4: Correlation of retained variables medial and lateral trochlear inclination

	Medial trochlear inclination	Lateral trochlear inclination
Medial trochlear inclination	1	- 0.49*
Lateral trochlear inclination	- 0.49*	1

*Significant at p = < 0.01

4.4.3.2 Knee based vs. Person Based Analysis

Debates surrounds the preferred unit of analysis when dealing with paired data [470]. The potential approaches to data analyses for Chapter 4 were: i) a person-based analysis, analysing single knees for each participant; or ii) a knee-based analysis analysing both knees (specifically all symptomatic knees). Due to the known correlations between knees, 'double dipping' the data [470] and analysing at knee level creates a lack of independence of the data and violates the statistical assumptions [471]. Conversely, a person-based analysis relies on the participants selecting a knee. Typically the 'worst' knee is selected, however, as Doherty and Jones (1998) [472] highlight the 'worst' knee may vary from week to week and attributing separate scores to each knee is difficult. There is also a suggestion that the 'best' knee is a better method as an individual can compensate to a degree for a poorer knee [471]. Other possible selection criteria include selecting the dominant limb or collapsing paired data into single measures by taking the average [470]. Even with the best intention for a person-based analysis, as each knee has three compartments there is still an argument that pooling of data is occurring [472]

If a knee-based analysis is used, the statistical plan needs to be evaluated in order to conform to statistical assumptions. Possible solutions include spreading the analyses and analysing each side separately, however, this has the effect of reducing statistical power and makes results difficult to interpret especially if results are different [471]. For Chapter 4, consideration was made to using both approaches. Ancillary analysis of those participants within the PFP group with two knees, which satisfied the inclusion criteria, showed only 19 additional knees. It was deemed that these additional knees would have limited impact on the statistical power and thus did not justify the introduction of the more advanced statistical techniques e.g. generalised estimating equations (GEE). Furthermore, conceptually this chapter investigates whether any of these 3D structural features predict pain. If the outcome was solely structural progression this would justify a knee-based analysis [470], however, as pain is multidimensional construct [473] then person based factors may play a significant role. These reasons justify the use of a person-based analysis with the 'worst' knee selected from highest pain score (WOMAC score) given during stairs.

4.4.4 Linear discriminant analysis

Linear discriminant analysis (LDA) of 3D shape explored whether any overall 3D shape or spatial position of the bones could discriminate between those with and without PFP, irrespective of the pre-selected thirteen imaging features. Linear Discriminant analysis (LDA) is indicated when evaluating the ability of variables to linearly discriminate between any groupings. LDA has been used previously as a statistical means of investigating gender recognition [474, 475]. The validity of this approach was examined by assessing if the method could discriminate between men and women, who are known to have different bone shapes [450]. Using the masks in Figure 4.3, the bone surface of the trochlear femur, and the subchondral patellar were extracted from each knee (533 knees). These corresponded points were used to build a shape model of the isolated PF joint, which accounted for 98% of the shape variance. This resulted in 40 principal components. Subsequently, individual PF joints were represented as a series of principal components, which taken together provide an accurate representation of the 3D shape of the two bones, and includes the position and articulation of the femur and patella.

LDA of two groups expressed as 40 principal components is expected to find at least one hyper-plane capable of separating out the groups (expressed as the distance

between the two means of the groups projected onto the LDA hyperplane). A Monte Carlo experiment was used to assess whether the separation achieved by LDA of the groups was better than that expected by chance [476]. Monte Carlo experiments are statistical analyses using random samples. The Monte Carlo experiment mimics the important elements of the experiment and replicates these at random to solve a deterministic problem [476]. Sawilowsky (2003) [476] identified that Monte Carlo experiments could be used in applied statistics to: i) compare smaller samples under realistic data conditions; ii) implementation of hypothesis testing that is more efficient than permutation testing when there is too many possible data combinations. This justifies the use of Monte Carlo in Chapter 4, as the sample is relatively small in terms of the high level of dimensionality of the data and the stochastic nature of the data correspondences. For 10,000 repeats, each knee was randomly assigned a label in the same proportions as the dataset. A pseudo p-value is calculated from the number of repeats, which provides a better segmentation than the actual labelling.

4.5 Results

Based on our inclusion criteria we included 115 in the PFP group and 438 in the control group. The mean age was 59.7 years (SD 8.78) for the PFP group and 63.6 years (SD 9.14) for the control group, with 58.2% and 52.9% women in the PFP and control groups respectively. The mean BMI was 27.5kg/m^2 (SD 5.29) for the PFP group and 26.9 kg/m^2 (SD 4.52) for the control group.

4.5.1 *Primary aim*

Overall group comparison showed no statistically significant differences between people with and without PFP for any of the thirteen 3D imaging features (all $p > 0.004$) (Table 4.5). In addition, the sensitivity analysis similarly showed no statistically significant differences for any of the 3D imaging features (results not shown).

Univariable models showed no association between the individual 3D imaging features and PFP (Table 4.6). Results from the multivariable models revealed that combining 3D imaging features also showed no significant association with PFP ($p > 0.05$) and all the odds ratios remain close to the value of 1 indicating a lack of relationship to pain having adjusted for gender (Table 4.6).

Table 4.5: The mean difference between PFP and No PFP groups

Feature	Groups (Mean (SD))		Mean Difference (95% CI)	P value [a]
	PFP	No PFP		
Patellofemoral contact area (ratio)	0.41 (0.16)	0.41 (0.15)	0.00 (- 0.03,0.03)	0.83
Patella medial-lateral position (mm	-1.17 (2.25)	- 1.02 (2.37)	- 0.15 (- 0.63, 0.33)	0.54
Patella inferior-superior position (mm)	- 21.03 (4.42)	- 21.34 (4.66)	0.30 (- 0.62, 1.23)	0.52
Patella anterior-posterior position (mm)	20.23 (2.04)	20.31 (1.93)	- 0.08 (- 0.48, 0.32)	0.69
Congruence angle (°)	9.04 (5.80)	8.68 (5.80)	0.36 (- 0.84, 1.55)	0.56
Patella medial/ lateral tilt (°)	- 0.14 (3.33)	0.00 (3.31)	0.35 (- 0.84, 1.55)	0.56
Medial trochlear Inclination (°)	30.39 (4.27)	30.44 (4.02)	- 0.05 (- 0.89, 0.55)	0.90
Lateral trochlear Inclination (°)	- 25.52 (3.11)	- 25.54 (2.70)	0.02 (- 0.55, 0.59)	0.93
Patella rotational alignment (°)	- 0.01 (2.53)	0.18 (2.77)	- 0.18 (- 0.75, 0.37)	0.63
Medial patella facet area (mm^2)	524.41 (81.57)	533.38 (85.12)	- 8.96 (- 26.34, 8.40)	0.31
Lateral patella facet area (mm^2)	667.45 (108.47)	681.48 (112.90)	-14.03 (- 37.08, 9.02)	0.23
Medial patella facet to lateral facet (ratio)	0.79 (0.02)	0.79 (0.02)	0.00 (- 0.00, 0.01)	0.18
Sulcus angle (°)	-124.09 (6.55)	-124.01 (5.80)	- 0.07 (-1.30, 1.15)	0.91

a. Independent Samples T-test

Table 4.6: The association between thirteen 3D imaging features and patellofemoral pain

	Univariable (unadjusted)		Multivariable (Gender-adjusted) [a]	
Imaging feature	**OR (95% CI)**	**P- value**	**OR (95% CI)**	**P- value**
Patellofemoral contact area (lower)	0.97 (0.65, 1.47)	0.89	0.95 (0.63, 1.43)	0.79
Patella medial-lateral position (mm)	0.97 (0.89, 1.06)	0.54	0.97 (0.89, 1.06)	0.50
Patella inferior-superior position (mm)	1.02 (0.97, 1.06)	0.53	1.01 (0.97, 1.06)	0.65
Patella anterior-posterior position (mm)	0.98 (0.88, 1.09)	0.69	1.00 (0.89, 1.12)	0.99
Congruence angle (°)	1.01 (0.98, 1.05)	0.56	1.01 (0.98, 1.05)	0.52
Patella medial/lateral tilt (°)	0.98 (0.93, 1.05)	0.68	0.99 (0.93, 1.05)	0.64
Medial trochlear inclination (°)	0.99 (0.95,1.05)	0.90	0.99 (0.94, 1.04)	0.73
Lateral trochlear inclination (°)	1.00 (0.93, 1.08)	0.93	1.01 (0.94, 1.09)	0.80
Patella rotational alignment (°)	0.98 (0.90, 1.05)	0.51	0.97 (0.90, 1.05)	0.45
Medial patella facet area (mm^2)	0.99 (0.99, 1.00)	0.31	0.99 (0.99, 1.00)	0.65
Lateral patella facet area (mm^2)	0.99 (0.99, 1.00)	0.23	0.99 (0.99, 1.00)	0.49
Medial patella facet to lateral patella facet (lower)	0.55 (0.36, 0.83)	0.01	0.56 (0.36, 0.85)	0.01
Sulcus angle (°)	0.99 (0.96, 1.03)	0.91	0.99 (0.96, 1.03)	0.72
Gender (female)	1.24 (0.81, 1.88)	0.31		
Combined imaging features [b]				
Patella medial-lateral position (mm)			0.98 (0.89, 1.09)	0.73
Patella inferior-superior position (mm)			1.00 (0.95, 1.06)	0.93
Patella anterior-posterior position (mm)			1.03 (0.89, 1.18)	0.66
Patella medial/lateral tilt (°)			0.97 (0.89, 1.05)	0.47
Medial trochlear inclination (°)			0.99 (0.94, 1.07)	0.98
Lateral trochlear inclination (°)			1.03 (0.93, 1.14)	0.52
Patella rotational alignment (°)			0.96 (0.89, 1.05)	0.37
Medial patella facet area (mm^2)			1.01 (0.99, 1.03)	0.25
Lateral patella facet area (mm^2)			0.99 (0.98, 1.00)	0.18

a. Adjusted for gender (female). OR: Odds ratio; CI: confidence interval

b . Variables removed: Medial patella facet to lateral facet (ratio); Sulcus angle (°); Congruence angle (°); Patellofemoral contact area (ratio)

4.5.2 Secondary aim

The results of the LDA showed that the overall 3D shape was unable to significantly discriminate between groups with and without PFP showing a classification of 55.5%. The pseudo p-value from the Monte Carlo experiment was p=0.79, indicating that the PFP/without PFP labeling separated out the groups no better than random chance. In contrast, the overall 3D shape was able to significantly discriminate between men and women with a classification of 90.6%. The pseudo p-value from the Monte Carlo experiment was ($p < 0.0001$), indicating that it is unlikely that there is any labeling that separates the groups out better than gender. An orthogonal projection of the gender differences is shown in Figure 4.6.

4.5.3 Assessing the accuracy of the model

The accuracy of the model was conducted using root mean squared (RMS) error. RMS is calculated by firstly obtaining the total squared error expressed as the sum of the individual squared errors. The total squared error is then divided by the sample size and then the square root of this mean square error forms the RMS [477]. The advantaged of the RMS is that it is expressed in the units of interest thus improving the interpretation of the error [477]. RMS mean point-surface accuracy of the femur and patella AAMs was 0.12mm, 95^{th} percentile 0.38mm. The voxel sizes were 0.36 x 0.36 x 0.7mm in size. This demonstrates that the model is accurate at almost all points to within one pixel on the MRI image.

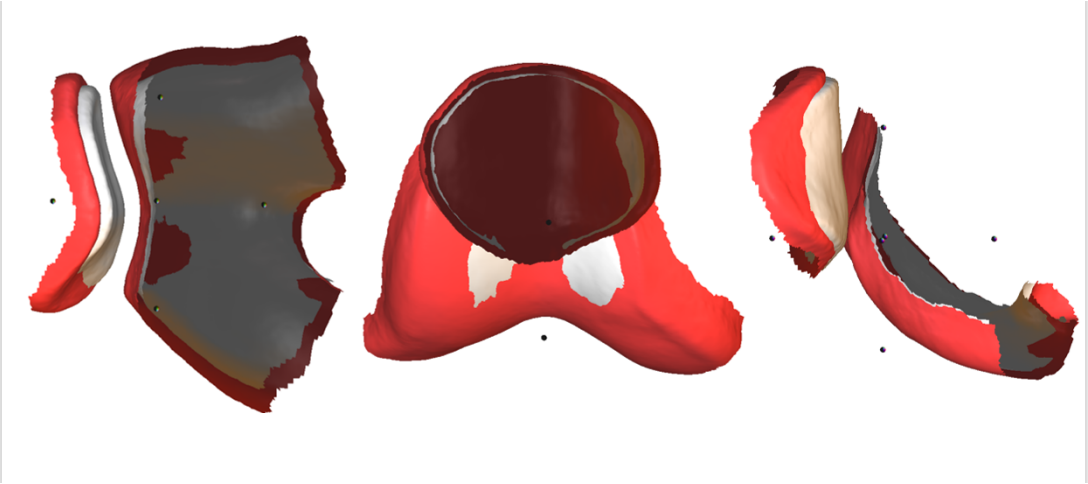


Figure 4.6: An orthogonal view of the gender difference

This shows that in men the patella shape extended more superiorly leading to higher overall COG. The higher COG found in men was not result of the patella sitting more cephalic as the bottom of the patella was similarly positioned in both genders. Image courtesy of Imoprhics™ Ltd

4.6 Discussion

The findings of this chapter suggest that when commonly used patellofemoral imaging features are examined using accurate 3D quantification, no statistically significant differences are found between a group with and without PFP. Furthermore, no single 3D imaging feature, or combination of features, was associated with the presence of PFP. The results of the LDA experiment shows, using bone shapes fitted with sub-voxel accuracy, that there is nothing within the 3D shape of the joint able to classify the presence of PFP better than chance; at least using shape expressed as principal components.

In this analysis the lack of association of the 3D imaging features with PFP is robust but is in contrast to previous reports based on 2D imaging shown in Chapter 3. A recent systematic review [478] of patellofemoral morphology, in patellofemoral osteoarthritis (PFOA), demonstrated strong evidence that PFOA is associated to trochlear (femoral) morphological features. A possible explanation for the contrast to the present findings is highlighted by a previous study [367] of 30 knees assessed by MRI, which also found a lack of differences in femoral shape between people with and without PFP. By subgrouping people with PFP into lateral and non-lateral

maltracking groups, Harbaugh *et al.* (2010) [367] found that these subgroups lie on opposite sides of the healthy average, suggesting that underlying subgroups may be masking the differences between people with and without PFP[367]. A lack of established thresholds to define PFJ imaging feature subgroups did not allow this to be verified in the current chapter but strengthens the case for subgrouping as addressed in Chapter 5.

These findings further contrast with a MRI study of 240 knees [479], which showed that a medially inclined patella (similar to medial patella tilt in this analysis) was associated with less pain. This disparity may be because the assessments were performed on a single MR slice at the mid-point of the patella in the sagittal plane, and as noted previously, these methods may be open to measurement error by not controlling for relative limb position and orientation. Shibanuma *et al.* (2005) [441] showed that alterations in limb position led to statistically significant differences in the PFJ features recorded for both men and women. Patella alignment values including medial-lateral position and tilt have been shown to be influenced by the relative tibial and femoral rotation and varus angulation [440]; whilst single slices along one plane are known to misrepresent the true anatomy of the PFJ [480] (see Figure 4.1).

The PFJ imaging features used to inform the development of the 3D features in the current chapter have been published previously [164, 170, 406, 479]. Our findings are comparable to a previous study that analysed trochlear morphology in 881 middle-aged knees using MRI [481]. Stefanik *et al.* (2012) [481] reported similar values for sulcus, lateral trochlear inclination and medial inclination angles of 130.9°, 25° and 24.4° respectively, though the novel assessment methods used here preclude direct comparison with Stefanik *et al.* (2012) [481]. This is because, in contrast to traditional methods, the geometrical centre of gravity was used here as a more representative reference point for 3D shape (see Section 4.3.4.1). The use of statistical shape models has also been applied previously in the PFJ [447], however, this is the first time these methods have been employed on a large, symptomatic group with a comprehensive range of traditional features converted into their 3D equivalents.

Gender is widely considered to influence PFJ imaging features [449-451]. Validation of these new 3D imaging features was achieved by using the shape data from the 3D imaging features, coded as principal components, showing that gender was classified at a 90% level of accuracy. This is similar to the classification of 93.5% in

sex determination using 3D computed tomography features of the patella *in vitro* [450]. Our model expands on this work by applying 3D MR imaging features from both the patella and femoral trochlea *in vivo*. Given that there are significant differences by gender for PFJ imaging features, it seems likely that previous studies have been affected by a mix of genders within their sample. Subsequent review of Chapter 3 (systematic review) showed that, of studies including mixed gender cohorts, 80% failed to report women and men separately. Therefore previous studies may simply have been describing differences related to their gender mix. As a result, it is recommended that future studies follow the lead of recent studies [294] by reporting gender separately or conducting single gender analyses.

4.6.1 Limitations

This chapter presents with a number of limitations with regards to the sample and methodology

Sample. This analysis was conducted on a sample older than a typical PFP patient and thus caution is advised when extrapolating these findings to a younger population. Furthermore, all selected patients had KL grade 0 within the tibiofemoral joint but there were no lateral or skyline x-rays available to view the PFJ radiographically. Without lateral or skyline x-ray we cannot assert that all participants were without radiographic PFOA, however previous studies have suggested that in the absence of OA in the tibiofemoral joint, approximately 75% of this age cohort will have no other compartmental OA [380, 482]. Despite being a large sample size compared to previous literature, the sample size is probably still small considering the high dimensionality of the data, which may have limited the power of the analyses to detect differences.

Methodology. The features were based on MRI images taken in non-weight bearing with no knee flexion. As highlighted in Chapter 3, weight bearing and knee flexion are known to influence the features observed [12, 378] and may have impacted on the overall findings. In this chapter, PFP was determined at a single time point (24 months) and pain based on dichotomised value (pain/no pain) rather than a graded severity scale. It is possible that a relationship between imaging and pain is more likely when the pain outcome is more sensitive with a greater number of grading levels [395]. Our analysis included a range of quantitative 3D measures, together with an examination of the principal components from the associated shape model.

The use of principal component analysis for one of the measures may have resulted in the loss of some 3D information, and it is possible that other advance methods of shape analysis and machine learning could reveal a relationship that our methods cannot.

4.7 Conclusion

The analysis within this chapter shows using 3D quantitative analysis that no statistically significant differences were found between people with and without PFP. These 3D findings are in contrast to the current perception, which has relied on studies using what are effectively 2D measurements applied with a lack of consistent joint positioning. Analyses of the overall 3D shape in relation to gender validates these novel 3D measures and also suggests that future PFP cohort analyses should be stratified for gender. Further work is needed to assess whether 3D quantitative analysis can discriminate shape differences related to PFP in a younger population, more representative of the real-world PFP population.

Chapter 5 - The development of data-driven diagnostic subgroups for people with patellofemoral pain using modifiable clinical, biomechanical and imaging features

This chapter describes a longitudinal cohort study with a cross-sectional analysis which identifies subgroups within a PFP cohort using clinical, biomechanical and imaging features. By following up participants at 12-months, the chapter also describes the prognosis of these subgroups.

5.1 Introduction

As highlighted in Chapter 2, unfavourable outcomes for patients with PFP have been attributed to the belief that subgroups within the PFP population respond differently to treatment [20]. However, a paucity of evidence currently exists for subgrouping and subsequent stratification of care.

Recommendations for subgrouping research suggests that prior to testing the effect of subgrouping, a hypothesis-setting stage is required which attempts to identify clinically important subgroups and explore the prognostic effect attributed to subgroup membership [363] (Figure 5.1). Data-driven diagnostic subgroups are advantageous as they can later be studied against a range of treatments [364, 483] rather than groups being based on the response to only one treatment (i.e. treatment effect modifiers). Diagnostic PFP subgroups have been suggested by a number of studies based on single factors [180, 230, 243, 367]. However, only a few studies [254, 366, 374] have identified diagnostic subgroups comprising of multiple factors from multiple domains. Of these studies, only Selfe *et al.* (2016) [254] derived subgroups from rigorous statistical methods. The three diagnostic subgroups they identified are of high clinical utility, requiring only six simple clinical tests. However, these subgroups are unable to incorporate PFJ structure [180, 230] and biomechanics, testing of which requires complex equipment and evaluation [243, 484]. Overall, the prognostic value of these subgroups remains unknown [485].

5.2 Aims

The primary aim of this chapter was to combine modifiable clinical, biomechanical and imaging features to identify data-driven diagnostic subgroups within a PFP cohort. Based on data from a 12-month follow-up, the secondary aim was to explore the prognosis of these data driven subgroups.

5.3 Methods

5.3.1 Study design

This longitudinal cohort study comprised of a cross-sectional analysis and a 12-month follow-up. Figure 5.1 shows the conceptual stages of research into subgrouping [363] in which the stages considered in Chapter 5 are highlighted in grey. This chapter will consider the hypothesis setting stage whereby the aim to is identify clinical important subgroups from a range of characteristics and generate a hypotheses in terms of prognostic factors [362]. Ethical approval was obtained (14/NE/1131) and all participants completed written informed consent prior to entering the study.

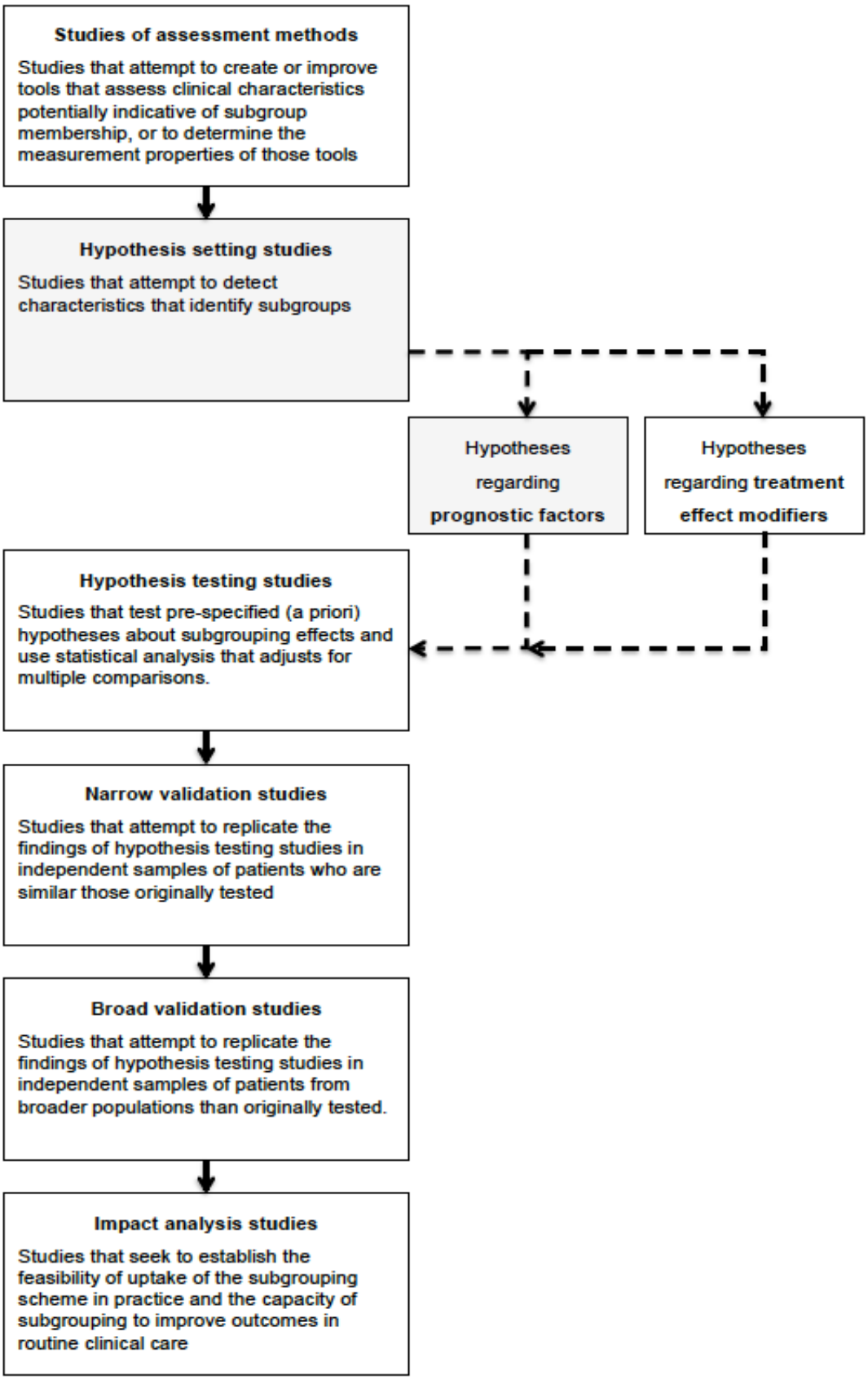


Figure 5.1: Conceptual stages of research into subgroups.
Adapted from Kent *et al.* (2010) [363]

5.3.2 Selection of the sample size

The sample size was based on the recommended rule of thumb for cluster analyses of n =2^k (whereby *k* is the number of variables) [486]. For our model, variables were analysed within selected health domains: strength impairment, flexibility impairment, movement impairment and structural impairment. We allowed at most 6 variables (*k*), representing the selected domains and thus requiring a minimum of 64 participants (2^6). To account for a potential 20% drop-out rate, we aimed to recruit 77 participants. This chapter was reported in accordance with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines [453].

5.3.3 Setting

All assessments were conducted at a UK teaching hospital from November 2014 to April 2016. Participants from the general population were recruited from a local National Health Service (NHS) musculoskeletal service via clinician referral, posters in local sports clubs and university alumni. Further electronic searches of the local NHS musculoskeletal database were also made for patients previously diagnosed with either ‘anterior knee pain’ or ‘patellofemoral pain’.

5.3.4 Participants

Participant eligibility was based on: i) being aged 18-40 years; ii) with an insidious onset of anterior or retropatellar knee pain; and iii) pain on two or more of the following activities: prolonged sitting, kneeling, squatting, running, patellar palpation, hopping, stair walking, stepping down or isometric quadriceps contraction [115]. Participants were excluded if: i) clinical examination showed another cause of knee pain such as, but not restricted to: meniscal pathologies, quadriceps tendon injuries, patella tendinopathy, tibial tubercle apophysitis; bursitis; ii) any history of significant knee surgery; iii) any competing pathology identified on the MRI report [127]; iv) any contraindication to MRI ; and v) any physiotherapy or podiatric treatment within the last three months. Previously published recommendations made by Cook *et al.* (2010) [127] were applied using available MRI reports. The MRI results were not used to confirm PFP but to exclude participants with competing diagnoses. Competing diagnoses included, the same conditions considered during clinical examination, such as patella tendinopathy, meniscal tears etc. Despite the recognised debate around the association between symptoms and imaging features,

the use of this an extra layer of eligibility criteria was seen to improve the likelihood of a more accurate diagnosis of PFP [127].

5.3.5 Variables

In order to select appropriate, clinically relevant variables for analysis, consideration was made to using directed acrylic graphs (DAGs) [487], as used in Chapter 4. However, for the DAG to be constructed it relies on the identification of an outcome variable (Y) e.g. relationship X on Y [468]. During this cross-sectional analysis, no outcome variable is present with all variables considered exclusive.

To capture the multifactorial nature of PFP; a range of features were considered to inform the diagnostic subgrouping. Variables were derived from systematic reviews which identified features associated with PFP [194, 378, 488] and from analyses conducted for this thesis (see 5.3.6) informed from Chapter 2 (literature review). Variables were selected if they satisfied all the following criteria:

i) supported association with PFP from at least two or more studies;
ii) published thresholds and/or normative data that can be used to clinically interpret findings;
iii) considered clinically modifiable with conservative treatment.

5.3.6 Justification for selected variables

The justification for the variables selected for the cluster analyses is presented below. Forest plots were created to support the interpretation and to justify the selection of variables using published guidance [489]. Variables are presented within local (e.g. knee), distal (e.g. ankle) and proximal (e.g. hip) regions as applied previously [14].

5.3.6.1 Local variables

5.3.6.1.1 Local clinical features

Patella mobility was considered for inclusion as this was one of the clinical test utilised by Selfe *et al.* (2016) [254]. Figure 5.2 shows that neither the pooled estimates of patella lateral (MD -0.03 [-0.94, 0.88]; Z = 0.07; p= 0.94) (Figure 5.2a), patella medial (MD 0.22 [-0.76, 1.21]; Z = 0.44; p= 0.66) (Figure 5.2b) or total patella mobility (MD -0.15 [-1.26, 0.97]; Z = 0.26; p = 0.79) (Figure 5.2c) showed an

association with PFP. Based on our selection criteria this was not included but total patella mobility was collected and reported descriptively across the subsequent subgroups.

5.3.6.1.2 Local biomechanical features

Peak knee flexion angle was included despite a number of single studies showing no significant difference between PFP and controls. Figure 5.2d shows a meta-analysis of five studies measuring peak knee flexion angle. The inclusion was justified because when data is pooled, due to Crossley *et al.* (2004) [236] contributing a relatively larger sample size and 32.7% weight of the overall pooled sample, it shows that reduced peak knee flexion angle is significantly associated to PFP (MD -0.35 [-0.67, -0.03]; Z = 2.14; p = 0.03).The selection of *knee extensor strength* is supported by the meta-analysis by Lankhorst *et al.* (2013) [194] (MD -37.47 [-71.75, -3.20]; Z =2.14; p=0.03).

5.3.6.1.3 Local imaging features

The meta-analyses in Table 3.7 support the inclusion of *MRI bisect offset* and *MRI patella tilt.* Despite the findings in Table 3.7, *MRI patellofemoral contact area* has no published thresholds and limited normative data to allow interpretation of clusters and *MRI sulcus angle* has not been shown to be modifiable with conservative interventions so was not considered

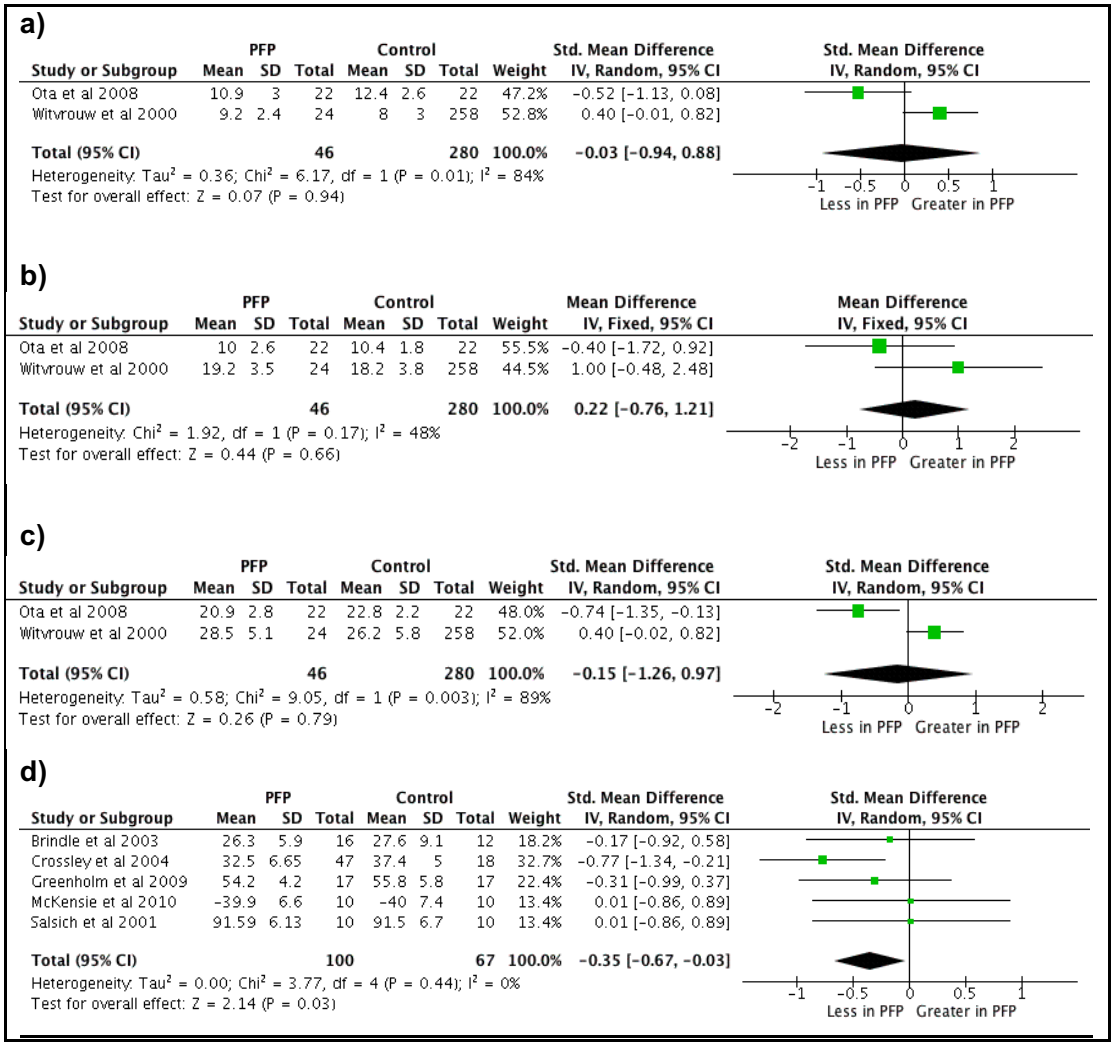


Figure 5.2: Forest plots of local variables

a) patella lateral mobility (mm); b) patella medial mobility (mm); c) total patella mobility (mm); d) peak knee flexion angle (º).

5.3.6.2 Distal variables

5.3.6.2.1 Distal clinical features

As discussed in Chapter 2, there are a number ways in which *foot posture* has been measured and represented. Figure 5.3a shows a meta-analysis of three studies measuring foot pronation and the association of increased foot pronation with PFP (MD 1.04 [0.63, 1.45]; Z = 5.00; p <0.001). However, the methods applied are slightly varied. The methods include foot posture index [490], relaxed foot posture using motion capture [491] and rearfoot angle using a goniometer [492]. The presumed heterogeneity in methods may indicate that a meta-analysis is not appropriate, however, an I^2 = 3% indicates that these constructs show homogeneity which is perhaps unsurprising considering they are aiming to measure the same construct. Foot posture index was chosen over the other available methods as it has validated thresholds [260] that allow easier interpretation of eventual clusters.

5.3.6.2.2 Distal biomechanical features

Figure 5.3b shows that *peak ankle dorsiflexion angle* was not associated with PFP (MD 0.16 [-0.38, 0.71]; Z = 0.58; p= 0.56) so this variable was not included.

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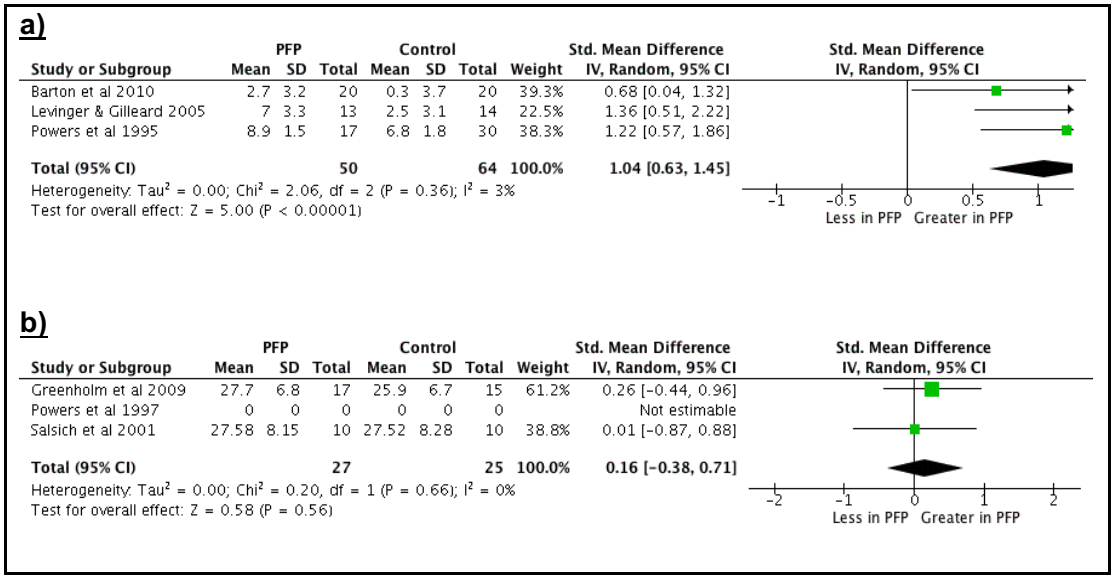

Figure 5.3: Forest plots for distal variables

a) static foot posture; b) peak ankle dorsiflexion angle (°)

5.3.6.3 Proximal variables

5.3.6.3.1 Proximal clinical features

Static Q-angle was not included despite being shown to be associated with PFP [194] (MD 2.08 [0.64, 3.53]; Z =2.83; p=0.005) based on nine separate studies. It is widely debated whether static Q-angle is clinically modifiable with conservative interventions [194] thus this feature did not meet the selection criteria.

5.3.6.3.2 Proximal biomechanical features

In terms of hip strength, both *hip abductor strength* (MD -3.30 [-5.60, -1.00]; Z =2.81; p=0.005) and *hip external rotation* strength (MD -1.43 [-2.71, -0.16]; Z = 2.21; p=0.03) are supported by the meta-analyses by Lankhorst *et al.* (2013) [194]. Based on measurements taken on 501 athletes, hip abduction strength and hip external rotation strength have been shown to be highly correlated (r=0.66; p <0.01) [493]. Due to the fact that hip internal rotation angle kinematics were also included, a decision was made to select only the hip abductor angle in order to represent frontal plane movement and to prevent collinearity of variables (between hip abductor and external rotation strength).

In terms of kinematics, the pooled estimates of *hip internal rotation angle* during stair descent (Figure 5.4a) demonstrates that a greater hip internal rotation angle is associated with PFP (MD 1.01 [0.42, 1.61]; Z =3.33; p = <0.001). Figure 5.4b and Figure 5.4c show that *hip adduction angle* (MD 0.51 [-0.26, 1.28]; Z = 1.31; p = 0.19) and *hip flexion angle* (MD 0.31 [-0.39, 1.01]; Z=0.88; p = 0.38) during stair descent has no association with PFP so these variables were not included.

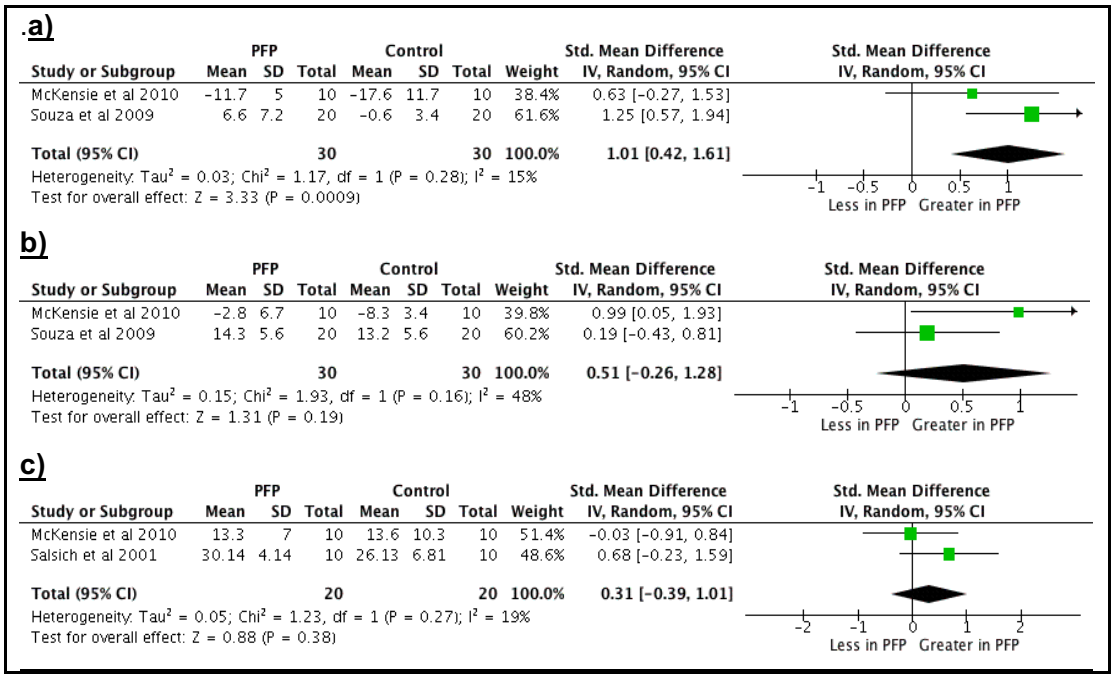

Figure 5.4: Forest plots of proximal variables

a) hip internal rotation angle (°); b) hip adduction angle (°); c) hip flexion angle (°)

5.3.6.4 Regional variables

5.3.6.4.1 Regional clinical features

Figure 5.5a and Figure 5.5b show that a reduced *quadriceps length* (MD -0.54 [-0.98, -0.11]; Z = 2.46; p=0.01) and reduced *hamstring length* (MD -0.55 [-1.02, -0.08]; Z = 2.31; p=0.02) are associated with PFP. To calculate the hamstrings flexibility, on this occasion when the SD was not available for Patil *et al.* (2010) [244] it was estimated from the White *et al.* (2009) [247] data as it is known that this is the same research group and the same individual measuring the angle. This estimation approach was based on methodology used in previous meta-analyses [194].

The pooled estimates calculated for *gastrocnemius length* (Figure 5.5c) showed no association with PFP (MD -0.64 [-1.73, 0.44]; Z = 1.16; p=0.25) partly due to the contrasting relationship found in Barton *et al.* (2010) [258] i.e. PFP more flexible than control group. However, gastrocnemius was shown to be associated to PFP in at least two studies [55, 246] – satisfying the criteria set in Section 5.3.5. Furthermore, Selfe *et al.* (2016) [254] found gastrocnemius to be one of three variables (along with hip abductor and knee extensor strength) that demonstrated significant different across all subgroups. This demonstrates the discriminatory effect of gastrocnemius and justifies the inclusion of this measure in the study.

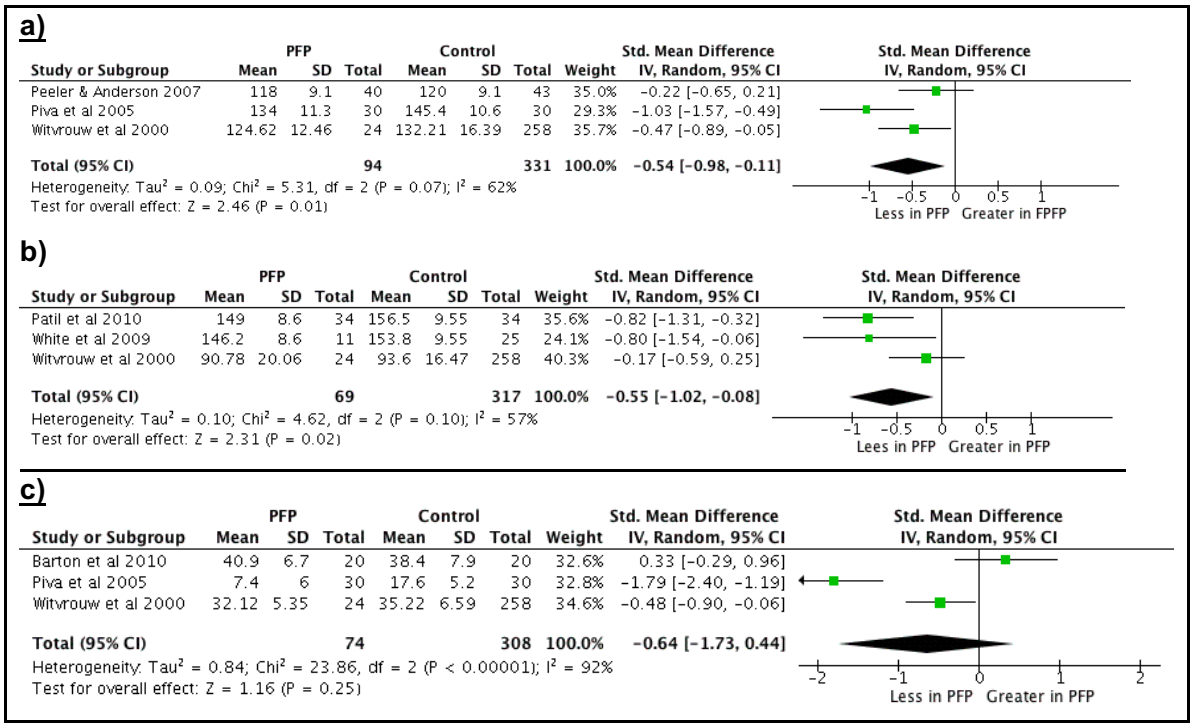

Figure 5.5: Forest plots of regional variables

a) quadriceps length; b) hamstring length; c) gastrocnemius length

5.3.7 Data sources

An overview of the supporting evidence for the selected variables is provided (see Table 5.1). Figure 5.6 illustrates how the variables were collected. Participants completed assessments in the following order: clinical, biomechanical and MRI. Additional variables including patient related factors (e.g. demographic data and patient reported outcomes measures) and supplementary clinical descriptors were collected and applied to each of the final subgroups.

Table 5.1: A summary of supporting evidence

Potential Variables	Supportive Evidence	Type of evidence
MRI patella tilt	Lankhorst *et al.* (2013) [194], Drew *et al.* (2015) [378]	Systematic review
MRI bisect offset	Drew *et al.* (2015) [378]	Systematic review
Peak Hip Abductor strength	Lankhorst *et al.* (2013) [194]	Systematic review
Peak knee extensor strength	Lankhorst *et al.* (2013) [194]	Systematic review
Peak angle hip internal rotation	Souza and Powers (2009) [200], McKenzie *et al.* (2010) [207]	Case-control studies
Peak knee flexion angle	Grenholm *et al.* (2009) [206], McKenzie *et al.* (2010) [207], Brindle *et al.* (2003) [210], Crossley *et al.* (2004) [236], Salsich *et al.* (2001) [494]	Case-control studies
Hamstring flexibility	Patil *et al.* (2010) [244], White *et al.* (2009) [247]	Case-Control studies
Quadriceps flexibility	Witvrouw *et al.* (2000) [55], Peeler and Anderson (2007) [245], Piva *et al.* (2005) [246]	Case-control studies
Gastrocnemius flexibility	Witvrouw *et al.* (2000) [55], Piva *et al.* (2005) [246]	Case-control studies
Static foot pronation	Barton *et al.* (2010) [258], Levinger and Gilleard (2005) [491], Powers *et al.* (1995) [492]	Case-control studies

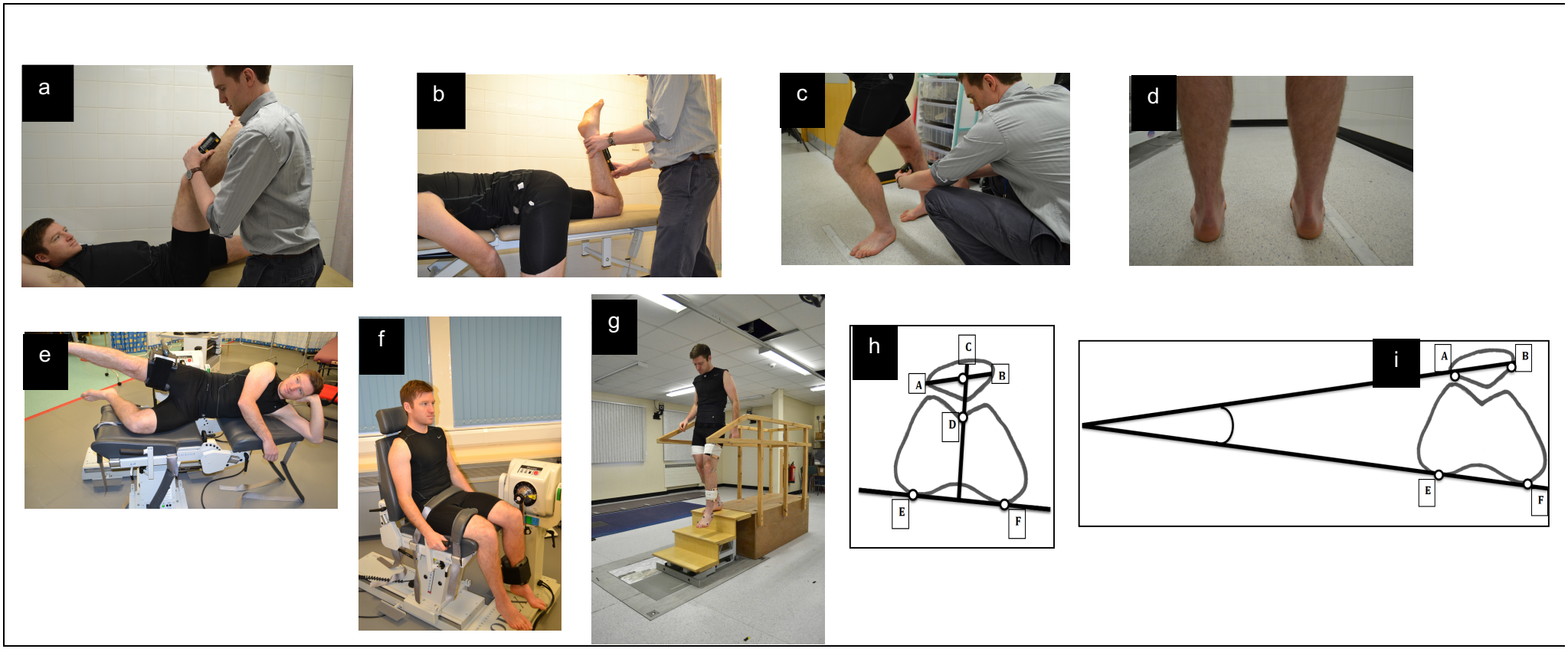

Figure 5.6: Assessment procedures for the selected variables

a) Hamstring flexibility; b) Quadriceps flexibility; c) Gastrocnemius flexibility; d) Foot posture index; e) Biodex hip abductor strength; f) Biodex knee extensor strength; h) MRI bisect offset: length of AC / length of BC x 100%; i) MRI patella tilt: angle formed by a line between AB and EF;

5.3.8 Clinical assessment

The hamstrings (Figure 5.6a), quadriceps (Figure 5.6b) and gastrocnemius (Figure 5.6c) flexibility were measured using a digital inclinometer in accordance with previously published methods [495]. The static foot posture (Figure 5.6d) was measured using the Foot Posture Index (FPI)(Table 5.2) [496].

Digital inclinometers have shown intraclass correlation coefficients (ICCs) of 0.53-0.98 for the knee [497] and 0.91-0.97 for the ankle [498] range of movement. Compared to the universal two-arm goniometer, digital inclinometer do not rely on exact anatomical positioning of both lever arms thus on for a PFP population known to vary in body mass profile [254] there is less likelihood for human error [497]. Caution has also been advised about using both methods interchangeably due to the limits of agreement up to 20 degrees [499] so in this thesis only digital inclinometers were used.

5.3.8.1 Hamstring flexibility

Figure 5.6a shows how hamstring flexibility was measured. The passive knee extension test was chosen instead of the straight leg raise test which measures the angle of the hip [55]. The passive knee extension test has been shown to be associated to PFP [244, 246, 247] and shown to have excellent reliability [500]. With the participant supine, the digital inclinometer was used to ensure the thigh was positioned at 90 degrees at the hip. The leg was then passively extended to the point of firm resistance to the movement [247] whilst the other hand supported the thigh. The digital inclinometer was placed on a mid-point of the tibia and the angle recorded. Three measurements were taken and a mean value recorded.

5.3.8.2 Quadriceps flexibility

Figure 5.6b shows how quadriceps flexibility was assessed. The passive prone knee bend was selected in accordance with previous studies in PFP [55, 495]. This method was selected instead of the Elvey test [245] that has been used in other PFP studies [245, 246] because it is thought that the planted foot of the contralateral limb would help prevent compensatory posterior pelvic rotation. The participant was placed in prone towards the edge of the plinth. The contralateral leg was placed on the floor at 90 degrees hip range of movement. The leg was passively flexed to the point of firm resistance and the digital

inclinometer placed on the mid tibia where the angle was recorded. Three measurements were taken and a mean value recorded.

5.3.8.3 Gastrocnemius flexibility

Figure 5.6c shows the gastrocnemius flexibility was measured. The weight bearing (WB) ankle dorsiflexion test was chosen as this has been used in previous studies for PFP [55, 344] and has shown an association to PFP [55]. Other studies assessing the gastrocnemius flexibility in PFP have used measures in prone lying [246] and supine lying [501].WB and NWB measures have only showed moderate correlation [502] so using these measures interchangeably is not advised and WB has been shown to produce more than twice than that of NWB [502]. Using the WB test in this thesis will produce a greater ROM and a value that most represents true length. A 0.6m line was marked on floor and the participant was advised to lean against the wall with the tested limb behind the contralateral limb and both toes pointing anteriorly. The participants were asked to keep the tested limb extended at the knee and attempt to maximally flex the ankle whilst keeping the heel on floor [55, 495]. The mid tibia angle was measured using the digital inclinometer. Three measurements were taken and a mean value recorded.

5.3.8.4 Foot posture index

The Foot posture index is a six item clinical tool that quantifies the static foot position with the criteria shown in Table 5.2 [503]. Participants stood in double limb support in a relaxed stance (Figure 5.6d). They were advised to march on the spot for few seconds in order to adopt a comfortable stance [503]. Each item of the FPI derives a score from -2 to +2 depending on item description. The values are tallied, with large positive values indicating a pronated foot posture [503].

Table 5.2: How to score the foot posture index
– adapted from Redmond (2005) [42]

Construct	Score				
	-2	-1	0	1	2
1) Talar head palpation	Talar head palpable on lateral side but not on medial side	Talar head palpable on lateral side/ slightly palpable on medial side	Talar head equally palpable on lateral and medial side	Talar head slightly palpable on lateral side/ palpable on medial side	Talar head not palpable on lateral side but palpable on medial side
2) Supra and infra lateral malleolar curvature	Curve below the malleolus either straight or convex	Curve below the malleolus concave but flatter more than the curve above the malleolus	Both infra and supra malleolar curves roughly equal	Curve below the malleolus more concave than curve above malleolus	Curve below the malleolus markedly more concave than curve above malleolus
3) Calcaneal frontal plane position	More than an estimated 5° inverted (varus)	Between vertical and an estimated 5° inverted (varus)	Vertical	Between vertical and an estimated 5° everted (valgus)	More than an estimated 5° everted (valgus)
4) Prominence in the region of the talonavicular joint	Area of TNJ markedly concave	Area of the TNJ slightly but definitely concave	Area of the TNJ flat	Area of TNJ bulging slightly	Area of TNJ bulging markedly
5) Congruence of the medial longitudinal arch	Arch high and acutely angled towards the posterior end of the medial arch	Arch moderately high and slightly acute posteriorly	Arch height normal and concentrically curved	Arch lowered with some flattening in the central portion	Arch very low with severe flattening in the central portion- arch making ground contact
6) Abduction/ adduction of the forefoot on the rearfoot	No lateral toes visible. Medial toes clearly visible	Medial toes clearly more visible than lateral	Medial and lateral toes equally visible	Lateral toes clearly more visible than medial	No medial toes visible. Lateral toes clearly visible

5.3.9 Biomechanical assessment

5.3.9.1 Strength testing

The Biodex isokinetic system 4 (IRPS Mediquipe, UK) was used to assess muscle strength. Data was collected by Biodex Advantage Software (IRPS Mediquipe, UK). Biodex has shown test- retest reliability of 0.95 ICC for knee extensor strength [504] and 0.81-0.95 ICC for hip abduction strength [192]. The testing procedure for both hip abduction and knee extensor strength commenced with practice testing on the contralateral limb before moving onto the index limb. Testing the index limb second minimises any learning-effect variability [505]. Weighing of the limb was completed prior to each testing to allow for automatic gravity correction for all torque data [506]. For the assessment of hip abduction strength, the participant was positioned in a side-lying position and the symptomatic side superior in a neutral angle (0° flexion, abduction, rotation) (Figure 5.6h). This positional procedure is in accordance with previously published literature [200].

For the assessment of knee extensor strength, the angle of testing was set at 60°/s which is considered safer and better tolerated by people with knee pain [507] (Figure 5.6i). The same testing protocol was used for both hip and knee strength and included three sub-maximal practice movements, similar to previous strength testing protocols used in PFP [508]. Participants were then asked to perform five maximal effort movements. During testing, the participant was verbally encouraged to push away and towards the pad during testing [509].

The concentric strength measures of interest were: i) peak hip abduction torque based on the maximum hip abduction torque across five repetitions; (ii) peak knee extension torque based on the maximum knee extension torque across five repetitions. These strength measures were normalised to body weight (Nm/kg).

5.3.9.2 An overview of isokinetic dynamometers

An isokinetic dynamometer i.e. Biodex is a rotation device with a fixed axis of rotation which can apply a constant, user selected angular velocity [510] – the rate of change in angular displacement. Figure 5.7 shows how the angular velocity is monitored continuously at approximately 1,000 times per second as the individual applies force to the arm. This represents a closed feedback loop mechanism in which the actual velocity is constantly

compared to the pre-set target angular velocity [510]. If the actual velocity exceeds the target velocity a braking mechanism is initiated and vice versa for reduced actual velocity [510]. The output from the IKD, in this context the peak torque, is based on the moment of force around the axis of rotation when adjusted for the moment exerted by the braking system and gravitational moment (corrected automatically in Biodex using the passive weight of the particular segment) [510].

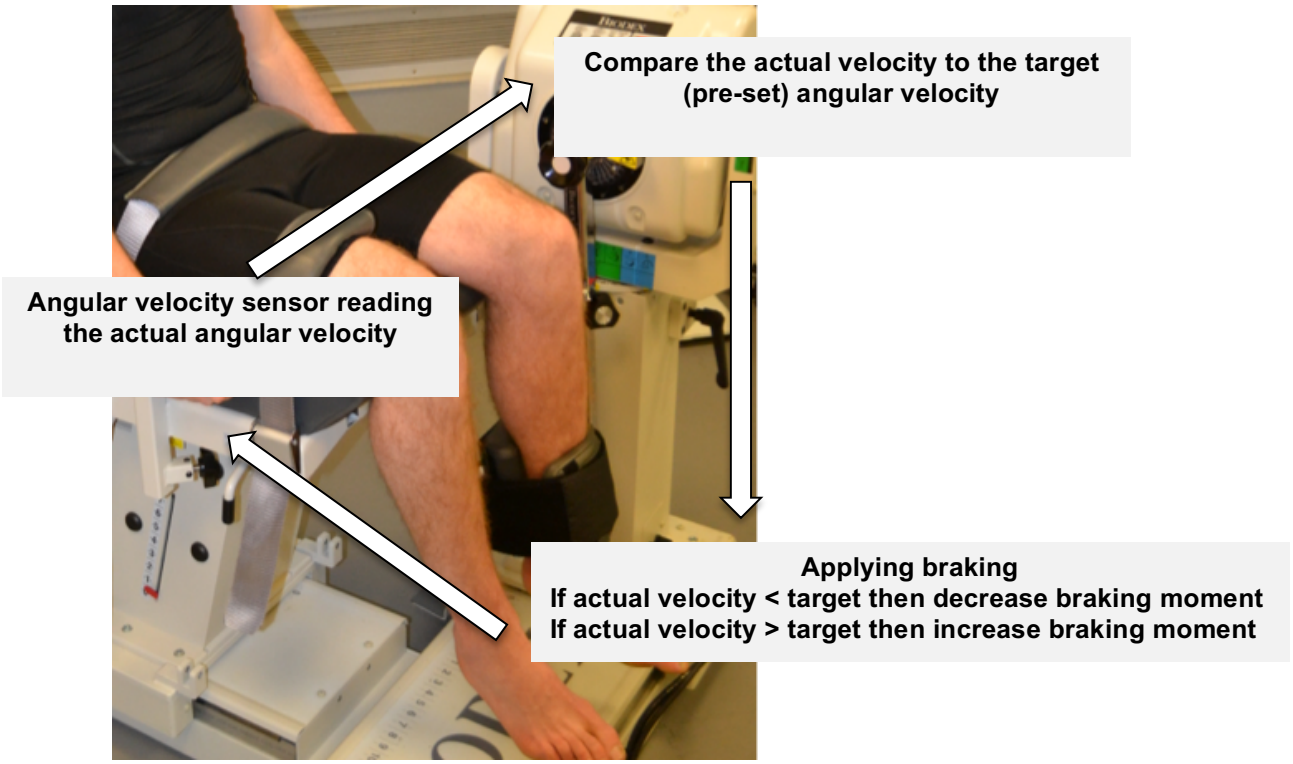

Figure 5.7: Feedback loop mechanism controlling the angular velocity – adapted from Payton and Bartlett (2007) [510]

5.3.9.3 Kinematic testing

Three-dimensional kinematics were assessed during stair descent using a VICON-passive, 10-camera, motion capture system (Vicon Nexus Version 1.6; Vicon Motion Systems, Oxford Metrics, Oxford, UK). The marker configuration for the chapter was based on the calibrated anatomical systems technique (CAST) [511]. The CAST methodology, first proposed by Cappozzo *et al.* (1997) [511], is seen as the gold standard protocol for 3D kinematic analyses [512] (Figure 5.8). The benefit of the CAST model is that it allows measurement in six degrees of freedom [512]. It uses 'static' markers placed on recognised anatomical

landmarks to calibrate the model and define the proximal and distal segments. The 'dynamic' tracking markers (mounted plates comprising of four retroreflective markers) then capture the movement and the interaction between these marker sets to allow modelling of the segment [512]. This marker protocol is able to isolate angular movement within the rotational plane which is not possible with a single marker placement [512]. This justifies the use this protocol in the following chapter for measuring the hip in the transverse plane. Tracking clusters were positioned to the lateral thighs, lateral shanks and sacrum. A static calibration trial was collected prior initiating the stairs. In order to determine anatomical reference points, retroreflective markers were attached to distal 1st metatarsal, distal 5th metatarsal, lateral and medial femoral epicondyles, right and left greater trochanters, right and left iliac crests and anterior superior iliac spines (ASIS) and posterior superior iliac spines (PSIS). Knee and ankle joint centres were calculated based on midpoint between the femoral epicondyles and malleoli respectively [513]. Hip joint centres were based on the recommendations made by Bell *et al.* (1989) [514]. Additional markers were used to control for marker occlusion by the stairs which included proximal 1st metatarsal, sustenaculum tali, lateral talar process, proximal calcaneus, and calcaneal tuberosity.

A **B**

Figure 5.8: Marker set up for stair descent
A) anterior view; B) posterior view

5.3.9.4 Stair descent

Motion capture has been widely used in PFP research to provide a greater understanding of kinematics and kinetics. Studies have captured data during a number of functional activities including walking, [258] stair ascent [494], stair descent [188] running [204], single leg squat [515] and jumping[516]. Barton *et al.* (2011) [517] has suggested that task selection should be made with consideration of a task that is likely to reproduce pain and is known to be limiting in PFP. It is widely considered that people with PFP report experiencing pain with both running and stair descent [126]. Discussion with the patient and public involvement (PPI) group suggested that stair descent would be more appropriate as many people with PFP will not run as a result of their pain.

5.3.9.5 Selection of gait cycle

The choice of gait cycle is thought to influence the findings observed [518]. Whatling and Holt (2010) [518] investigated the differences between two gait cycles by measuring knee kinematics from different steps during stair descent. Using a three-stair set up, as used in Chapter 5 and 6, they showed in a small sample (n=10) no difference in kinematics between cycles which included peak knee flexion.

Based on a similarly small sample (n=10), Yu *et al.* (1997) [519] found that a gait cycle between a middle step to the floor showed the lowest reproducibility. These findings were based on multiple correlations between joint angles of the ankle, knee and hip in three planes. The authors [519] attribute this variation to the sudden loss of constraint in the step length after transitioning to the floor although it's unclear why this motor performance would change between the three trials. Nevertheless, in accordance with these findings the gait cycle in Chapter 5 was exclusively analysed during initial contact on the second step in order to minimise the influence of transitioning from the platform or to the floor.

Figure 5.9 shows the gait cycle for stair descent. The gait cycle for the involved limb (determined from the subjective examination) was completed in accordance with previous studies [520] analysing stair descent. Participants were asked to descend the stairs at a self-selected speed. Each participant completed a minimum five successful stair descents. The descent was deemed successful when the involved limb was placed on the second step in the absence of any stumbles or hesitation. The kinematics of interest were: i) peak hip internal rotation angle of the thigh with respect to the pelvis; ii) peak knee flexion angle of the thigh with respect of the shank were calculated using the an X-Y-Z Euler rotation sequence [521]

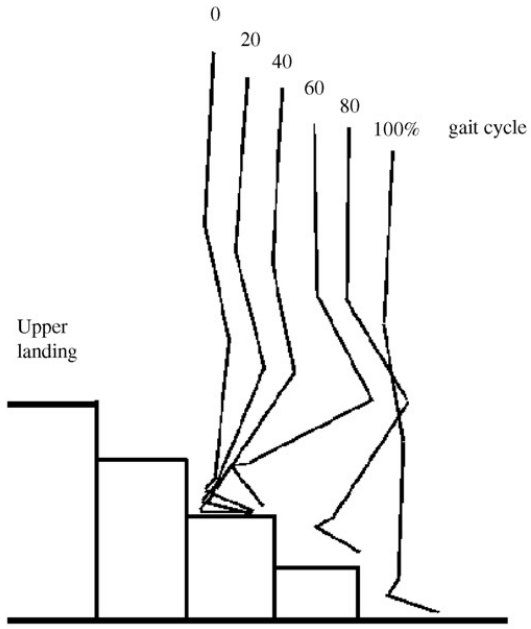

Figure 5.9: Stair descent gait cycle
Reprinted with permission of Elsevier, Gait & Posture[520]

5.3.10 MRI assessment

Sagittal, transverse and coronal plane images were acquired with a 3.0T scanner (Siemens Magnetom Verio, Siemens Healthcare, Germany) while participants were supine with the knee in extension and the quadriceps relaxed. The imaging protocol is shown in Table 5.3.

Table 5.3: MRI sequences showing key imaging parameters

	Sequences	Field of view (FoV)	Resolution	Slice thickness	Repetition time (ms)	Time to echo (ms)	Flip angle
1	PD TSE TRA FS	150	384 x 70%	3mm	3540	35	150
2	PD TSE COR FS	160	320 x 100%	3mm	4610	33	150
3	PD TSE SAG FS	160	384 x 70%	3mm	3630	34	150
4	STIR COR	160	320 x 80%	4mm	4190	41	150
5	T2 TSE SAG FS	160	384 x 70%	3mm	5100	82	150
6	T1 TSE SAG	150	384 x 100%	2mm	71	19	160
7	T1 VIBE SAG 3D	150	416 x 100%	0.6mm	10	1.64	30

PD = proton density; TSE = turbo spin echo ; TRA = transverse: COR = coronal ; FS = fat suppression ; SAG = sagittal ; STIR = short tau inversion recovery ; VIBE = Volumetric interpolated breath-hold examination

The two variables of interest were MRI bisect offset (BSO) and MRI patella tilt angle (PTA) which measure the alignment of the patella. Figure 5.6h and Figure 5.6i show how both BSO and PTA were calculated respectively. The intra-reliability for both BSO and PTA was established for a single reader (a Consultant Musculoskeletal Radiologist) by re-scoring 10 participants scans. This showed an ICC (3, k) 0.94 (95% CI 0.74, 0.99) for BSO and an ICC (3, k) 0.98 (95% CI 0.91, 0.99) for PTA. In addition to the selected variables, a MRI osteoarthritis knee semi-quantitative score (MOAKS) [522] was calculated to quantify the degree of patellofemoral osteoarthritis (PFOA). PFOA was defined [523] by the presence (>1) within the patella and/or trochlear of i) a definitive osteophyte ii) partial or full thickness cartilage loss.

5.3.11 Statistical analysis

Statistical analysis was carried out in SPSS software, version 21.0 (Armonk, NY: IBM Corp). The proposed statistical analysis will apply data-driven statistical analysis. Data-driven analysis can be broken into two methods supervised and unsupervised [362]. Supervised techniques work backwards from an outcome by applying statistical techniques such as regression analysis. Unsupervised techniques do not use a dependant variable or outcome but instead look for relationships between characteristics and applying statistical techniques such as cluster analysis. The strengths and weaknesses of these methods are presented in Table 5.4.

Table 5.4: Strengths and weaknesses of data-driven statistical techniques
Adapted from Kent *et al.* (2010) [362]

Statistical technique	Examples	Strength	Weaknesses
Supervised technique	Regression analyses	Direct face validity as subgroups derived using clinically relevant variable (dependant outcome)	Dependant outcome will greatly influence the nature of the subgroups e.g. pain vs. return to work
Unsupervised technique	Cluster analyses	Can later be studied against a range of treatments Subgroup is not dependant on only one outcome	Potential for subgroups to have no clinical relevance More exploratory in nature

The reliance on solely data-driven cluster analysis can lead to subgroups being difficult to interpret and apply clinically [364]. As a result, a two-stage approach advocated by Kent *et al.* (2015) [364] was applied using the SPSS TwoStep cluster analysis (TwoStep CA). This approach requires variables to be classified into health domains. Guidance for this classification process was based on a previous classification for PFP [18] with domain names revised to reflect modern understanding. The 10 selected variables were classified into the health domains by the candidate and a clinical expert supporting this chapter with five and 30 years of specialist interest in PFP respectively.

5.3.12 Summary of the SPSSTwoStep cluster analysis

The TwoStep CA, first introduced by Chiu *et al.* (2001) [524], was developed to address the shortfall of traditional cluster analysis approaches. The algorithm allows the handling of mixed data types (both continuous and categorical), automatic selection of cluster numbers (using either Schwarz Bayesian information criterion [BIC] or Akaike information criterion [AIC]) and more efficient handling of large datasets [524]. The TwoStep CA is made of two components (‘steps’) that are computed together automatically. Step one is the pre-clustering stage where data is allocated to coarse set of sub clusters and step two uses agglomerative hierarchical cluster techniques [524]. In comparison with other traditional hierarchical cluster algorithms, Gelbard *et al.* (2007) [525] showed the TwoStep CA was the best performing compared to eleven other algorithms in terms of matching to original clusters of established datasets. Conversely, one drawback highlighted by a few authors [526, 527] is that despite being able to handle mixed data types there is problem with how this is represented. TwoStep gives different weighting to categorical and continuous variables with categorical variables implicitly given a greater weighting. Subsequently, a cluster profile will be influenced by the different combinations of categorical and continuous variables [526]. Kent *et al.* (2014) [527] recently compared TwoStep CA, Latent Class Analysis and SNOB with the Latent Class shown to outperform TwoStep CA in terms of higher cluster sensitivity and better handling of mixed data. However, for the purposes of Chapter 5, the data at each stage will not include mixed data types; continuous at stage one and categorical at stage two. Kent *et al.* (2014) [527] also showed that the sensitivity of cluster detection for TwoStep CA is markedly less than the other cluster analysis methods showing a difference of 4 -37 clusters across four datasets. Nevertheless, Selfe *et al.* (2016) [254] points out that the cluster solution should be feasible to implement into clinical practice. Clearly a 37-cluster solution is not feasible and the average solution number for the Latent Class was 8.5 (across four datasets), which is still likely to lack feasibility and clinical

applicability. As clinical applicability and interpretation will determine the number of cluster solutions then a software's cluster detection sensitivity should have limited impact.

5.3.12.1 First stage of clustering

The first stage of clustering, of the two-stage approach, was performed only *within* each health domain. This was conducted using the TwoStep CA analysis using a log-likelihood similarity measure. One of its benefits over hierarchical cluster analysis (HCA) is that it is capable of dealing with binary outcomes. According to the developers of the statistical software [528], clustering binary outcomes using hierarchical cluster analysis should be avoided. Binary variables were expected so a TwoStep CA chosen instead. A HCA was, however, applied as a means of validating the eventual stability of the clusters.

The optimal number of cluster solutions was derived using the Schwartz Bayesian Information Criterion (BIC). Prior to performing the cluster analysis, data variance, normality and outliers were checked. After completing the first stage of clustering, cross tabulation was used to observe how the variables were distributed across the clusters within each domain. Variables were compared between clusters to inform cluster interpretation, at two-tailed significance ($p<0.05$). Independent samples t-tests (for two clusters) and ANOVA (for greater than two clusters) with Tukey post-hoc tests were performed for continuous variables. Chi-squared tests with Bonferroni-adjusted pairwise multiple comparisons were calculated for categorical variables. Labeling the clusters (hereafter referred to as *groups*) was guided predominantly by statistical differences and normative means derived from published literature (Table 5.5) to form the domains (categorical variables). For both BSO and PTA, previous thresholds have been established under a full weight bearing protocol [230] but only BSO shown to differ under non-weight bearing [425]. To account for these procedural differences, an extra 5% was added to the published thresholds for BSO.

The stability of cluster solutions from both stages was examined against a hierarchical HCA performed using Wards methods, with a squared Euclidean distance similarity measure and standardized to Z scores. For the HCA, the agglomeration schedule was used to identify coefficients of the cluster procedures. Tables were constructed for each domain showing the coefficient change at each cluster stage. This allows identification of large changes (or 'jumps') in coefficient, which indicates the preferred number of groups. Kappa coefficients were calculated to quantify the stability between TwoStep CA and HCA methods and interpreted using recognised criteria [529].

5.3.12.2 Second stage of clustering

Using the first stage domains and the same methodology, a second stage clustering was performed to identify groups across all domains. TwoStep CA is also known to be sensitive to the order of cases [527] so a random number generated order was computed and kappa coefficients (k) calculated to compare with the original order. Similar to the first stage, the groups were cross tabulated and compared clinically and statistically between groups.

Table 5.5: Subgrouping variable mean (SD) and normative data or defined thresholds

Subgrouping variable	Mean (SD)	Normative data			
		- 2 SD	- 1 SD	Mean	+ 1 SD
Peak hip abductor strength (Nm/kg) [530]	1.5 (0.4)	1.4	1.6	2.1	2.5
Peak knee extensor strength (Nm/kg) [530]	1.5 (0.6)	1.2	1.9	2.4	2.9
Peak angle hip internal rotation (°) [531]	- 8.8 (5.6)	-27.6	- 16.8	-5.8	4.8
Peak knee flexion angle (°) [531]	74.9 (10.0)	54.8	64.1	73.4	82.7
Quadriceps flexibility (°) [55]	125.1 (10.1)	99.4	115.8	132.2	148.6
Gastrocnemius flexibility (°) [55]	38.8 (6.8)	22.0	28.6	35.2	41.8
Hamstring flexibility (°)[532] *	154.0 (10.1)	127.1	136.9	146.7	156.5
		Defined Threshold			
Foot posture index [260]	4.3 (2.9)	6			
MRI bisect offset (%) [402, 425] *	57.2 (7.4)	68.3% (65 +5%)			
MRI patella tilt (°)[425]*	8.7(4.5)	9°			

* Gender specific thresholds combined

5.3.12.3 Subgroup prognosis

To determine the prognosis of the eventual groups, a logistic regression was applied with an 11-point Global Rating of Change Scale (GROC) (score from -5 to +5) as an outcome and dichotomised into favourable (≥ 2 points) and unfavourable outcome [533]. The model was adjusted for factors known to influence prognosis in PFP [19, 298] which included duration of symptoms (categorised into 3-12 months; greater than 12 months); baseline Anterior Knee Pain Score (AKPs) [534] (continuous outcome) as well as treatment attendance (categorised into Yes or No). Duration of pain as a continuous outcome violates the assumption of normality (Figure 5.10). The decision was to categorise the outcome in accordance with how it has been analysed in previous literature [19, 298]. Collins *et al.* (2013) [19] categorised duration of symptoms to: 3-6, 6-12 and >12 months. Applying this method to this chapter only revealed n= 10 for the first category thus the 3-6 months and 6-12 months categories were combined For those participants lost to follow up without GROC and treatment attendance data, outcomes were estimated using multiple imputations on the assumption that data was missing at random. Twenty imputed datasets were created [535]. In addition to the final analysis model variables, the imputation model included previous treatment at baseline and worst numerical rating score (NRS) as predictive auxiliary variables (Table 5.6 and Table 5.7). A sensitivity analysis was conducted examining the differences between the original and imputed datasets.

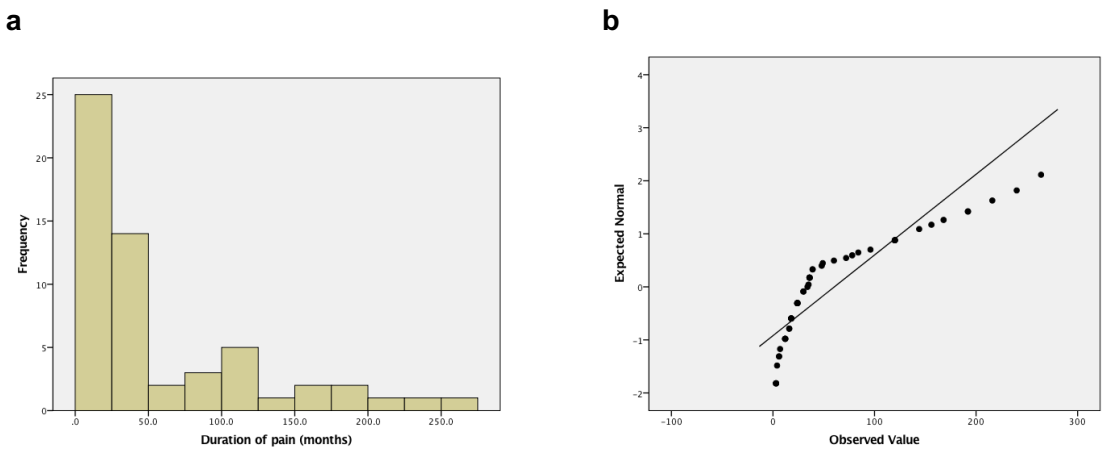

Figure 5.10: Duration of pain
a) Distribution of duration of pain; b) Normal Q-Q plot for duration of pain

5.3.13 Multiple imputation

Multiple imputation is a statistical technique used for handling missing data [536]. Multiple imputation commonly assumes the data to be missing at random (MAR) and uses the distribution of the known (observed) data to estimate the missing values [536]. A framework used for classifying missing data [537] identifies the following types of missing data:

- Missing completely at random(MCAR) – no systematic difference between missing values and observe values[538] ;
- Missing at random (MAR) – the probability of data being missing does not depend on the unobserved data but conditional on the observed data [536];
- Missing not at random (MNAR) - systematic difference exist between the missing values and the observe values even after observed data is considered [538].

The dataset was explored to understand whether there was any reason for the missingness and the pattern of missingness. Initially, a logistic regression was used to determine whether missingness (Missing or Not Missing) was influenced by the other values. This was done separately for both GROC and treatment attendance. Pearson correlations were then calculated in order to select auxiliary variables (coefficient >0.7)

It is shown in Table 5.6 and Table 5.7 that worst NRS predicted the missingness of GROC at 12 months and previous treatment (and baseline AKP) predicted the missingness of treatment attendance. Pearson correlations showed that no variables showed any correlation greater than 0.7 and so no further auxiliary variables were included based on correlation.

The imputation model included variables used in the original model (symptom duration, baseline AKP, treatment attendance) plus the auxiliary variables of previous treatment and worst NRS

Table 5.6: Predictors of Global Rating of Change Scale (GROC) missingness

Predictors	Multivariable	
	OR (95% CI)	P- value
Age	0.8 (0.7,1.0)	0.06
Gender (female)	13.9 (0.9, 205,8)	0.06
BMI	1.1 (0.9, 1.3)	0.13
Physical activity	1.3 (0.9, 1.9)	0.22
Duration of symptoms	0.9 (0.9, 1.0)	0.84
Anterior Knee Pain scale	0.9 (0.8, 1.0)	0.12
Worst NRS	0.5 (0.2, 0.9)	0.03*
S-LANNS	1.1 (0.9, 1.3)	0.18
Working hours	0.9 (0.9, 1.0)	0.21

*Significant at <0.05

Table 5.7: Predictors of Treatment attendance missingness

Predictors	Multivariable	
	OR (95% CI)	P- value
Age	0.8 (0.7,1.1)	0.26
Gender (female)	0.4 (0.0, 9.8)	0.59
BMI	0.9 (0.8, 1.2)	0.79
Working hours	0.9 (0.9,1.0)	0.63
Duration of symptoms	1.0 (0.9, 1.0)	0.17
Anterior Knee Pain scale	0.8 (0.7, 0.9)	0.048*
Worst NRS	0.6 (0.3, 1.2)	0.17
Previous treatment (No)	214.9 (3.8, 12173.5)	0.009*
Clinician referral (No)	6.7 (0.3,164.3)	0.24

*Significant at <0.05

5.4 Results

5.4.1 Participants

In total, 148 participants were invited to participate in the study. Twenty-four of these declined to take part and 47 were excluded following eligibility screening. Seventy-seven participants were consented to the study. Based on previous procedures for PFP recruitment [127], the MRI reports for all participants were checked for competing diagnoses. Seven participants were withdrawn at baseline due to competing diagnoses which included patellar tendinopathy (n=3), meniscal tear (n=2), infrapatellar bursitis (n=1) and one participant who was unable to tolerate the MRI due to unexpected claustrophobia (n=1).Seventy participants were included in the cluster analyses at baseline. Table 5.8 shows the characteristics for the participants analysed at baseline. Of these 70 participants, 58 completed outcomes at 12 months (dropout rate 17.1%). There were no significant baseline differences between the

participants who dropped out (n=12) and those that completed the outcomes at 12 months (n=58).

Table 5.8: Participant characteristics and descriptors. Values are means (SD) unless stated otherwise

Characteristics	Baseline cohort (n=70)
Age (years)	31.03 (5.32)
No (%) of females	43 (61.4)
BMI	26.25 (5.52)
Height	1.71 (0.09)
Weight	76.65 (18.57)
Physical activity level (hours/week)	3.12 (2.59)
Median (interquartile range) duration of knee pain (months)	35.50 (18.0-73.5)
No (%) of participants who had received previous treatment	53 (75.7)
No (%) with bilateral knee pain	36 (51.4)
Beighton score (/9)[539]	2.75 (2.48)
Anterior Knee Pain Scale	77.19 (11.73)
Worst pain	4.59 (2.28)
Average pain	2.96 (1.83)
No (%) of participants with joint crepitus	40 (57.1)
% Impact on work productivity (WPAIQ subscale) [540]	15.48 (23.02)
S-LANSS [541]	5.16 (5.41)

WPAIQ: Work Productivity and Activity Impairment Questionnaire; S-LANSS: Self completed Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale ; NRS: Numerical Rating Scale

5.4.2 Stability and profiling of the clusters

Figure 5.11 provides an overview of the results at each stage of clustering. At both the first cluster stage (5.4.2.1) and second cluster stage (5.4.2.2), the results of the TwoStep CA solutions were compared with the HCA to verify the stability of the cluster solutions. In addition, at both stages profiling and interpretation of the groups from the TwoStep CA was guided by the statistical differences between groups and interpreted using the normative data.

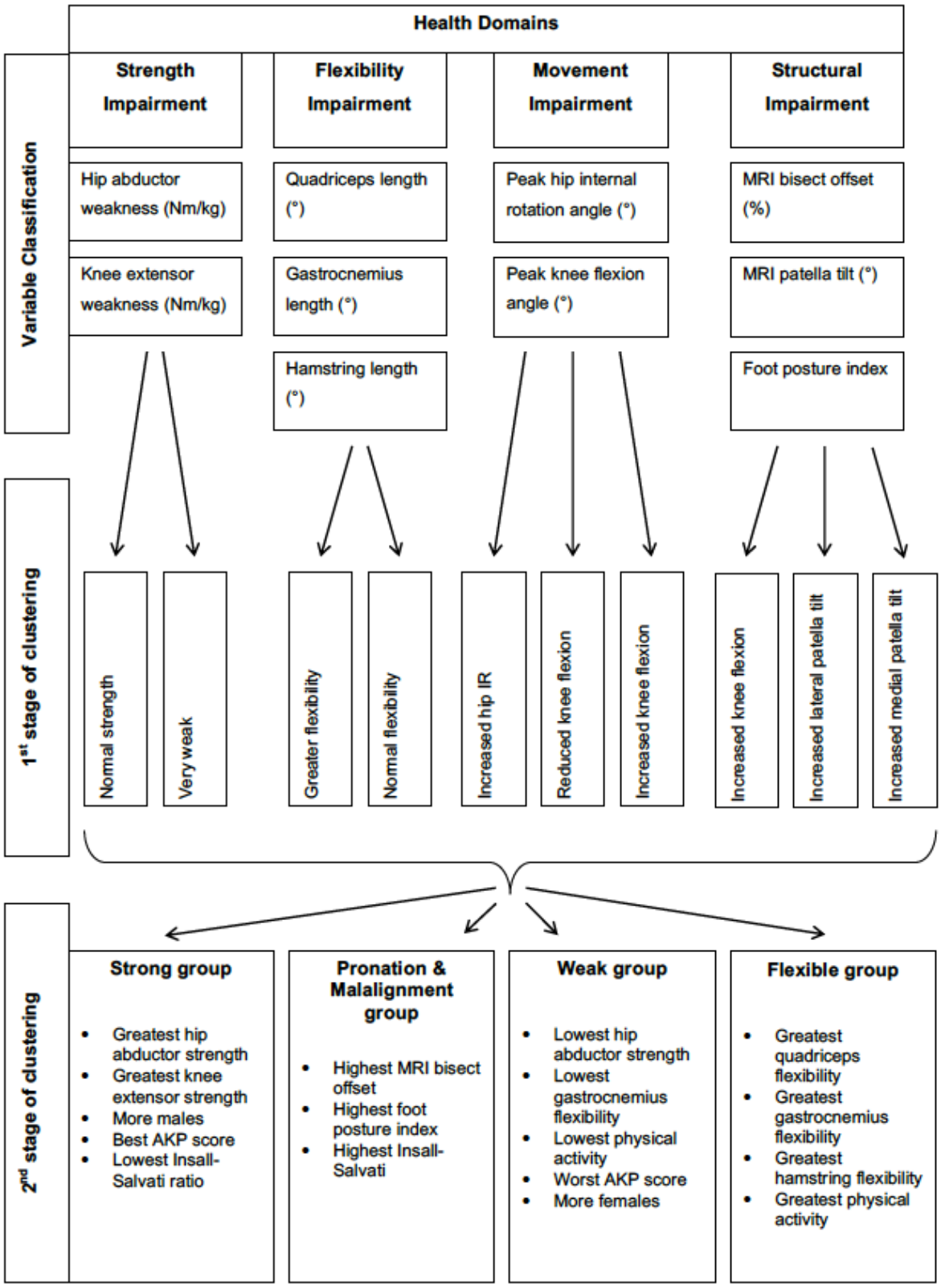

Figure 5.11: Two stage cluster approach

5.4.2.1 First cluster stage

5.4.2.1.1 Flexibility domain

The TwoStep CA identified a two cluster solution (Table 5.9) and the HCA a three cluster solution (Table 5.10).The HCA proposed three clusters to account for the differences in gastrocnemius and hamstring length. Being able to distinguish between a flexible hamstring and flexible gastrocnemius group is unlikely to be clinically useful. Therefore, collapsing down to a two-cluster solution appears preferential. The TwoStep CA shows that, statistically all the variables in Group 1 were significantly greater than Group 2 despite the clinical profile only indicating greater hamstring flexibility. Based on the TwoStep CA findings, Group 1 was labelled 'Greater Flexibility' and Group 2 'Normal Flexibility'.

5.4.2.1.2 Strength domain

The TwoStep (Table 5.11) and HCA (Table 5.12) proposed the same number of clusters and yielded the same clinical and statistical profiles. The TwoStep provides a more equal distribution across the two groups. The clinical and statistical profile mimic each other with the clinical profile providing context to the results suggesting the Group 1 is 'Normal strength' and Group 2 is 'Very weak'.

5.4.2.1.3 Movement domain

Both cluster methods proposed a three cluster solution (Table 5.13 and Table **5.14**). Group 1 from the TwoStep CA is similar to Group 3 from the HCA. Both show a statistically significant increase in hip internal rotation angle without it being considered to have clinically increased. The TwoStep CA, shows that Group 1 differed statistically from each of the other two groups in terms of peak knee flexion and peak hip internal rotation. Group 2 is similar in both cluster methods except that the findings of the HCA showed no statistical difference for peak knee flexion angle. In terms of the TwoStep CA, Group 2 differed statistically from each of the other two groups in terms of peak knee flexion and based on the normative data it's also borderline (+1SD) in terms of showing an increase in peak knee flexion. Group 3 is similar to Group 1 from HCA. Both showed a statistical and clinical reduction in knee flexion. Based on all these findings, Group 1 was labelled 'Increased hip internal rotation', Group 2 labelled 'Increased knee flexion' and Group 3 labelled 'Reduced knee flexion.

5.4.2.1.4 Structural domain

The TwoStep CA proposed a three-cluster solution (Table 5.15) whereas the HCA (Table 5.16) proposed two cluster solution. By applying a three-cluster solution, a third cluster (Group 3) represents individuals with a PTA value indicating more medial bias which is lost if the solution is constrained to only two clusters. Using the TwoStep CA solution, Group 1 was statistically different to all other groups for BSO and FPI and the clinical profile suggests excessive scores for all variables based on the defined thresholds. Group 2 clinically has increased patella tilt angle but the mean value was very similar to Group 1 (10.7º vs 10.3º). Group 3 shows an increased medial tilt which was statistically significant but no clinical thresholds exists for medial bias so labelling was led solely by the statistics. Based on these findings, Group 1 was labelled ‘Increased BSO and FPI’, Group 2 labelled ‘Normal’ and Group 3 labelled ‘Increased medial PTA’.

Table 5.9: TwoStep cluster solutions for flexibility domain

	Two Step				
	1		2		MD (95% CI)
Distribution (n)	**29**		**41**		
Hamstring length (°)	162.18 *	> 1 SD	148.25	μ	13.93 (10.36, 17.50)
Gastrocnemius length (°)	41.42 *	μ	36.89	μ	4.54 (1.41, 7.66)
Quadriceps length (°)	131.28 *	μ	120.79	μ	10.49 (6.30, 14.69)
Clinical Profile	Flexible hamstrings		Normal Flexibility		
Statistical Profile	Greater flexibility		Normal flexibility		

* Significantly different from other groups ($p < 0.05$)

μ = clinical value within the normal clinical threshold; > 1SD = greater than 1 standard deviation from the normative mean

Table 5.10: Hierarchical cluster solutions for flexibility domain

	Three cluster solution					
	1		2		3	
Distribution (n)	**37**		**12**		**21**	
Hamstring length (°)	149.32	μ	169.27*	> 1SD	153.57	μ
Gastrocnemius length (°)	35.07	μ	36.26	μ	46.71*	> 1SD
Quadriceps length (°)	121.95†	μ	126.42	μ	130.00	μ
Clinical Profile	Normal flexibility		Flexible hamstring		Flexible gastrocnemius	
Statistical Profile	Tighter quadriceps		Flexible hamstring		Flexible gastrocnemius	

* Group significantly different from each of the other two ($p < 0.05$)

† All groups significantly different from each other ($p<0.05$).

μ = clinical value within the normal clinical threshold; > 1SD = greater than 1 standard deviation from the normative mean

Table 5.11: TwoStep cluster solutions for strength domain

	TwoStep				MD (95% CI)
	1		2		
Distribution (n)	**30**		**40**		
Knee extension strength (Nm/kg)	2.05 *	μ	1.14	< 2SD	0.91 (0.71, 1.10)
Hip abduction strength (Nm/kg)	1.80 *	μ	1.2	< 2SD	0.60 (0.45, 0.76)
Clinical Profile	Normal strength		Very weak		
Statistical Profile	Normal strength		Less strength		

* Significantly different from the other group (p <0.05)

μ = clinical value within the normal clinical threshold; < 2SD = less than 2 standard deviation from the normative mean

Table 5.12: Hierarchical cluster solutions for strength domain

	Hierarchical			
	1		2	
Distribution (n)	**11**		**59**	
Knee extension strength (Nm/kg)	2.39*	μ	1.37	< 2SD
Hip abduction strength (Nm/kg)	2.13*	μ	1.33	< 1SD
Clinical Profile	Normal strength		Weak hip and very weak knee	
Statistical Profile	Normal strength		Less strength	

* Significantly different from the other group (p <0.05)

μ = clinical value within the normal clinical threshold; < 2SD = less than 2 standard deviation from the normative mean;

< 1SD = less than 1 standard deviation from the normative mean

Table 5.13: TwoStep cluster solutions for movement domain

	TwoStep						Group comparison; MD (95% CI)
	1		2		3		
Distribution (n)	**29**		**24**		**17**		
Peak knee flexion angle(°)	77.05 †	µ	81.76†	µ	61.69†	< 1SD	1 vs 2; -4.70 (-8.93, -.47)
							1 vs 3; -15.35 (10.67, 20.04)
							2 vs 3; -20.06 (-24.92, -15.20)
Peak hip internal rotation (°)	-3.82 *	µ	-12.89	µ	-11.53	µ	1 vs 2; 9.07 (6.68, 11.47)
							1 vs 3; 7.71 (5.05, 10.36)
							2 vs 3; -1.37(-4.12, 1.39)
Clinical Profile	Normal movement		Normal movement		Reduced knee flexion		
Statistical Profile	Increased hip IR		Increased Knee flexion		Reduced knee flexion		

* Group significantly different from each of the other two (p <0.05)

† All groups significantly different from each other (p<0.05).

µ = clinical value within the normal clinical threshold; < 1SD = less than 1 standard deviation from the normative mean;

Table 5.14: Hierarchical cluster solutions for movement domain

	Hierarchical					
	1		2		3	
Distribution (n)	**26**		**23**		**21**	
Peak Knee Flexion Angle (°)	65.43*	µ	82.48	µ	78.44	µ
Peak hip internal rotation angle (°)	-10.14	µ	-12.88	µ	-2.69*	µ
Clinical Profile	Reduced knee flexion (trend)		Increased knee flexion (trend)		Hip internal rotation (trend)	
Statistical Profile	Reduce knee flexion		Normal movement		Increased hip internal rotation	

* Group significantly different from each of the other two (p <0.05)

µ = clinical value within the normal clinical threshold

Table 5.15: TwoStep cluster solutions for structural domain

	TwoStep						Group comparison; MD (95% CI)
	1		2		3		
Distribution (n)	10		43		17		
Foot posture index	8*	>t	3.7	μ	3.5	μ	1 vs 2; 4.23(2.10; 6.36) 1 vs 3; 4.53 (2.11, 6.95) 2 vs 3; -0.30 (-2.04, 1.44)
Bisect Offset (%)	70.3†	>t	56.6†	μ	50.9†	μ	1 vs 2; 13.72 (9.87, 17.56) 1 vs 3; 19.36 (14.99, 23.72) 2 vs 3; 5.64 (2.50, 8.78)
Patella tilt angle (°)	10.3	>t	10.7	>t	2.5*	μ	1 vs 2; -0.40 (-2.87, 2.06) 1 vs 3; 7.81 (5.01, 10.60) 2 vs 3; 8.21 (6.20, 10.22)
Clinical Profile	Pronated feet & patella maltracking		Increased lateral patella tilt		Normal		
Statistical Profile	Increased bisect offset & foot posture		Normal		Increased medial patella tilt angle		

* Group significantly different from each of the other two (p <0.05)

† All groups significantly different from each other (p<0.05).

μ = clinical value within the normal clinical threshold; >t = exceeds the normative threshold

Table 5.16: Hierarchical cluster solutions for structural domain

	Hierarchical			
	1		2	
Distribution (n)	30		40	
Bisect offset (%)	61.03*	μ	54.28	μ
Patella tilt angle (°)	10.91*	>t	6.96	μ
Foot posture index	6.8*	>t	2.43	μ
Clinical Profile	Pronated foot & Increased patella tilt angle		Normal	
Statistical Profile	Excessive structure		Normal structure	

* Significantly different from other group (p <0.05)

μ = clinical value within the normal clinical threshold; >t = exceeds the normative threshold

5.4.2.2 Second cluster stage

During the second cluster stage, four groups were identified from the cluster patterns (Table 5.17). This cluster solution was compared to the random case ordering showing a substantial agreement [529] between orders, k = 0.68 (p< 0.001, 95% Confidence Intervals [CI] 0.55, 0.81). Comparison with the output from the HCA cluster solution (Table 5.18) showed a moderate agreement, k = 0.59 (p < 0.001, 95% CI 0.46, 0.73). Profiling of the clusters identified the following groups:

5.4.2.2.1 Strong group

The Strong group showed a significantly greater hip abductor (1.8 Nm/kg) and knee extensor strength (2.1 Nm/kg) compared to each of the other groups. Their gastrocnemius flexibility was also significantly greater compared to the Weak group (40.5 ° vs 35.0°). Based on the clinical thresholds, this group demonstrated all variables within normal limits including the strength measures. This group had significantly more males (59.3% vs 9.1%) and significantly less functional disability (i.e. higher AKP) compared to the Weak group (82.4 vs 73). They also had a significantly smaller Insall-Salvati ratio compared to the Pronation & Malalignment group (1.2 vs 1.4) and the greatest patellofemoral contact area (154.1 mm^2) (non-significant).

5.4.2.2.2 Pronation & Malalignment group

The Pronation & Malalignment group showed the largest BSO (73.6%) and FPI (8.0) which was statistically significant compared to each of the other groups. Based on the clinical thresholds, this group showed a mean BSO and FPI value that exceeded the defined thresholds suggesting increased patella malalignment and foot pronation. In addition, clinically they exceeded the defined normative threshold for PTA (10.3°) and demonstrated marked weakness in hip abductor strength (< 2 SD) and moderate weakness in knee extensor strength (< 1 SD). This group showed the highest BMI (29.4 kg/m^2) and duration of symptoms (73.9 months) but neither was statistically significant across groups. They showed the highest Insall-Salvati ratio which was significantly greater than the Strong group and the lowest patellofemoral contact area (109.5 mm^2) (non-significant). Within this group, 30% and 40% of the group had MRI defined osteophytes and PFOA respectively. Compared to all other groups, both these variables showed a p-value of 0.02 but this was not considered statistically significant based on Bonferroni adjustment (p <0.008).

5.4.2.2.3 Weak group

The Weak group demonstrated the least hip abductor strength (1.1 Nm/kg) and knee extensor strength (1.0 Nm/kg) but with only the hip abductor strength showing statistical significance between the Flexible and Strong group This group also demonstrated the least gastrocnemius flexibility which was significantly lower compared to the Strong group. Based on the clinical thresholds, this group demonstrated marked weakness for both hip abductor (< 2 SD) and knee extensor strength (<2 SD) with all other variables within normal limits. This group comprised of a significant number of females (90.9%), with the lowest AKPS compared to the Strong group. They also demonstrated significantly lower physical activity compared to the Flexible group (1.7 vs 4.9 hours/ week).

5.4.2.2.4 Flexible group

The Flexible group demonstrated the greatest quadriceps (135.7°), gastrocnemius (43.4°) and hamstring flexibility (158.0°) with quadriceps being statistically different to each of the other groups and gastrocnemius and hamstring statistically different to the Weak group. Based on the clinical thresholds, this group demonstrated greater flexibility for gastrocnemius (> 1 SD) and hamstrings (> 1 SD) in addition to a moderate weakness in hip abductor strength (< 1 SD) and knee extensor strength (< 1 SD). All the other variables were within normal limits including quadriceps flexibility. This group was significantly more physically active compared to the Weak group.

Table 5.17: Mean values (SD) across the four subgroups

Variables	2nd stage subgroups				
	Strong (n=27) Mean (SD)	**Pronation & Malalignment (n=10) Mean (SD)**	**Weak (n=22) Mean (SD)**	**Flexible (n=11) Mean (SD)**	**ANOVA**
Peak hip abductor strength(Nm/kg)	1.8 (0.3) †	1.3 (0.5)	1.1 (0.3) *	1.4 (0.2) *	F =19.67 p <0.001
Peak knee extensor strength (Nm/kg)	2.1 (0.5) †	1.4 (0.6)	1.0 (0.3)	1.3 (0.1)	F = 24.502 p <0.001
Peak angle hip internal rotation (°)	-9.1 (5.4)	-10.8 (6.3)	-7.0 (5.1)	-9.9 (5.9)	F = 1.448 p = 0.24
Peak knee flexion angle (°)	73.5 (10.5)	73.6 (13.4)	75 (9.4)	79.6 (11.0)	F = 1.032 p = 0.38
Quadriceps flexibility (°)	125.0 (10.3)	122.1 (11.3)	121.4 (6.1)	135.7 (8.0) †	F = 6.75 p < 0.001
Gastrocnemius flexibility (°)	40.5 (6.8) §	37.5 (7.5)	35.0 (4.6) * §	43.4 (6.4) *	F = 5.53 p = 0.002
Hamstring flexibility (°)	155.4 (11.8)	154.0 (10.3)	150.3 (6.9)	158.0 (9.3)	F = 1.81 p = 0.15
Foot posture index	3.7 (2.3)	8.0(2.1) †	3.6 (2.8)	3.8 (3.0)	F = 8.17 p< 0.001
MRI bisect offset (%)	55.4 (6.3)	70.3 (4.7) †	54.1 (4.4)	55.6 (3.1)	F = 25.49 p < 0.001
MRI patella tilt (°)	8.1 (5.2)	10.3 (4.9)	8 (4.2)	9.8 (2.8)	F =0.96 p = 0.41
Patient related factors					
Age (years)	30.7 (5.13)	30.6 (5.3)	30.1 (6.2)	34 (2.9)	F =1.45, p=0.24
Gender (male %)	16 (59.3) *	5 (50.0)	2 (9.1) *	4 (36.4)	x^2 = 13.52, p =0.004
BMI (kg/m^2)	24.9 (4.6)	29.4 (7.8)	27.3 (5.7)	24.8 (3.3)	F =2.27, p =0.09
Physical activity (hours/week)	3.5 (2.4)	3.1 (2.6)	1.7 (1.6) *	4.9 (3.3) *	F=4.713, p=0.005
Duration of pain (months)	52.3 (58.9)	73.9 (72)	59.4 (68.8)	57.7 (82.7)	F=0.25, p=0.86
Previous treatment (%)	17 (63.0%)	8 (80.0%)	18 (81.8%)	10 (90.9%)	$x^{2=}$ 4.31, p =0.23
Bilaterality (%)	15 (55.6)	5 (50)	12 (54.6)	4 (51.4)	$x^{2=}$ 1.28, p =0.74
Beightons score (/9)[539]	2.1 (2.3)	3.8 (2.6)	2.8 (2.3)	3.3 (3.0)	F=1.35, p=0.27

Anterior Knee Pain Score	82.4 (9.7) *	75.1 (12.4)	73 (11.5) *	74.5 (12.9)	F=3.29, p=0.03
Average NRS	2.4 (1.6)	3.3 (2.7)	3.2 (1.6)	3.5 (1.6)	F=1.38, p=0.26
Worst NRS	4.0 (1.9)	4.2 (3.0)	5.0 (2.3)	5.5 (2.2)	F=1.42, p=0.24
S-LANSS [541]	4.1 (5.4)	5.1 (6.6)	6.9 (5.4)	4.2 (3.9)	F=1.21, p=0.31
WPAIQ subscale - % impact on work productivity [540]	8.5 % (15.4)	21.25% (26.9)	26.67% (25.9)	9% (25.1)	F=2.90, p =0.04
Supplementary clinical descriptors					
Total patella mobility (mm)	12.8 (4.6)	14.8 (5.0)	12.1 (4.4)	13.5 (4.0)	F =0.82, p=0.49
MRI cartilage loss (≥1)	9 (33.3)	6 (60%)	9 (40.9%)	3 (27.3%)	x^2 = 2.894, p =0.41
MRI osteophyte (≥1)	7 (25.9%)	4 (40%)	0 (0%)	0 (0%)	x^2 = 12.73, p = 0.005
PFOA (OA present %)	4 (14%)	3 (30%)	0 (0%)	0 (0%)	x^2 =8.81, p=0.03
Contact area (mm^2)	154.1 (39.2)	109.5 (44.8)	118.0 (55.8)	127.7 (55.8)	F=3.24, p=0.03
Insall-Salvati (ratio)	1.2 (0.1) *	1.4 (0.1) *	1.3 (0.2)	1.2 (0.2)	F =4.19, p=0.009

† Different from each of the other three groups (p<0.05)

* Subgroup pairs different (p<0.05)

§ Subgroup pairs difference (p<0.05)

Table 5.18: Mean values (SD) across the four subgroups generated by hierarchical cluster analysis

Variables	2nd stage subgroups			
	Group1 (n= 13) Mean (SD)	**Group 2 (n= 12) Mean (SD)**	**Group 3 (n= 29) Mean (SD)**	**Group 4 (n= 16) Mean (SD)**
Peak hip abductor strength(Nm/kg)	1.9 (0.3)	1.8 (0.3)	1.2 (0.4)	1.3 (0.3)
Peak knee extensor strength (Nm/kg)	2.1 (0.6)	2.1 (0.5)	1.2 (0.4)	1.3 (0.3)
Peak angle hip internal rotation (°)	-10.1 (4.9)	-8.2 (5.9)	-7.3 (5.5)	-10.8 (5.6)
Peak knee flexion angle (°)	73.6 (12.7)	75.1 (10.9)	73.4 (9.1)	78.7 (8.5)
Quadriceps flexibility (°)	129.7 (10.7)	122.6 (7.8)	120.0 (7.3)	133.0 (9.7)
Gastrocnemius flexibility (°)	41.2 (6.9)	39.6 (7.9)	35.8 (4.7)	41.6 (7.5)
Hamstring flexibility (°)	165.6 (7.3)	144.5 (6.1)	149.8 (6.3)	159.4 (8.3)
Foot posture index	3.4 (2.1)	5.6 (3.0)	3.7 (2.8)	5.3 (3.4)
MRI bisect offset (%)	55.1 (6.0)	62.2 (10.0)	54.7 (5.7)	59.6 (7.0)
MRI patella tilt (°)	7.8 (5.4)	12.1 (2.3)	7.2 (4.5)	9.4 (4.0)

5.4.3 Prognosis of subgroups

No clinically meaningful differences were noted between the original (Table 5.19) and imputed results and so the imputed dataset is presented. Overall the subgrouping variable was not statistically significant for predicting a favourable outcome (p=0.26). The results of the logistic regression (Table 5.20), using the Strong group (55% [15/27] favourable outcome) as the reference group, showed that there were no statistically significant differences between the groups in the odds of a favourable outcome. Descriptively, the Weak (31% [7/22]; Odds Ratio [OR] 0.30; 95% CI 0.07, 1.36) and the Pronation & Malalignment (50% [5/10]; OR 0.64, 95% CI 0.11, 3.66) groups were less likely to report a favourable outcome at 12 months. However, the Flexible group (63% [7/11]; OR 1.24, 95% CI 0.20, 7.51) were more likely to report a favourable outcome.

Table 5.19: Multiple logistic regression using *original* (non-imputed) data

Subgroup	Multivariable [a]	
	OR (95% CI) [b]	P- value
Pronators & maltrackers	0.50 (0.08, 2.95)	0.44
Weak group	0.27 (0.06, 1.33)	0.11
Flexible group	1.32 (0.20, 8.89)	0.77
Duration of symptoms (>12 months)	0.06 (0.01, 0.65)	0.02
Baseline AKP	1.03 (0.97, 1.08)	0.36
Treatment (no treatment)	0.45 (0.13, 1.53)	0.20

a. Adjusted for duration of symptoms (> 12 months); baseline AKP; treatment (no treatment)

b. Reference group: Strong group

Table 5.20: Multiple logistic regression exploring the association between subgroups and likelihood of a favourable outcome at 12 months

Subgroup	Multivariable [a]	
	OR (95% CI) [b]	P- value
Pronation & Malalignment group	0.64 (0.11,3.66)	0.62
Weak group	0.30 (0.07, 1.36)	0.12
Flexible group	1.24 (0.20, 7.51)	0.82
Duration of symptoms (>12 months)	0.08 (0.01, 0.77)	0.03
Baseline AKP	1.03 (0.98, 1.09)	0.28
Treatment (no treatment)	0.51 (0.15, 1.70)	0.27

a. Adjusted for duration of symptoms (> 12 months); baseline AKP; treatment (no treatment)

b. Reference group: Strong group

5.4.4 Determining a favourable outcome

A few approaches have been applied in previous PFP research to determine the 'improvement' of an intervention. The most common method is to use the Global Rating of Change Scale (GROC) and this has been applied in most of the recognised longitudinal analyses in PFP to date [19, 298, 377]. The thresholds used to determine improvement in the GROC are based on the recommendations from Kamper *et al.* (2009) [533] and modified depending on the number of scale points used in GROC e.g. 7 point versus 11 point scale. Alternative approaches have been applied recently. The study by Ferber *et al.* (2015) [268] , the largest RCT to date in PFP (n=199), determined improvement via two methods: i) improvement in AKP of 8 points *and* VAS on 2 points; ii) improvement in AKP of 8 points *or* VAS on 2 points.

The current study used an 11-point GROC and applied a 2 point threshold based on these recommendations [533]. However, consideration was made to relationship between these improvement thresholds. Using the original data (n=57) (not the imputed dataset), GROC improvement was cross-tabulated with: i) AKP or VAS improvement and ii) AKP and VAS improvement and descriptive results reported.

Comparison between GROC and AKP and VAS in terms of reporting favourable outcome shows only 31% (9/29) agreement but does show a 93% (26/28) agreement in terms of reporting an unfavourable outcome (Table 5.21). When GROC is compared to AKP or VAS the agreement for reporting a favourable outcome increases to 69% (20/29) but the agreement in terms of no improvement reduces to 39% (11/28) (Table 5.22).

Overall, the data from GROC shows that 51% (29/57) reported a favourable outcome compared to 19% (11/57) using the AKP and VAS approach and 65% (37/57) using the AKP or VAS approach. An improvement in half the sample, using the GROC, is perhaps more representative of the success rate observed in clinical practice at 12 months where 1 in 2 patients will improve rather than 1 in 5 [52]. The AKP or VAS approach shows a similar but slightly greater favourable outcome, however, GROC is the most commonly used outcome in PFP for this type of analysis and would allow future comparison with other studies. GROC was therefore retained as the method to determine improvement. The differences noted between GROC and AKP and VAS does, however, highlight the caution of comparing predictors across multiple studies if the threshold for 'improvement' is defined differently.

Table 5.21 Cross tabulation of GROC and 'AKP and VAS' thresholds

		AKP *and* VAS		
		0	**1**	**Total**
GROC	**0**	26	2	28
	1	20	9	29
	Total	46	11	57

Table 5.22 Cross tabulation of GROC and 'AKP or VAS' thresholds

		AKP *or* VAS		
		0	**1**	**Total**
GROC	**0**	11	17	28
	1	9	20	29
	Total	20	37	57

5.5 Discussion

This chapter has demonstrated that four subgroups within a PFP cohort can be identified using modifiable clinical, biomechanical and imaging features that are potentially amenable to treatment. There was no statistical significance between the groups in the odds of a favourable outcome, descriptively however, the Weak group were the least, and the Flexible group the most, likely to report a favourable outcome at 12 months

This chapter has further enhanced our knowledge of PFP subgroups by incorporating recognised biomechanical and imaging features to refine previously identified subgroups based on clinical measures. The four groups identified in the current chapter are comparable to four empirical subgroups identified previously but these were not derived statistically [366, 374]. Deriving subgroups using cluster analyses, like the current chapter, Selfe *et al.* (2016) [254] identified three subgroups: 'Weak & Tighter', 'Strong' and 'Weak & Pronated'. The clinical tests they used included some of the same measures of quadriceps flexibility, gastrocnemius flexibility and FPI as used in the current chapter. Knee extensor and hip abductor strength were also used but were measured isometrically. Despite identifying only 3 groups, the groups identified by Selfe *et al.* (2016) [254] showed some similarities to those

of the current chapter. Both strong groups demonstrated high strength measures and were comprised predominantly of men. The Weak group show similarities with the Selfe *et al.* (2016) [254] Weak & Tighter group in terms of lowest strength, physical activity and poor functional scores. The Pronation & Malalignment and Flexible groups in the current chapter show some similarities with the Selfe *et al.* (2016) [254] Weak & Pronated group in terms of high FPI and the greatest gastrocnemius flexibility. The lack of complete agreement between studies is likely the result of slight variations in statistical methodology and the fact that the study reported in this chapter incorporated imaging and biomechanical features. Furthermore, the Selfe *et al.* (2016) [254] study had a slightly lower mean age (26 years) and a higher proportion of females (84%) which may have also contributed to the different categorisations. Nevertheless, these findings combined provide further support for the existence of these PFP subgroups, thereby providing a basis for a stratified rehabilitation management approach.

This chapter shows the long-term outcome of statistically derived PFP subgroups using clinical, biomechanical and imaging features. Despite finding no statistical significance in terms of 12 month outcomes, there was a directional trend showing that the Weak group were the most likely to report an unfavourable outcome at 12 months. This is perhaps unsurprising as this group were found to have the weakest hip abductor and knee extensor strength both statistically and clinically compared the other groups and report the least physical activity and worst AKP scores. Less knee strength [301, 510] and poor baseline function [298] have previously been shown to lead to a poor long-term response to treatment in PFP. The Flexible group which showed the greatest flexibility in quadriceps, gastrocnemius and hamstrings and being the most physically active were the most likely to report a favourable outcome. This group may represent people who, due to their increased physical activity, are transiently exceeding joint loading which has been linked to an increase in PFP symptoms [68]. Simple activity modification may have explained the improvement in this group, however this is difficult elucidate from the data available. Only one other study [366] has investigated the long-term follow up of PFP subgroups, which were empirically derived. In a three-year follow up, Keays *et al.* (2015) [366] reported no improvement in pain for any of their four subgroups: hypermobile stance group; hypomobile group; faulty movement pattern group; and PFOA group. The contrast in findings to the current chapter may be the result of a longer follow-up period or that groups were derived clinically rather than statistically. Furthermore, they recruited a wider age group of participants (13-82 years) which may have contributed to the observed discordance.

5.5.1 Clinical Implications

The identification of diagnostic subgroups provides the opportunity for a range of interventions to be matched accordingly [363] and largely confirms the subgroups identified by Selfe *et al.* (2016) [254] . With the exception of the Strong group, all the other groups were considered clinically weak. This disparity in strength between the Strong group and the other groups is shown graphically in Figure 5.12. This shows graphically that, by applying the 1 SD threshold (Figure 5.12) to the normative data, only members of the Strong group were classed as normal strength for both the knee and hip. With the exception of four members of the other subgroups who showed normal strength in either knee extension or hip abduction, all the members of the other subgroups demonstrated clinical weakness in both hip abductor and knee extensor strength. These results provide a rationale for continuing to prescribe standard knee and hip strengthening based exercises, associated with current practice [542], to the other three subgroups but with a greater consideration of the exercise parameters (load, repetitions etc.) which are known to influence strength gains in PFP [543] .

As the Strong group showed normal strength levels they are unlikely to gain any further benefit from additional routine strengthening exercises [544]. This group may instead be better targeted with movement retraining based interventions which have been shown to be effective in runners with PFP [204, 205, 276]. The Pronation & Malalignment group demonstrated excessive structural features (largest BSO and FPI) and therefore might benefit from passive interventions such as knee braces and foot orthotics which have been showed to reduce BSO [148] and FPI [490] respectively. From a clinical service provision viewpoint, these prognostic findings highlight who might be unlikely to benefit from additional treatment [21, 357]. Our findings suggest that the most active, Flexible group may represent a self-limiting form of PFP which may require simple advice on load management [545] and limited follow up. In contrast, the Weak group may require increased service provision with more physiotherapy input. The prognosis of PFP subgroups remains a research priority and further evaluation of other datasets is required before these results can be applied within clinical practice.

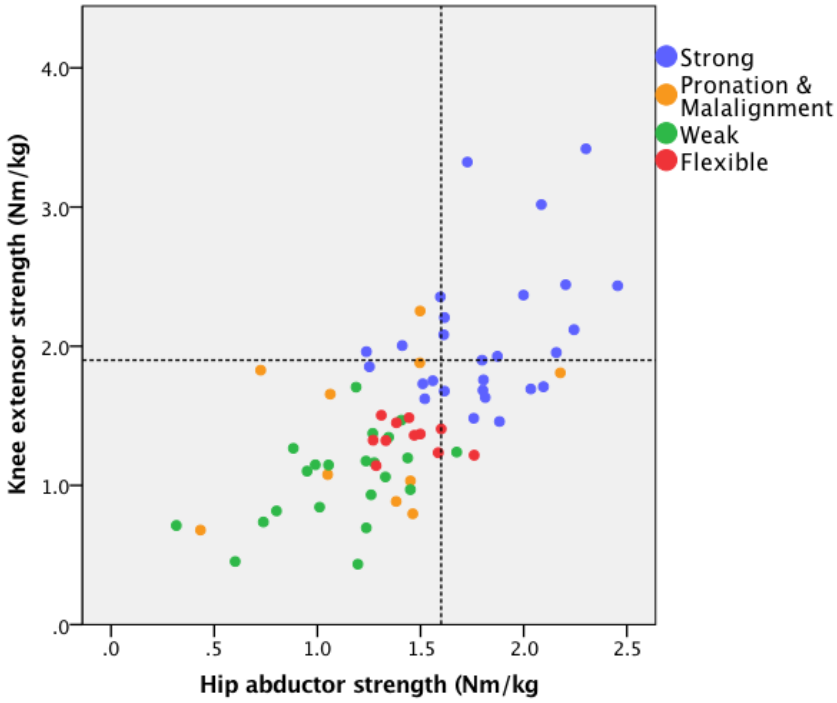

Figure 5.12: Clinical profile of the subgroups in terms of knee extensor and hip abductor strength.
Line represents < 1 SD

5.5.2 Limitations

Sample size. These chapter findings are based on a relatively small cohort, however, the use of a rule of thumb [486] for cluster analysis was intended to minimise the over fitting of data. Dolnicar (2002) [546] conducted a review into 248 studies that utilised data-driven cluster analysis which was not specific to medicine and instead related to business administration but demonstrates that sample sizes vary between 10 to 20 000 with a mean of 698. The number of variables used varied between 10-66 with a mean of 17. This author suggested that whilst no rules exist, consideration should be made to the question: is the dimensionality of the variables too high for the cases to be grouped? In response to this concept of dimensionality and absence of any other recommendations, Dolnicar (2002) [546] supports the rule of thumb ($n=2^k$) advocated by Formann (1984) [486] an authority on latent class analysis and used in this chapter. Furthermore, consideration was made to the fact that the prevalence of PFP has been shown to be just over 10% in the general public [7, 44] and up to 25% in more active populations such as athletes or military [42]. Recruiting to a single site, predominantly from the National Health service (NHS) has been acknowledged as being challenging [375]. Consideration was made to the feasibility of achieving

recruitment within a 24-month period. Despite, the benefit of identifying patients via the SystmOne database (see 5.3.3), these people are of working age with likely dependants e.g. children and/or elderly relatives competing for their time.

Assessment. Strict criteria were used for the selection of variables and in particular to the selection of movement domain variables which were related to the assessment task i.e. stair descent. It is known that other kinematic variables would have satisfied selection criteria based on other tasks such as running. Stair descent was selected in consultation with a patient and public involvement group and is considered to be achievable for both active and sedentary individuals thus identified subgroups are likely to represent the wider population.

Prognostic homogeneity. One of the concerns with using a cross-sectional subgrouping approach is that causal homogeneity does not necessarily imply prognostic homogeneity [358]. For example, individuals that are grouped together based on baseline features may still demonstrate a different symptom course over time or respond differently to the same treatment. This is demonstrated by the Weak group who collectively showed a reduced odds of favourable outcome (0.30 [0.07, 1.36]) but still had 46% (7/15) of members that did show a favourable outcome and two members of the group that reported a GROC score of 4. There is no pattern in the data to explain these elevated scores.

Cluster profiling. To support the interpretation and clinical profiling of the groups normative data was used. For the MRI bisect offset and MR patella tilt gender-specific thresholds were combined as the complexity of the statistics did not allow for this additional factor. The findings of Chapter 4 (3D imaging study) suggested this not good practice due to the known differences in joint shape for males and females. Nevertheless, group profiling was predominantly driven by the statistical profile and informed using the normative data (which incorporated the thresholds) so the effect of combining data should have been minimised.

5.6 Conclusions

The data presented in this chapter suggests that using modifiable clinical, biomechanical and imaging features that four data-driven diagnostic subgroups can be identified. These PFP subgroups provide the opportunity for a range of interventions to be matched accordingly. Furthermore, an improved understanding of the prognosis of subgroups could inform future service provision suggesting increased investment in the management of the

Weak group and potential disinvestment in the Flexible group, however, this warrants further investigation. Further research is required to explore whether these subgroups can be replicated in larger PFP data sets and whether treatment can be matched to the respective subgroups. Despite the likely clinical implications, this study design does not allow us to conclude that a stratified treatment approach would be effective; this will be explored within the next chapter.

Chapter 6 - The effect of targeted treatment on people with patellofemoral pain: a pragmatic, randomised controlled feasibility study

This chapter describes a randomised controlled feasibility study investigating a targeted hip strengthening intervention, matched to a subgroup with baseline hip weakness and compared to usual care management. The chapter also explores the mechanism of action for hip strengthening in a subgroup defined as 'weak'. The results from this chapter have been published as: Drew BT, Conaghan PG, Smith TO, Selfe J, Redmond AC. (2017). The effect of targeted treatment on people with patellofemoral pain: a pragmatic, randomised controlled feasibility study. BMC Musculoskeletal Disorders. 18 (1), 338. [544].

6.1 Introduction

In Chapter 5, four diagnostic subgroups were identified, in parallel to this chapter, by combining clinical, biomechanical and imaging features. It is thought that subgroups of people with PFP will benefit from being stratified and matched to specific interventions [22]. Despite successive international consensus papers since 2011 recommending subgrouping [14, 20, 34, 547], very little literature has focused on targeted therapy.

As highlighted in the literature review (Chapter 2), reduced hip muscle strength is considered an important associated feature of PFP [62]. Previous studies have reported promising clinical outcomes after prescribing hip strengthening exercises [265, 268, 271, 273, 275]. Individuals with PFP typically present with a propensity towards increased hip adduction and internal rotation during dynamic movement [548]. These kinematics have been shown to be significant predictors of PFP [549], thought to be linked to increasing patellofemoral joint contact stress [162]. Correcting this altered movement pattern is often seen as a desired outcome in interventional studies [198].

Conflicting findings surround the mechanistic effect of hip strengthening in PFP [198]. Some studies have demonstrated a post-interventional change in kinematics [275, 279], whilst others have reported no change [266, 280]. The explanation for the conflict in findings is unclear, however, the previous studies showing no kinematic change [266, 280] have included athletic cohorts and with one of the cohorts [266] clearly showing a higher than normal baseline strength. As expanded on in Chapter 2, recently PFP has been classified into three subgroups: 'strong', 'weak and tighter' and 'weak and pronated foot' [254]. Of these subgroups, 22% were classified into the 'strong' subgroup with higher knee extension and hip abduction strength. This group is unlikely to gain anything from a treatment approach based on strengthening. A strengthening intervention would likely have the greatest effect on the kinematics of those with baseline weakness.

6.2 Aims

Based on the evidence, there is a need to explore stratified treatment approaches for PFP in large trials. To ensure the success and effectiveness of such trials however, a number of feasibility questions need to be answered. The primary aim of this chapter was therefore to explore the feasibility of providing treatment matched to the specific clinical criteria of a selected subgroup compared to usual care (UC) management to inform a future stratified approach to PFP treatment. The *a priori* selection of a subgroup with a specific characteristic such as hip abductor weakness also provides the opportunity, as a secondary aim, to explore the mechanism of effect recently advocated for trials of physical interventions [550].

6.3 Methods

6.3.1 Study design

This chapter reports a pragmatic, randomised controlled feasibility study in which participants were selected from the 70 PFP participants in Chapter 5. Twenty-six participants were identified from the larger group (n=70) on the basis of having hip abductor weakness at clinical examination and were randomised into receiving either a matched treatment (MT) or UC in a 1:1 ratio. Ethical approval was obtained prior to commencement of the study (14/NE/1131). All participants completed written

informed consent prior to entering the study. The chapter has been reported in accordance with Consolidate Standard of Reporting Trials (CONSORT) [551] and Template for Intervention Description and Replication guidelines. (TiDieR) [552]. It was also registered on the ISRCTN registry (ISRCTN74560952).

6.3.2 Justification of feasibility methodology

The Medical Research Council (MRC) complex interventions guidance [553] provides a framework for developing and evaluating interventions like the stratified approach to PFP (Figure 6.1). This thesis is broadly based on the on the first three stages of the MRC complex interventions [553]. The pre-clinical phase is satisfied by Chapter 2 (literature review) and Chapter 3 (systematic review) whist Chapter 5 (PFP subgrouping) satisfies the modelling phase. The Exploratory trial phase is exploring the feasibility of a stratified intervention and forms the work in this chapter.

A debate surrounds the terms ‘pilot’ and ‘feasibility’ and how they affect the actual design [554]. The National Institute for Health Research (NIHR) separates these two designs by suggesting that the feasibility study is a piece of research done before a main study to answer ‘ Can this study be done?’ whereas the pilot study is miniature version of the main study. Eldridge *et al.* (2016) [554] suggests that, despite this clear differentiation, feasibility still remains the overarching concept of both designs and that a pilot study is often considered a subset of feasibility. The work undertaken in this chapter is reported as a feasibility study because, as advised by Lancaster *et al.* (2004) [555], rate of recruitment, acceptability, outcomes measures etc. were the primary outcomes. Furthermore, the selected subgroup (hip abductor weakness) was chosen as this could be easily identified clinically, however, this group has been further refined from the parallel work in Chapter 5. As a result, the findings of this chapter could be not be seen as miniature version of the main study but ultimately as a means of establishing the feasibility of *targeted* treatment in PFP.

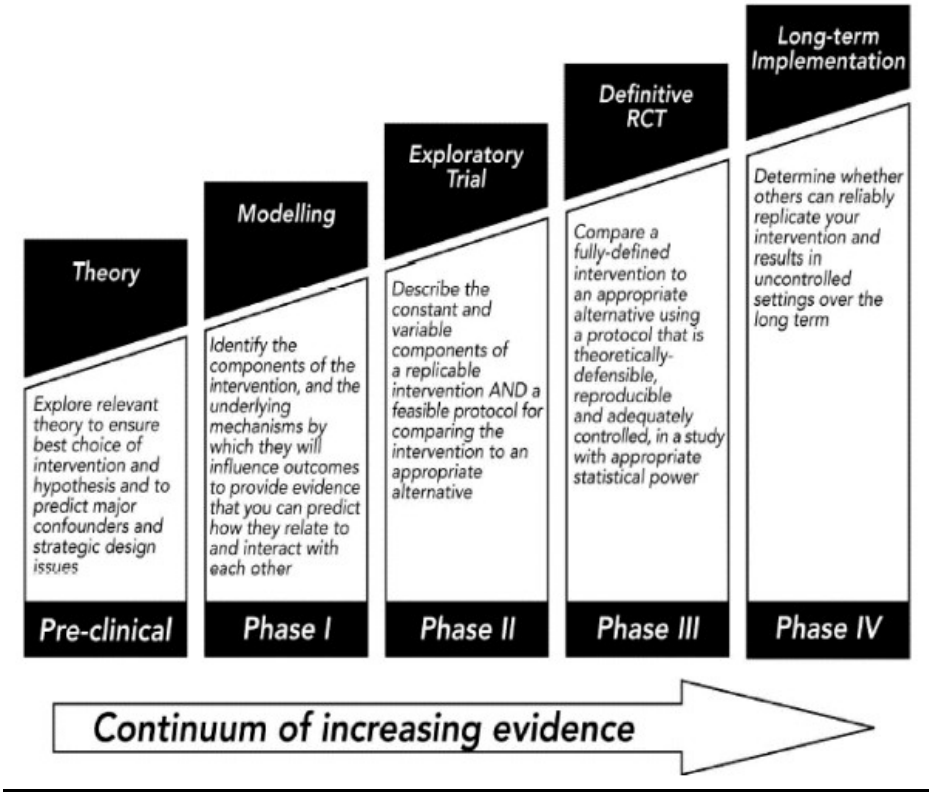

Figure 6.1: Phases of Medical Research Council (MRC) complex intervention guidance
Reprinted with permission from BioMed Central Ltd. [556]

6.3.3 Participants

Recruitment occurred between November 2014 to April 2016 from a large musculoskeletal and rehabilitation service through clinician referrals. Participants were identified from the SystmOne database (a local electronic healthcare database), posters displayed in the local hospital and a university alumni volunteers' website. Eligibility criteria were assessed both verbally and clinically to ensure that the inclusion criteria were addressed fully (Table 6.1). The most symptomatic knee, self-selected by the participant, was designated the index limb. Participants were stratified based on hip abductor strength measured using a Biodex isokinetic system 4 (IRPS Mediquipe, UK). Hip abductor weakness was based on thresholds defined *a priori* from age and gender normative data [530] (Table 6.1). The relevant normative mean minus one standard deviation (-1 SD) was used as the threshold for allocation to the "weak" stratum based on previous recommendations [260].

Table 6.1: Participant eligibility criteria

Inclusion criteria
• Aged 18-40 years
• Reported insidious (non-traumatic) onset of anterior or retropatellar knee pain;
• Pain on two or more of the following activities: prolonged sitting, kneeling, squatting, running, patella palpation, hopping, stair walking, stepping down or isometric quadriceps contraction
• Peak hip abduction torque values [530] : Females [18-29 years] ≤ 94.1 Nm; Females [30-39 years] ≤ 75.8 Nm; Males [18-29 years] ≤ 144.1 Nm; Males [30-39 years] ≤ 139 Nm
Exclusion criteria
• Presence of inflammatory arthritis; knee pain referred from the hip or lumbar spine; any history of significant knee surgery; other causes of knee pain such as, but not restricted to: meniscal pathologies, quadriceps tendon injuries, patella tendinopathy, tibial tubercle apophysitis; bursitis
• Received any treatment within the last three months including physiotherapy, podiatry etc.

6.3.4 Sample size

This chapter was designed to recruit 12 participants per group based on previous guidance for feasibility studies of this design [557]. Participants were followed up to eight weeks post-intervention as this has previously shown to be sufficient time to demonstrate an effect in PFP [265-267].

6.3.5 Randomisation

The random allocation sequence was made according to the output from a random number generator and concealed within pre-sealed, opaque envelopes [558]. All allocation and randomisation was conducted by the candidate (BD).

6.3.6 Blinding

The outcome assessor was unblinded, however, patient reported outcome measures (PROMs) were completed in a separate room with no input from the assessor. The biomechanical outcomes were acquired in accordance to a strict study protocol to minimise variation and bias [559]. Furthermore, the output from the biomechanical outcomes are automated which makes the lack of blinding less of an issue.

6.3.7 Interventions

Participants randomised to the MT group were asked to attend six supervised sessions of approximately 30 minutes in duration once per week for six weeks at a local hospital. Each week they also performed two additional sessions on non-consecutive days independently at home, with the intervening days allowing adequate rest [560]. The intervention comprised of three exercises aimed at targeting coronal, sagittal and transverse strength of the hip using resistance bands (see Table 6.2). The choice of exercises was informed from previous RCTs using hip strengthening in PFP [265, 271], discussion with clinical experts and with consideration of the exercises shown to provide the greatest isolated gluteal activity [561, 562]. The order of exercises was compiled based on the clinical experience of the candidate and advice from clinical experts supporting this chapter. Consideration was made to the recommended determinants of resistance exercise [563] when developing the intervention. The intervention aimed to gradually progress participants over six-weeks from non-weight bearing exercises to dynamic full weight bearing whilst minimising the amount of quadriceps activity to ensure that the hip strength was being targeted. The inclusion of isometric exercises was in accordance with previous hip strengthening regimes in PFP [273, 564] and recommendations from the clinical experts supporting this chapter. An exercise diary issued to participants each week provided pictures and descriptions of the prescribed exercises.

The sessions were face to face, 1:1 sessions provided by the candidate, a senior musculoskeletal physiotherapist with over nine years of clinical experience. During these sessions, participants were given education and justification of the treatment to support adherence. Each week at least one of the exercises would change with the aim of providing variation and minimising tedium [565]. The supervision sessions served as a means of ensuring both treatment fidelity and tailoring. Fidelity was ensured by checking the exercise technique and making corrections to performance prior to these being performed independently at home. Subsequent visits ensured this instruction had been correctly applied or not. Tailoring the intervention based on progressive loading was in line with current recommendations [198]. Participants were issued yellow (least resistance), red or green (most resistance) resistance tubing (66fit Ltd ™) and were allowed to take it home. To progress the load and resistance, a Borg Rate of Perceived Exertion scale (RPE) [566] was used based on the recommendations when using resistance band [567]. A RPE of >6 was considered desirable [560] and participants were monitored after a few repetitions to ensure this was what was being achieved. As participants were stratified for strength, the intervention required participants to perform ten repetitions within three

sets as recommended for strength training [560]. Participants were advised to ensure the time under tension was eight seconds (three seconds concentric, two seconds isometric hold and three seconds eccentric contraction). The selection of the hold times for the isometric exercises were chosen to cause a significant fatigue (a RPE of >6) by the end of the second set which has been suggested to be an appropriate level of stimulus for muscle strengthening [568]. Strengthening was performed on each leg alternatively providing a standardised rest between sets. Exercise diaries, issued to participants, provided a reminder of the exercises and allowed a measure of adherence. Participants were asked to document each time each exercise was performed on their diary sheet and return these at each visit.

Participants randomised to the UC group continued with the same management of their condition as they were planning to receive prior to the commencement of the study. This included planned physiotherapy, podiatry or no intervention, depending upon participant preference. The type of management and number of sessions was recorded for the UC group at follow-up.

Table 6.2: Overview of the matched treatment programme

Week	Exercise options & progression [a]				Sets & repetitions
	Basic level [b]	Moderate level	High level	Very high level	
1	Side-lying hip abduction	+ yellow band	+ red band	+ green band	3 x 10
	Double leg bridging	Single leg bridging	+ 10s holds	+ 20s holds	3 x 5
	Side-lying external rotation	+ yellow band	+ red band	+ green band	3 x 10
2	Side-lying hip abduction	+ yellow band	+ red band	+ green band	3 x 10
	Side-lying external rotation	+ yellow band	+ red band	+ green band	3 x 10
	Prone lying hip extension	+ yellow band	+ red band	+ green band	3 x 10
3	Prone lying hip extension	+ yellow band	+ red band	+ green band	3 x 10
	Hip raises on lateral step	+ yellow band	+ red band	+ green band	3 x 10
	Standing hip external rotation against wall	+ 10s hold	+ 20s holds	+ 30s holds	3 x 5
4	Hip raises on lateral step	+ yellow band	+ red band	+ green band	3 x 10
	Standing hip external rotation against wall	+ 10s holds	+ 20s holds	+ 30s holds	3 x 5
	Standing hip extension	+ yellow band	+ red band	+ green band	3 x 10
5	Standing hip extension	+ yellow band	+ red band	+ green band	3 x 10
	Lateral walking hip abduction + yellow band	+ red band	+ green band	-	10 x 10 steps
	Lateral walking hip external rotation + yellow band	+ red band	+ green band	-	10 x 10 steps
6	Lateral walking hip abduction + yellow band	+ red band	+ green band	-	10 x 10 steps
	Lateral walking hip external rotation + yellow band	+ red band	+ green band	-	10 x 10 steps
	Quadrupled bent knee hip extension	+ yellow band	+ red band	+ green band	3 x 10

a Level determined using a Borg Rate of Perceived Exertion scale (RPE)

b Using body weight unless otherwise stated

6.3.8 Outcomes

There is a lack of agreed guidelines for outcomes in feasibility studies [555]. Therefore the primary feasibility outcomes were adapted from recommendations made by Bugge *et al.* (2013) [569] and Shanyinde *et al.* (2011) [570]. The questions posed by Bugge *et al.* (2013) [569] (

Table 6.3) offered a structure in which to analyse the feasibility comprehensively. These questions satisfied the important broad groups of feasibility: process (key aspects of the study e.g. recruitment rates), resources (time and resource problems during the study), management (human and data management problems) and scientific value (treatment safety and effect) [571].

Table 6.3: Feasibility outcomes*

Methodological issues
1. Did the feasibility/pilot study allow a sample size calculation for the main trial?
2. What factors influenced eligibility and what proportions of those approached were eligible?
3. Was recruitment successful
4. Did eligible participants consent?
5. Were participants successfully randomized and did randomization yield equality in groups?
6. Were blinding procedures adequate?
7. Did participants adhere to the intervention?
8. Was the intervention acceptable to the participants?
9. Was it possible to calculate intervention costs and duration?
10. Were outcome assessments completed?
11. Were outcome measured those that were the most appropriate outcomes?
12. Was retention to the study good?
13. Were the logistics of running a multicenter trial assessed?
14. Did all components of the protocol work together?

*adapted from Bugge *et al.* (2013) [569]

6.3.8.1 Feasibility outcomes

6.3.8.1.1 Recruitment and eligibility:

Recruitment and eligibility was assessed using the rate of eligibility (%), the conversion of eligible to consent (%) and a breakdown of recruitment sources.

6.3.8.1.2 Randomisation & blinding:

The success of randomisation was assessed based on any problems being highlighted and whether the randomisation process yielded broad equality in both groups based on the difference in baseline characteristics. Intervention blinding is not possible for a physiotherapeutic intervention of this nature [572] and thus this could not be measured.

6.3.8.1.3 Adherence & acceptability:

Adherence was assessed by the adherence rate to treatment (%) using exercise diaries and adherence to appointments (%) based on the number of 'unable to attends' (UTAs). The acceptability was assessed by the attrition rate (%).

6.3.8.1.4 Outcome measures:

The outcome data was assessed based on the amount of missing data (%) found in each case report form.

6.3.8.1.5 Resources & study management:

The study management was assessed qualitatively by the candidate in terms of the logistics of running the study and the safety of all study components.

6.3.8.1.6 Treatment efficacy:

PROMs provided assessments of the efficacy for the chapter in terms of improvements in pain and disability at eight-week follow-up. The following outcomes were selected based on current Initiative on Methods, Measurement and Pain Assessment in Clinical Trials(IMMPACT) guidelines [573]:

- Pain was assessed using two numerical rating scales (NRS) with a 11-point scale for: i) the average pain in the knee over the last week ii) the worst pain in the knee over the last week.

- Function was assessed using the Anterior Knee Pain scale (AKPS), a 13-item knee specific self-reported questionnaire [534] in which 100 is the maximum achievable score and lower scores indicate greater pain and disability
- Rating of change measured on a 11-point global rating of change scale (GROC) anchored with “very much worse” to “completely recovered” [533]. Responses were dichotomised with values greater than 0 (“unchanged”) indicating an improvement.

6.3.8.2 Mechanistic outcomes

6.3.8.2.1 Kinematics

The secondary aim of this chapter was to explore the potential mechanistic effects of hip strengthening on the selected sample. A selection of biomechanical variables were selected *a priori* to prevent subsequent data mining [574]. The testing procedures are described in section 5.3.9.3. The stair set-up and procedure is shown in Figure 6.2. Stair descent was selected as this is a known aggravating factor for PFP [3], deemed challenging enough to observe a kinematic change[575] but achievable for both active and sedentary participants.

Data collected using the Vicon system described in Chapter 5 was analysed in Visual 3D (C-Motion, Rockville, Maryland). The pre-selected kinematics of most theoretical interest for explaining the proposed mechanism of action of the MT intervention were i) peak hip internal rotation angle (peak IR) of the thigh with respect to the pelvis; ii) peak hip adduction angle (peak ADD) of the thigh with respect to the pelvis; iii) total coronal hip range of movement (coronal ROM); iv) total transverse hip (ROM) (transverse ROM). These were calculated using the an X-Y-Z Cardan rotation sequence [521]. A reduction in the magnitude of all the kinematic variables measured post-intervention was considered a favourable outcome.

6.3.8.2.2 Muscle strength

A Biodex system 4 (IRPS Mediquipe, UK) isokinetic dynamometer (IKD) was used to assess muscle strength. The testing procedures are described in section 5.3.9.1. Data was collected by Biodex Advantage Software (IRPS Mediquipe, UK). The isokinetic strength measures of interest were i) peak hip abduction torque based on the maximum hip abduction torque across five repetitions; ii) peak knee extension torque based on the maximum knee extension torque across five repetitions.

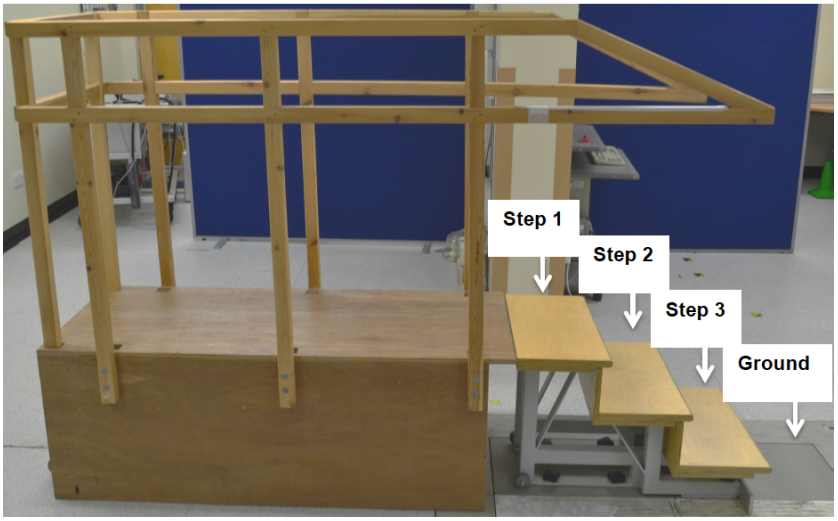

Figure 6.2: Stairs and platform
Participants descended the stairs at a self-selected speed. Each participant completed a minimum five successful stair descents. The descent was deemed successful when the index limb was placed on step two in the absence of any stumbles or hesitation. The gait cycle of interest was similar to that used in previous studies [520] between step two and ground floor. The variables of interest were captured during stance phase; between toe on and toe off on step two.

6.3.9 Statistical methods

Statistical analysis was undertaken using SPSS (version 21.0 (Armonk, NY: IBM Corp). As hypothesis testing is not advised for this size and type of exploratory study design [555], descriptive statistics along with point estimates, confidence intervals and effect sizes were presented for all PROMs and biomechanical outcomes. Within-group changes for all kinematic variables were expressed as a percentage change of the total ROM. Feasibility outcomes were described using descriptive statistics. To determine where possible, a quantifiable measure of the feasibility outcomes, predetermined thresholds were used to indicate either success or strategies required (Table 6.4). Where it was not possible to use quantitative data to demonstrate success, outcomes were reported narratively.

Table 6.4: Thresholds for feasibility outcomes

Outcome	Indicator	Successful	Unsuccessful - strategies required
Recruitment & eligibility	Conversion to consent (%)	> 90	< 90
Adherence & acceptability	Adherence rate to treatment (%)	> 90	< 90
	Adherence to appointment (%)	> 90	< 90
	Attrition rate (%)	< 10	> 10
Outcome measures	Missing data (%)	<5	>5
Treatment efficacy	Average NRS	MD > 1.5 [576]	MD < 1.5
	Worst NRS	MD > 1.5 [576]	MD < 1.5
	AKPs	MD > 8 [577]	MD < 8

MD = mean difference; NRS = numerical rating scale

6.4 Results

6.4.1 Feasibility outcomes

Figure 6.3 shows that 14 participants were randomised to MT and 12 participants to UC. Of the participants in the UC group, 55% received formal physiotherapy treatment, which may or may not have included a strengthening component. The remaining UC participants reported continuing with their normal self-management.

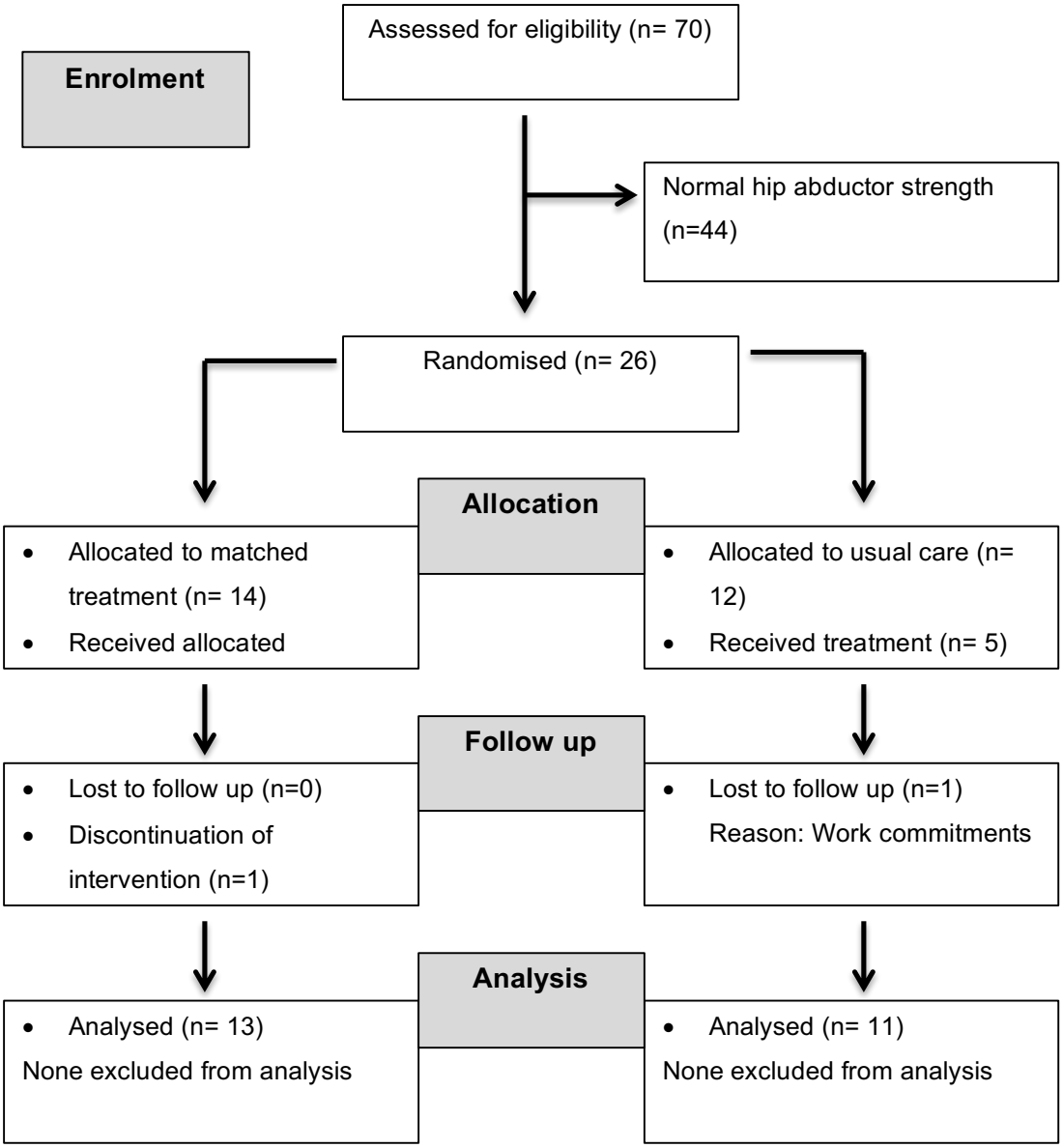

Figure 6.3: Flow of participants through the study

6.4.1.1 Recruitment and eligibility

Over 15 months, of the 70 who were screened, 26 were eligible based on hip weakness; an eligibility rate of 37.1%. All 26 eligible participants consented to the study (100% conversion to consent). Recruitment was predominantly from the SystmOne database 54% (14/26). Direct clinician referrals 15% (4/26), posters 23%

(6/26) and a university alumni online advert 8% (2/26) accounted for the other sources of recruitment.

6.4.1.2 Randomisation and blinding

No practical problems were highlighted in the randomisation procedure. The randomisation yielded reasonable equality in terms of demographics and baseline symptoms (see Table 6.5). The only notable difference was the larger number of people with bilateral knee pain in the MT compared to the UC group (64% vs. 33.3% respectively).

Table 6.5: Baseline characteristics. Values are means (SD) unless stated otherwise

Characteristics	MT group (n=14)	UC group (n=12)
Age (years)	29.1 (6.3)	29.3 (5.5)
No (%) of females	7 (50%)	8 (66.7)
Body Mass Index (kg/m^2)	25.9 (4.8)	27.7 (7.9)
Median (interquartile range) duration of knee pain (months)	30 (16.5 - 75.25)	33 (10.5 -54)
Physical activity (hours/week)	3.1 (2.6)	3.9 (3.7)
No (%) with bilateral knee pain	9 (64.3)	4 (33.3)
Anterior Knee Pain Scale	74.6 (9.9)	74.75 (12.3)
Worst pain	4.7 (1.68)	5.4 (2.3)
Average pain	3.0 (1.4)	3.9 (2.2)
No of participants who had received previous treatment (%)	10 (71.4)	9 (75.0)

6.4.1.3 Adherence and acceptability

At post-treatment (8 weeks) follow-up, two participants did not complete the study, an attrition rate of 8%. In the MT group, one participant did not attend their second treatment session and was then lost to follow up. In the UC group, one participant was unable to complete the post-treatment analysis due to work commitments. Table 6.6, illustrates that in the MT group, five participants reported a 100% adherence to treatment with an overall average adherence to treatment of 94%. Treatment sessions required rearranging on seven occasions; three times for illness, three times for work commitments and once for childcare. This shows an adherence to appointment rate of 92%. Data on adherence to treatment and appointments was not collected in the UC group.

6.4.1.4 Outcome measures

All questionnaires were completed fully without any missing data yielding a missing data indicator of 0%.

6.4.1.5 Treatment efficacy

Based on the GROC, overall the MT group demonstrated a larger improvement compared to UC group (61.54% vs. 9.09% respectively). The MT group demonstrated a greater improvement in AKP score compared to UC group (Mean Difference (MD) -6.41, 95% CI: 14.23, 1.41) with a medium effect size (*d*=0.70) (see Table 6.7). Both worst pain NRS (-0.41; 95% CI: -1.93, 1.12) and average pain NRS (-0.02, 95% CI: -1.01, 0.96) demonstrated no difference between groups.

6.4.1.6 Resources and study management

The 9% of appointments that needed rescheduling required time to make these changes. No safety issues were reported.

Table 6.6: Adherence to treatment for MT group

Participant	Week 1 (%)	Week 2 %)	Week 3 (%)	Week 4 (%)	Week 5 (%)	Week 6 (%)	Participant adherence (%)
1	100	100	100	100	100	100	100
2	100	100	100	100	100	100	100
3	100	100	100	100	100	100	100
4	100	100	100	100	66.66	33.33	83.33
5	100	100	100	100	100	100	100
6	100	100	66.66	33.33	100	66.66	77.77
7	100	100	100	100	100	100	100
8	66.66	100	100	100	100	100	94.44
9	100	100	100	66.66	33.33	100	83.33
10	100	100	100	66.66	100	100	94.44
11	66.66	100	100	100	100	100	94.44
12	100	100	100	100	66.66	100	94.44
13 *	-	-	-	-	-	-	-
14	100	100	88.88	100	100	100	98.15
Weekly adherence (%)	94.87	100	96.58	96.58	89.74	92.31	**93.87**

* Patient 13 did not attend (DNA) after the first session.

Table 6.7: Clinical outcomes. Mean (SD) unless otherwise stated

Outcome	Group	Baseline (SD)	Post Treatment (SD)	Mean difference (baseline –post) (SD)	Confidence intervals (95%)	Mean difference (MT-Control) (95% CI)	ES (*d*) (MT-Control)
AKP	**MT**	75.08 (10.09)	80.31 (8.66)	- 5.23 (10.17)	- 11.37, 0.91	- 6.41 (-14.23, 1.41)	0.70
	UC	73.64 (12.23)	72.45 (16.94)	1.18 (7.91)	- 4.13, 6.49		
Worst NRS	**MT**	4.85 (1.68)	4.62 (2.10)	0.23 (2.05)	- 1.01, 1.47	- 0.41 (-1.93, 1.12)	0.23
	UC	5.27 (2.33)	4.64 (2.16)	0.64 (1.43)	- 0.33, 1.59		
Average NRS	**MT**	3.08 (1.38)	2.46 (1.33)	0.62 (1.33)	- 0.19, 1.42	- 0.02 (-1.01, 0.96)	0.02
	UC	3.73 (2.19)	3.09 (1.87)	0.64 (0.92)	0.02, 2.28		
GROC	**MT**	[redacted]	61.5% (8/13)				
	UC		9.1% (1/11)				

AKP = anterior knee pain scale; MT = matched treatment; UC = usual care group; NRS = numerical rating scale: GROC = global rating of change scale; ES = effect size

6.4.2 Mechanistic outcomes

The results from the mechanistic outcomes are shown in Table 6.8. Evaluation of the peak torque measures showed that both MT and UC groups showed an increase in peak hip abductor torque from baseline to follow up but no evidence of a systematic effect between groups was observed (-0.63 Nm; 95% CI: -13.35, 12.09). In terms of peak knee extensor torque, the UC group showed a much larger increase yielding a MD of 7.96 Nm (95% CI -2.88, 18.79; *d* = 0.62).

The between-group comparisons of the kinematics showed that the MT group had a reduction in peak IR whereas the UC had a slight increase (1.70°; 95% CI: -2.56, 5.97) yielding a small effect size (*d* = -0.34). Both MT and UC groups showed an increase in peak ADD (-0.17° vs. -0.04° respectively). Coronal ROM showed that the MT group had a reduction whereas the UC group showed a slight increase (1.12°; 95% CI: -0.72, 3.06) yielding a medium effect size (*d* = -0.53). Transverse ROM showed an increase in both the MT and UC groups (-0.32° vs. -0.78°) respectively.

The within-group comparisons of the kinematic outcomes are presented in Figure 6.4. The MT intervention led to a reduction in peak IR of 13.1% of the total transverse ROM. There was a small reduction in coronal ROM (4.8%) whilst peak ADD and transverse ROM demonstrated a small increase. The UC group demonstrated an increase for all kinematic variables.

Table 6.8: Mechanistic outcomes. Mean (SD) unless otherwise stated

Outcome	Group	Baseline (SD)	Post Rx (SD)	Mean difference (baseline-post) (SD)	Confidence intervals (95%)	Mean difference (MT-UC) (95% CI)	ES (*d*) (MT - UC)
Hip abductor strength (Nm)	**MT**	91.02 (28.45)	99.40 (27.89)	8.39 (15.28)	- 17.62, 0.85	- 0.63 (-13.35, 12.09)	- 0.04
	UC	81.82 (31.76)	89.57 (33.43)	7.76 (14.59)	- 17.56, 2.05		
Knee extensor strength (Nm)	**MT**	91.44 (28.21)	93.12 (27.19)	1.677 (14.57)	- 10.48, 7.12	7.96 (-2.88,18.79)	0.62
	UC	94.32 (44.10)	103.95 (46.09)	9.64 (10.15)	- 16.46, - 2.82		
Peak Hip Adduction (°)	**MT**	5.74 (2.70)	5.92 (2.79)	- 0.17 (2.84)	-1.89, 1.54	- 0.14 (-3.12, 2.85)	0.04
	UC	3.70 (3.68)	3.74 (4.99)	- 0.04 (4.18)	-2.84, 2.77		
Peak Hip Internal Rotation (°)	**MT**	- 4.49 (3.26)	- 5.95 (5.26)	1.45 (4.98)	- 1.56, 4.46	1.70 (-2.56, 5.97)	- 0.34
	UC	- 6.11 (4.82)	- 5.86 (7.22)	- 0.25 (5.06)	- 3.65, 3.15		
Total coronal hip ROM (°)	**MT**	9.77 (3.62)	9.29 (2.60)	0.47 (2.19)	- 0.86, 1.79	1.12 (-0.72, 3.06)	- 0.53
	UC	10.04 (4.69)	10.74 (4.79)	- 0.70 (2.27)	- 2.23, 0.82		
Total transverse hip ROM (°)	**MT**	11.08 (2.65)	11.39 (2.08)	- 0.32 (2.49)	- 1.83, 1.19	0.46 (-1.45, 2.38)	- 0.20
	UC	9.12 (5.76)	9.90 (5.02)	- 0.78 (1.93)	- 2.08, 0.52		

MT = matched treatment; UC = usual care group; ROM = range of movement; ES = effect size

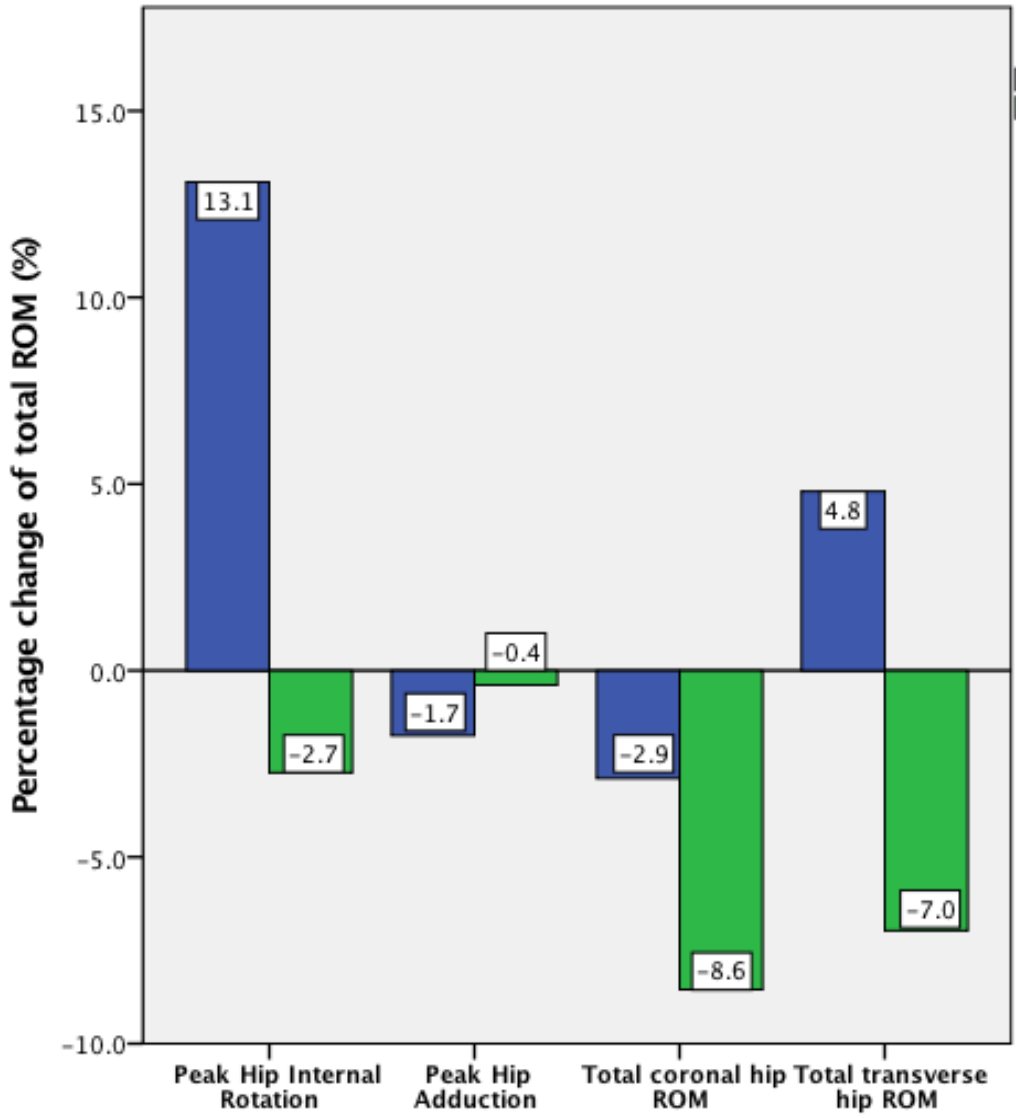

Figure 6.4: Percentage change of total range of movement in kinematic outcomes (post intervention – baseline)
Percentage (%) change in range of movement labelled in box for MT group (blue) and UC group (green)

6.5 Discussion

This chapter aimed to: i) determine the feasibility of treatment matched to the specific characteristics of selected PFP sub group and ii) explore the proposed mechanism of effect of employing strengthening in a subgroup with baseline hip weakness. A definitive randomised controlled trial (RCT) appears achievable in terms of adherence, attrition, eligibility and outcome data. Some consideration is required to develop strategies to enhance the ability to quantify clinical differences between groups. In terms of the potential mechanism of effect for hip strengthening, an improvement was shown for peak hip internal rotation angle following matched treatment.

6.5.1 Feasibility outcomes

Using our eligibility thresholds for selecting a 'weak' hip group, we predetermined that for feasibility; eligibility should reach or exceed 32%. Our observed eligibility rate of 37% provides reassurance. This eligibility rate for hip weakness is less than the 88% (at 1SD) reported by Selfe *et al.* (2016) [254] but may be explained by the current chapter measuring an isokinetic contraction rather than an isometric contraction and as a consequence the different strength thresholds applied. In order to minimise potential bias, future multicentre RCTs would also need to ensure cross-site calibration of the isokinetic systems and site visits to monitor fidelity of the strength assessment procedures.

A greater adherence to treatment has been associated with an increased probability of better outcomes in people with PFP [11]. An adherence to treatment and adherence to appointments over 90% is promising. Approximately 30% (4/13) achieved complete adherence to all treatment sessions and only 9% of appointments required rearranging. The adherence rate in this chapter is comparable to a larger RCT [268] which had a 80.3% adherence rate for a six week hip strengthening in PFP. It is anticipated that rearranging appointments for participants would be more challenging for a larger sample over multiple sites. Consequently, strategies to enhance adherence with the use of activity monitoring technology and reminder services need to be considered [578]. Unfortunately, two systematic reviews [578, 579] provide no conclusive strategies for enhancing the adherence in physiotherapy interventions. The novel use of the BandCizer™ has been explored recently in PFP [580], which is a sensor applied to the theraband that measures the stretch

and thus load applied. Employing an activity monitoring technology like this provides an objective measure of treatment adherence but also measures whether the quantity of the loading is sufficient [581].

Between group differences showed no differences for either the average or worst NRS values. This might be explained by the difference in almost a score of one in average baseline NRS, a feature that would likely be minimised in a larger full-scale trial. Previous RCTs [268, 339] have also used eligibility criteria requiring a minimum NRS score of three out of 10 pain score. Setting a minimum pain score as part of the inclusion criteria e.g. at least 3 out of 10 on a visual analogues scale, is suggested for a future RCT.

The outcome measures were fully completed with no missing data. Equality between groups was only clearly different in terms of the proportion of participants with bilateral knee pain. This is notable as bilateral knee pain has been suggested to indicate poorer prognosis [301] and may influence the clinical outcomes seen. Consideration of matching to confounding variables such as bilaterality should be considered.

The AKP score did not reach the predetermined minimal clinically important difference (MCID) of eight points [577] between groups, although there was a trend (mean difference 6.4 points) towards a meaningful benefit. AKP score evaluates functional limitations as a result of PFP and, despite the strength gains, the motor skill development needed for functional gains may require a longer intervention duration [582]. Our findings are similar however, to the only other RCT [340] to have stratified a PFP cohort which investigated a foot orthotic intervention over six weeks. Mills *et al.* (2012) [340] selected their participants based on predictors shown to predict success with foot orthotics, which included age, height, baseline pain severity and a static foot measure. They also found a significant difference between groups in terms of GROC with no differences in AKP score or VAS pain. They suggest that GROC is able to capture the multidimensional nature of PFP (characterised by pain, disability and functional limitation) compared to AKP score and VAS pain which are more one dimensional [340].

6.5.2 Mechanistic outcomes

The group receiving the matched treatment (MT) showed a reduction of approximately 13% for peak IR. This is important considering that an increase peak IR has been associated with PFP during stair descent [200, 207]. This reduction in peak IR occurred with a slight increase of their transverse ROM suggesting that following treatment, people in the MT group were

initiating stance phase in a more desirable externally rotated hip position. A reduction in peak IR and a slight increase in peak ADD are perhaps surprising considering that participants were stratified for hip abductor weakness. However, recent strength measures conducted on 501 healthy athletes [493] have shown that hip abductor and hip external rotation strength are highly correlated (r=0.66) indicating this subgroup were likely to have also demonstrated weakness into both hip abduction and external rotation. Measuring hip external rotation in addition to hip abduction strength should be considered for future clinical trials to further understand the mechanism of effect.

Both groups demonstrated similar increase in hip strength, which is likely the result of over a third of participants in the UC group being engaged in physiotherapy. Post-hoc analysis of those participants in the UC group who received *no treatment* show an increase of only 3.9 Nm in hip abductor strength. This is almost less than half the increase shown by the whole UC group (mean 7.76 Nm). In the MT group the change in hip strength was 9%, which is a comparable improvement to previous hip strengthening programmes over a similar training duration [266, 273]. There is some discrepancy around the expected gains from a hip strengthening programme [274]. This may be the result of known differences in strength gains between untrained and trained individuals [565]. PFP is recognised as being present in both very active and sedentary people [3]. In the current chapter, self-reported physical activity (hours/week) varied from as much as 0 to 10 hours per week in the MT group, which may reflect an individual's level of training. Muscular strength increases are reported to be approximately 40% in untrained to 16% in trained individuals over a four week to two year period [565].

With reference to the delivery of this intervention within a multicenter RCT, one challenge with using strength as a selection feature across multiple sites is that different IKDs devices may give varied results due to differences in calibration, testing procedures, personal and verbal feedback. In terms of the testing procedures and verbal feedback, a standard operating procedure would need to be used in order to standardise the procedures and site visits would need to be scheduled to ensure assessment fidelity. In terms of the IKD calibration, regular calibration before use would be enforced, however, no guidance exists for cross-site calibration. Cross-site calibration processes have been applied previously for other medical equipment used in research [583]. In line with procedural checks used at single sites, a set weight (provided with the IKD) could be taken to each site prior to beginning of the study and be checked along with the scheduled fidelity visits.

The increase in strength for both groups, but with only kinematic improvements seen in the MT group, might suggest that strength, on its own, cannot explain the improvement seen in peak IR. Direct comparison with previous studies [266, 275, 279, 280] remains difficult due to the differences in assessment tasks (e.g. running, stairs etc.) and the specific kinematic outcomes (e.g. peak, average angles etc.) investigated. Previous studies [266, 280] that have observed the effect of hip strengthening on running kinematics in people with PFP found no change in kinematics despite increases in hip abductor strength. Only Baldon *et al.* (2014) [275] reported changes in kinematics, during a single leg squat, following a hip strengthening programme. Yet, this training programme, did include constant feedback on lower limb alignment which suggests a more movement retraining approach[276] rather than pure strength training. It remains possible that the improvements observed in peak IR in the current chapter were the result of using progressive loading within a tailored treatment regime and selecting participants who were most likely to benefit from strengthening.

6.5.3 Limitations

This chapter presents with several limitations related to the study design, outcomes and intervention.

Study design: Firstly, in relation to the study design, the study was performed in a single centre. Future RCTs would be required to be multicentre to improve generalisability, which is anticipated to introduce new feasibility issues. The findings of the current chapter would, however, inform the documentation of standard operating procedures in terms of recruitment; data collection and intervention provision to ensure any future study could be operationalised across different geographical locations.

Outcomes: In terms of outcomes, any kinematic changes are very dependent upon the task used [575]. In the current chapter we used stairs descent which may not demanding enough to utilise these strength increases and elicit large changes in the frontal and transverse plane [584]. Stairs were chosen based on recommendations from the patient and public involvement group involved in the programme of work.

With regards to measuring strength, consideration was made to normalising strength to body weight as is done in Chapter 5. Normalising strength measurements is recognised as particularly important when comparing between different body sizes e.g. males vs. females [585]. The normative data was, stratified for age and gender thus there was some natural

anthropometric control. In this context, with the aim of identifying weakness, failing to normalise to body weight may lead to recruiting smaller people. Bazett-Jones *et al.* (2011) [585] highlights strength is commonly normalised by body mass but that this may wrongly assume a proportional relationship [586] . Instead, to reflect this variable relationship an allometric scaling component can be applied to body mass [586] informed from an allometric scaling analyses. This process may be more accurate, however, practically the complex analysis involved would have prevented participants being identified and then randomised at the same visit. Delays in randomisation may have had a detrimental impact on recruitment and retention.

In this chapter, the collective BMI, height and weight of both groups were 26.8 kg/m^2, height 1.7m, 75.9 kg respectively. As mentioned, these participants were recruited from a larger group of 70 PFP cases analysed in Chapter 5. A sensitivity analysis of the other PFP patients (n=44) whose hip strength was not weak enough to be included in this chapter show that their collective BMI, height and weight was 26.1 kg/$m^{2,}$ 1.7m, 76.5kg. This reassuringly shows that the participants are representative of the wider PFP population and that, in this case, not normalising strength to body weight does not appear to have led to the recruitment of smaller participants.

The current chapter did not blind assessors to group allocation, which could lead to potential bias [587]. Every effort was made for participants to complete PROMs in isolation and objective biomechanical outcomes were acquired in accordance with strict protocols with little chance of introducing bias. Future RCTs should make every effort to introduce outcome assessor blinding and consider measuring the level of this outcome assessor blinding [588]

Intervention: Lastly, limitations related to the intervention concern the nature of the UC group. The use of a UC group was intended to represent the heterogeneity of management available in real, daily practice and thus improve the external validity [589]. For the purposes of exploring the mechanism of hip strengthening, however, the fact that over half of the UC group received physiotherapy input potentially dilutes the between-group findings. Comparison with a control group receiving no active intervention would remedy this issue.

6.6 Conclusion

The potential benefits associated with stratification and subgrouping within PFP have been advocated since the first International Patellofemoral Pain Retreat Consensus statement [34]. This chapter suggests that targeted treatment for hip abductor weakness in people with PFP provides a greater improvement in overall function and self-reported improvement in comparison to usual care. Additionally, the improvements seen in peak IR following MT suggest this may be a plausible mechanism of effect for hip strengthening when treatment is matched to an appropriate subgroup. Strategies to enhance the ability to detect clinical difference should be considered and might be improved by selection of participants with a minimum pain score. Ultimately, a pragmatic, multicentre RCT with a sufficiently powered cohort appears achievable and should be conducted to determine the clinical and cost-effectiveness of a stratified treatment approach versus usual care for people with PFP.

Chapter 7 - Discussion, future directions and conclusions

7.1 Thesis synopsis

This thesis is concerned with the stratification of PFP and specifically describes: the structural associations to PFP; the subgroups that exist within PFP; the natural prognosis of these PFP subgroups; and the feasibility of targeting PFP subgroups within a clinical trial. The observations made in this thesis in Chapters 3, 4, 5 and 6 are summarised as follows:

Chapter 3 - Which patellofemoral joint imaging features are associated with patellofemoral pain? Systematic review and meta-analysis

The aim of this chapter was to establish which PFJ imaging features are associated with PFP compared to those without PFP. Forty studies describing 1043 people with PFP and 839 controls were included.

- This systematic review demonstrated that PFP is associated with a number of PFJ imaging features, in particular, MRI bisect offset and CT congruence angle. Furthermore, some of the features identified, including MRI bisect offset and MRI patella tilt, have been shown to be modifiable with conservative interventions.
- A sensitivity analysis showed the effect of full weight bearing (FWB) on imaging outcomes and demonstrated that under FWB, differences between a PFP and a healthy control group increased.
- Limitations within the literature were found in terms of the participant selection and outcome assessment. Poor reporting of the recruitment source and failure to report the reliability of the imaging assessment were considered largely responsible for these conclusions.

Chapter 4 - Patellofemoral joint morphology of middle aged people with patellofemoral pain measured using 3D MRI quantitative technology: data from the Osteoarthritis Initiative

The aim of this chapter was to investigate whether 3D equivalents of commonly used PFJ imaging features and overall 3D bone shape differ between people with and without PFP and to explore whether the overall 3D bone shape differed between genders. This analyses included 115 people with PFP and 438 without PFP.

- This cross-sectional analysis from a large cohort demonstrated that no single or combined differences were found between a group with and without PFP for either the overall 3D shape or thirteen 3D imaging features.
- However, significant differences were found between men and women, with the overall 3D shape able to classify gender with a 90% level of accuracy.
- None of the 3D PFJ imaging features could be used to inform Chapter 5, however, this study highlights the importance of gender when interpreting imaging data.
- The findings suggest that previous outcomes using 2D methods may have been the result of mixed gender cohorts and thus future studies should ensure that adjustments are made for gender and that this is considered when interpreting findings.

Chapter 5 - The development of data-derived subgroups in patellofemoral pain using modifiable clinical, biomechanical and imaging features

The aim of this chapter was to identify diagnostic subgroups within PFP cohort using modifiable clinical, biomechanical and imaging features and to explore the prognosis of these subgroups at 12 months follow up. This longitudinal cohort study with cross-sectional analysis included 70 people with PFP.

- This two-stage, SPSS TwoStep cluster analysis identified four subgroups: Strong group, Pronation & Malalignment group, Weak group and Flexible group.
- The prognosis of these subgroups at 12 months showed, with reference to the Strong group, that the Weak group was the least likely to report a favourable outcome and the Flexible most likely. However, there were no statistical significance between groups in odds of a favourable outcome.

- Targeting treatment by matching interventions according to the subgroup baseline characteristics should be explored.
- Further research is required to see if subgroups can be replicated in larger PFP data sets and whether these subgroups can show different long-term outcomes.

Chapter 6 - The effect of targeted treatment on people with patellofemoral pain: a pragmatic randomised controlled feasibility study

The aim of this pragmatic randomised controlled feasibility study was to explore the feasibility of treatment matched to a specific clinical characteristic of a selected PFP subgroup compared to usual care (UC) management and to explore the mechanism of action for hip strengthening when targeted to a group defined as 'weak'. This study included 26 people with PFP; 14 in the matched treatment (MT) group and 12 in the UC group.

- The finding from the feasibility study indicates that a larger study is achievable in terms of high rates of adherence, retention and conversion to consent.
- Treatment efficacy showed promising findings in terms of self-reported improvement (using a GROC scale); however, strategies to enhance the ability to detect clinical differences are indicated.
- The mechanism of action for hip strengthening when targeting a group with defined hip weakness appears to be related to improvements in peak hip internal rotation.

7.1.1 Overall summary

In summary, this thesis has demonstrated that imaging features, in particular MRI features (measured in 2D) may be associated with PFP. Once converted into their 3D equivalents, however, the same differences were not observed in a large, older group with PFP. Using this knowledge of imaging features combined with clinical and biomechanical features four subgroups were identified in the PFP population with the Weak group the least likely to report a favourable recovery at long term follow up. The feasibility of targeting PFP subgroups has shown positive outcomes in terms of conversion to consent, missing data, attrition and adherence to both treatment and appointments whilst also highlighting the need for strategies to enhance the ability to detect clinical differences. On the whole, this indicates that a future multicentre RCT focusing on the stratification of PFP is achievable.

7.2 Thesis discussion

The findings derived from this thesis are supplemented below by an update of the extant literature since Chapter 2 was written. This has been presented within themes that have arisen from the overall findings of this thesis: imaging in PFP; subgrouping in PFP, prognosis of PFP subgroups and stratifying treatment in PFP. Details regarding the study design are included to offer methodological guidance to pre-existing shortfalls in the current literature.

7.2.1 Imaging in PFP

The findings of this thesis (Chapter 3) indicate that when loading status and flexion angle are controlled for, a number of MRI features are associated with PFP. In contrast, the study in Chapter 4 which converted common MRI features into their 3D equivalent found no difference between groups with and without PFP.

The apparent contrasting findings within this thesis could be the result of the 3D features providing greater accuracy in Chapter 4 (using the centroid as the reference point). This would suggest that all previous studies (and those included in the systematic review in Chapter 3) may have been influenced by inconsistencies in joint positioning or lack a standard reference point [438]. Alternatively, it may be because the findings of Chapter 4 were obtained in an older population and therefore may not reflect the results of younger population more synonymous with PFP.

The thesis findings are primarily based on malalignment-type features. None of the identified studies in the systematic review in Chapter 3 (which subsequently informed the measures in Chapter 4) investigated semi-quantitative MRI features. Semi-quantitative features focus more on structural abnormalities of the PFJ and have been proposed to be potentially important in PFP [590]. However, the few recent studies [590, 591] to have investigated semi-quantitative features have shown only minimal differences between groups with and without PFP. The only differences to have been noted are in the extensor mechanism and medial plica [591] but these findings from this recent study could simply be result of including a broader AKP group or the lack of covariate adjustment. As suggested recently [590], the failure to detect differences may lie in the fact that other clinical or biomechanical features e.g. kinematic, strength factors etc. might need to be present in order for the imaging features to cause pain [590].

Overall, based on the findings of this thesis imaging features, in particular MRI measures, should be considered for future clinical trials and utilised more in clinical practice as they have been demonstrated to be associated to PFP (Chapter 3), highlighted as being potentially modifiable (Chapter 2 and 3) and shown to differ across PFP subgroups (Chapter 5). However, it is recommended that these conclusions should be re-evaluated once further research has investigated the 3D features in a younger PFP population.

7.2.2 Subgrouping in PFP

Work has begun to explore subgrouping and stratification within PFP [254, 366, 374] but the findings of this thesis represent the first time that clinical features have been integrated with modifiable biomechanical and modifiable imaging features to identify PFP subgroups. The findings of this thesis show that four subgroups can be identified from a PFP cohort: 'Strong', Pronation & Malalignment', 'Weak' and 'Flexible' subgroups.

These subgroups show many similarities to the subgroups identified by Selfe *et al.* (2016) [254]. The addition of the imaging features, in particular MRI bisect offset, was an important factor for determining the 'Pronation & Malalignment' subgroup whereas the kinematic features showed no statistical difference across subgroups and thus appear a less important factor. Both the findings of the work described in this thesis and the Selfe *et al.* (2016) [254] study identified a 'Strong' group which supports the theory that a PFP subgroup exists with normal strength. This challenges current practice with a recent survey of UK physiotherapists [542] highlighting that 98% of physiotherapists prescribe closed chain strengthening exercise. This 'Strong' subgroup is unlikely to benefit from further strengthening and probably requires alternative interventions.

A recent editorial on stratification in musculoskeletal pathology [485] suggest that the overall aim of stratification should be to focus on cross-domain combinations. This is essentially the outcome of Chapter 5, however, due to the lack of supporting evidence for their inclusion, psychological and lifestyle factors were not included in the cluster analysis although were reported descriptively. A recent systematic review [592] on the psychological features present in PFP suggest that catastrophizing, anxiety and depression are correlated to physical function. However, correlation can only provide a strength of the linear relationship and is unable to account for the latent constructs involved in these complex relationships

[469]. It is also still clear that there is a lack of consistency in the psychological constructs investigated both in terms of the nomenclature and the outcome measures used. This would still limit the inclusion of these constructs in Chapter 5 (PFP subgrouping). In terms of lifestyle factors, body mass index (BMI), not directly investigated before in PFP, has recently been shown to be higher in PFP compared to healthy controls [593]. With reference to the subgroups in Chapter 5, the potential for overweight PFP subgroups is demonstrated with two of the subgroups the Pronation & Malalignment group and the Weak group showing mean BMI values that would be classed as overweight (> 25 kg/m^2). BMI remains a viable treatment target for future studies in PFP as weight reduction programmes have significantly improved those with knee OA [594].

Overall the subgroups identified in this thesis represent groups derived statistically using a unique combination of biomechanical, clinical and imaging features. Being intentionally based on modifiable features has ensured that subgroups are more likely to have clear treatment targets e.g. the Weak group is likely to respond to strengthening exercises etc. Based on recent evidence more consideration should be given to including psychological and lifestyle factors as these subgroups are investigated in larger data sets.

7.2.3 Prognosis of PFP subgroups

The prognostic analyses in this thesis (Chapter 5) suggests that despite finding no formal statistical difference, there was a trend towards the Weak subgroup being the least likely and the Flexible subgroup most likely to report a favourable outcome. It is speculated that the Weak subgroup who also report the most disability showed less improvement because both reduced knee strength and poor baseline function are known to lead to a poor long-term response to treatment in PFP [298, 301, 510]. Alternatively, the Flexible subgroup who had the highest physical activity might represent a group transiently exceeding joint loading and who are able to improve with simple rest and load management [595].

Only one other study has explored the long-term prognosis of PFP subgroups [596]. Similar to Chapter 5, Keays *et al.* (2016) [596] also found no statistical difference between PFP subgroups for pain and disability at follow up. These results and the thesis findings suggest that there are minimal differences in the long-term outcomes for PFP subgroups. It is worth noting however, that the unorthodox study design and the inclusion of participants with a

mean age of 45 years (range 13-82 years) in the Keays *et al.* (2016) [596] study precludes a direct comparison with the findings of the prognostic analysis in this thesis. Furthermore, both findings are based on low statistical power due to the relatively small sample sizes used and thus the prognostic outcomes of PFP subgroups remains inconclusive. Prognostic outcomes also remain largely the selection of covariates for statistical testing [597]. A recent systematic review [483] examined all the studies which investigated prognostic factors in PFP found that the only prognostic factor which was consistently identified was 'duration of symptoms' [483] thus supporting the selection of covariates used in Chapter 5.

Overall, the differences in long-term outcomes for PFP subgroups remain equivocal, although the inclusion of recognised covariates for the prognostic analyses in this thesis strengthens the conclusions that can be drawn from the findings. The trends towards an unfavourable outcome would suggest that more attention should be made to identifying the Weak group and research prioritised to identify the best management for this subgroup.

7.2.4 Stratifying treatment in PFP

The most recent International PFP consensus statement [115] again highlights the importance of stratification and targeted treatment. The results of this thesis demonstrated that in people with PFP selected for hip abductor weakness and targeted with progressive, isolated hip strengthening exercises, nearly two thirds reported an improvement at 8 weeks compared to fewer than ten percent of people receiving usual care. This improvement appears related to changes in lower limb kinematics (a reduction in peak internal rotation angle).

The few previous studies stratifying treatment are highlighted within this thesis but recently another study has been published [598] which uses similar methodology to Chapter 6 (feasibility study). Mølgaard *et al.* (2017) [598] investigated the effect of foot-targeted exercise and orthoses when patients were selected for an increased calcaneal valgus angle. Their findings also show that targeted treatment led to a significant improvement in pain (at four months) but no difference between groups at 12 months. Mølgaard *et al.* (2017) [598] selected covariates for analysis according to any baseline differences. Adjusting for baseline differences is discouraged by current guidelines [551] because what is important is the magnitude of the effect on the outcome, rather than the significance between groups [599].

Ill-informed adjustments may weaken the conclusions from this recent study [598] but their findings do corroborate the effectiveness of this treatment approach.

Overall, the positive outcomes shown by the feasibility study in this thesis and the similar outcomes observed by previous [340] and recent studies [598] supports the benefit of stratified treatment in PFP. Taken together these findings highlight the need for a future definitive multicentre RCT on targeted treatment in PFP and the need to ensure that improvements are maintained long term (≥ 12 months).

7.2.5 Study design in PFP studies

Since writing the narrative literature review in Chapter 2, the latest patellofemoral pain consensus statement [115, 547] has been published following the biennial International Patellofemoral Pain Research Retreat in 2015. This statement has, for the first time, clearly defined PFP as *" pain around or behind the patella, which is aggravated by at least one activity that loads the patellofemoral joint during weight bearing on a flexed knee (e.g. squatting, stairs, running, jumping)" [115].* This is important as the findings of Chapter 2 & 3 show that eligibility criteria vary in terms of the number of activities that need to reproduce pain; potentially limiting the comparison between cohorts. The PFP cohort used in Chapter 5 & 6 recruited participants which were aggravated by *two* activities. Theoretically, using a less strict definition of *one* aggravating activity should make recruitment easier. However, *post hoc* analysis of the potential participants that failed screening (n=47) in Chapter 5 suggests that none of these failed due to the number of aggravating activities (i.e. only reporting one activity). This suggests that people with PFP are typically affected by more than one aggravating activity. Ultimately, this more recently accepted definition will provide consensus for future eligibility criteria in PFP research and strengthen any future comparisons between studies.

The feasibility of targeted treatment in PFP was the focus of Chapter 6. The intervention duration of six weeks was based on previous literature and usual care, and not standardised in order to be pragmatic. Pragmatic trials aim to investigate interventions that will be useful within an everyday clinical setting, to maximise applicability [600]. Based on a recent survey into current UK practice of PFP [542], there may be some iterative improvements needed for the methods used in Chapter 6. In this survey of UK based physiotherapists [542], the majority of respondents would see their patients for 3-6 sessions; similar to the 6 sessions

used in Chapter 6. However, the result of this survey [542] show that a large variation exists for the typical length of treatment from 3 weeks to 6 months. The weekly sessions used in Chapter 6 may represent a more intense physiotherapy intervention compared to standard UK clinical practice. Careful consideration needs to be made of this detail when designing future interventional studies that are intended not only to reflect current clinical practice but also to be implemented successfully.

The improvement seen in Chapter 6 was made using a six week treatment period so there remains the possibility that a longer treatment period may have led to more people reporting a favourable outcome. The targeted treatment delivered by the Mølgaard *et al.* (2017) [598] study employed double the treatment period (3 sessions per week during a 12 week period) compared to Chapter 6 (3 sessions per week during a 6 week period) but despite this they only showed an successful outcome in 60% (12/20) (versus 67% in Chapter 6) receiving their matched treatment. This could contradict the theory that a longer treatment period in Chapter 6 would have led to more people reporting a favourable outcome. Instead, in addition to the hip strength, targeting the other characteristics of the subgroup (e.g. knee strength or physical activity) refined in Chapter 5 might improve the number of favourable outcomes reported.

The encouraging feasibility outcomes shown in Chapter 6 supports the future design of a definitive randomised controlled trial focused on stratified treatment in PFP. Based on the evidence above, this could be enhanced by: careful consideration of the clinical eligibility and the use of the current recommended criteria [115, 547]; allowing a more pragmatic approach to the length of the treatment period which reflects current practice; and targeting more refined subgroups (based on more than one characteristic) – as identified in Chapter 5 (PFP subgrouping).

7.3 Limitations of the current work

The limitations of each chapter have been discussed in detail in the relevant chapters. To contextualise the main findings of the thesis an overview of the thesis limitations concerning the research design and outcome measures is provided here.

7.3.1 Sample size

The sample sizes of the preceding chapters within this thesis varied considerably. The sample size used in Chapter 4 benefited from a pre-existing data set in which to select relatively large comparative groups and the sample size used in Chapter 6 was deemed appropriate for a feasibility design. Chapter 5 relied on a recruitment of an age group 18-40 years old. Prior consideration was made to the difficulties with recruitment and retention of this 'emerging adulthood' group [601] following discussion with experts. This age group are known to be experiencing many life changes including graduating, entering the job market, having children, moving house etc. [601] which may limit their recruitment availability. As a result, a realistic recruitment target of n = 77 was considered achievable for a single-centre site for patient with PFP. A larger sample size would enable more substantial clusters and reduce the potential for spurious groupings [602]. An attempt to address this issue was made by using a two-stage clustering process which is considered a dimensionality reduction technique [364] as described in Chapter 5. The impact that the sample size has on the final clusters will only become apparent once validation of these subgroups are made on other cohorts of people with PFP [254, 364] as suggested in Chapter 5.

7.3.2 Treatment duration

A treatment duration of 6 weeks was used in Chapter 6 based on previous literature. The intention in this chapter was to explore the feasibility in terms of recruitment, adherence and retention. As a result, a standardised treatment duration was selected in order not to introduce another independent variable. It is plausible that both clinical and mechanistic outcomes might require a longer duration for these outcomes to show a greater effect. One of the potential issues for a longer treatment duration, however, could be its deleterious effect on adherence [603] and the increase in resources e.g. staff costs, time etc.

7.3.3 Non-weight bearing MRI

As mentioned in the preceding chapters, the MRI data used in Chapter 4 and 5 were based on supine, non-weight bearing scan MRI protocols. The sensitivity analysis, shown in Chapter 3, demonstrates that this will have an impact on imaging outcomes including bisect offset and patella tilt. Weight bearing and loaded scans were not used in this thesis as a weight bearing MRI scanner was not available and no protocols existed within the department to safely load the knee. Consideration was made to this potential issue when understanding the findings in Chapter 4 and adjustments were made to the normative MRI

data for interpretation of the subgroups in Chapter 5. These adjustments should have minimised the impact of procedural variation.

7.3.4 Marker based motion capture

One of the inherent problems with marker-based motion capture analysis is the likely systematic error introduced by skin artefact and the test-retest reliability of such data [604]. The industry standard CAST marker set up was applied, which has previously shown high test-rest reliability [605, 606]. A systematic review of three dimensional kinematic gait measurements [607] suggest that the reliability of sagittal and coronal kinematic measures are on average greater than 0.7 (coefficients of multiple correlations or interclass correlation coefficients). This would suggest that the peak knee flexion angle used in Chapter 5 and the peak hip abduction angle and total coronal hip ROM used in Chapter 6 are adequately reliable measures. Caution is advised, however, when interpreting the peak hip rotation angle results in both Chapter 5 and 6 as the same review showed that overall hip transverse rotation demonstrated the lowest reliability and the widest variation, compared to other planes. Nonetheless, they [607] did identify at least five studies that showed a small error indicating that a greater reliability value for hip transverse measurement is achievable. [607]. Previous literature shows that hip transverse plane kinematics during stair descent for PFP patients yields an promising between-day reliability of ICC 0.75 with a SEM of 4°[188]. One of the potential factors influencing the retest reliability is the known discordance between skin markers and the movement actually occurring in the underlying bone [604]. A comparison of skin markers with surgical attached bone-pin markers demonstrated this discrepancy [604] and highlights the need to consider this fact when interpreting these findings clinically. Nevertheless, the alternative bone–pin markers are not a viable option for any of the experiments conducted in thesis due to their invasive nature.

7.4 Directions for Future Research

7.4.1 Imaging in PFP

Imaging in PFP appears to be important as structural differences have been reported in this thesis to exist between those with and without pain. However, the contrast in findings between the extant literature using 2D measures (Chapter 3) and careful 3D analysis (Chapter 4) which removes many projectional problems which confound this area adds

substantially to the debate on the importance of imaging in PFP. To address these issues, firstly the 3D PFJ features developed in Chapter 4 need to be explored in a younger population with PFP and investigated longitudinally to see whether changes in pain and disability are related to changes in shape. Likewise, if followed up for long enough these 3D PFJ features could provide a useful biomarker for elucidating the potential link between PFP and PFOA. Finally, the effect of conservative interventions such as hip strengthening or foot orthoses on structural features should be explored, similar to the investigation by Chiu *et al.* (2012) [166] which has been discussed in the preceding chapters.

7.4.2 Link between PFP and PFOA

Experts believe that PFP may represent a precursor to the development of PFOA [5]. In the subgrouping in Chapter 5, the only published MRI definition for PFOA [523] was applied, and thus osteophytes were scored accordingly. This definition was developed from a Delphi consensus panel [523] that considered the presence of an osteophyte important enough to be one of the two components of their agreed definition (a definite osteophyte and partial or full thickness cartilage loss). A recent systematic review [608] including 85 studies on the prevalence of PFOA concluded that the prevalence of BML and cartilage defect was 32% and 52% respectively in two symptomatic populations, one over and one under 50 years. This was based on cartilage and BMLs only as the osteophyte component was omitted and thus the prevalence of PFOA may be overestimated in this review [608]. In support of this osteophyte omission, the original Delphi study [523] does state that what constitutes a ‘definite osteophyte’ within the PFJ needs to be further delineated. Therefore future research is required to explore the characterisation of a PFJ osteophyte and agree on the exact definition of PFOA.

The findings from Chapter 5 suggest that the Pronation & Malalignment group showed the most MRI features (osteophytes & cartilage loss) associated with PFOA. Understanding the possible link between PFP and future PFOA continues to be of great importance to the PFP research community [5] and, as highlighted in section 7.4.1, recent studies are beginning to develop suitable outcomes and biomarkers to identify this relationship. A recent study showed that those that reported having adolescent AKP were 7.5 times more likely to develop symptomatic PFOA later in life [609] which supports previous findings [38] . One of the major problems with these retrospective designs is the approximately 50 years of recall needed. Ultimately, this question will only be answered by prospective longitudinal studies

with data captured from individuals at regular time points from adolescence to late adulthood. Ancillary research is also essential to ensure that appropriate techniques and biomarkers e.g. imaging features are available to identify the potentially subtle transition into an osteoarthritic state [610].

7.4.3 Subgrouping in PFP

While this thesis used robust methods to identify subgroups, consideration should be given to including additional features for which evidence has developed since the conception of the thesis. As discussed, there was a paucity of research on psychosocial factors and thus none of these factors satisfied the variable selection criteria. Firstly, future research should consider refining subgroups using variables such as catastrophizing, fear avoidance etc. Emerging evidence around somatosensory function has also indicated that both adults [611-613] and adolescents [614, 615] with PFP have significantly reduced pain pressure threshold (PPT). As a result, future research is warranted to see how pain pressure thresholds might relate to the subgroups identified from this thesis

Investigating the prognosis of the subgroups suggested in Chapter 5 is a key strength of this thesis. Crepitus is a commonly reported feature of PFP [3] which has previously been under investigated in terms of its effect on patient outcomes. A recent qualitative investigation [616] on the effect of crepitus on health beliefs highlighted that crepitus may ultimately lead to fear avoidance behaviour which as noted by the author *"are in direct conflict with the usual aims of a physiotherapy intervention"* [616]. Therefore it remains possible that the presence and/or negative beliefs held about crepitus may be confounding the prognostic outcomes seen. Further research is required to investigate the impact of crepitus on physiotherapy outcome and consideration should be made to adjusting for presence of crepitus during analyses.

7.4.4 Mechanism of action for PFP interventions

Without the knowledge of how exercise enhances pain and function in PFP, then future therapeutic interventions cannot be optimised [617]. Future PFP interventions should be required to consider the task and function they aim to improve. During even more demanding tasks such as running and stairs descent, the range of hip movement is minimal with the muscles instead required to provide a quick, efficient stabilising function [618]. Accordingly, one novel mechanism recently explored the rate of force development (RFD) [618]. It has been shown in people with PFP that impairments in RFD exist during hip

abduction and hip extension but vary between the levels of torque. These results suggest that future research should explore the effect of a more explosive, power based rehabilitation on clinical outcomes and subsequent kinematics.

The effect of education on patient outcomes is relatively under investigated in PFP [377]. Education did form part of the first session of the intervention in Chapter 6, however, this included more a justification of the proposed treatment rather than formal education on managing PFP. A recent RCT [545] investigating runners with PFP demonstrated that education alone provided significant improvement in all pain outcomes (VAS during running, at worst and usual) and the addition of either gait retraining or exercise provided no additional benefit. As expected, education alone resulted in no differences in mechanical outcome including strength measures and running mechanics. This raises the question of what the mechanism of action might be for education in this group. To answer this question qualitative research is needed to understand how people with PFP are benefiting from education. Additionally, this concept of education alone needs to be explored within the general population with PFP as the content and the delivery is likely to differ from runners.

7.4.5 Stratified PFP interventions

The findings of this thesis have shown that targeting treatment in PFP is feasible. This provides an important foundation for designing a future definitive multicentre RCT to investigate the clinical and cost effectiveness of targeted treatment in PFP. Further research should be directed towards discovering interventions that match to the novel subgroups identified in this thesis and thus allowing each subgroup to be individually targeted, in particular those subgroups less likely to improve with standard treatment. In these future studies, outcomes need to be measured at short, medium and long term time points. They also need to include a mechanistic assessment to provide knowledge on the mechanism of effect and allow the subsequent refinement of the matched interventions.

7.5 Addressing the central hypothesis

The central hypothesis of this thesis was that **“improved subgrouping of people with PFP based on modifiable features will enable stratification and targeting of interventions”.** The programme of work within this thesis used a set of linked research projects designed to

examine and address the gaps within the current literature and inform the development of subgroups within the PFP population using modifiable features. The subsequent feasibility study (Chapter 6) demonstrated the potential success of target treatment and supports the future evaluation of stratified treatment, utilising these PFP subgroups, beyond this PhD thesis. Overall this would suggest that the findings of the thesis support the central hypothesis.

7.6 Conclusion

PFP is a multifactorial condition with inconsistent treatment outcomes and is considered by many to be a potential precursor to future PFOA. Subgroups are thought to exist in PFP but currently this theory remains under-investigated. The work described in this thesis has improved the understanding of the PFJ structure and identifies a number of features associated with PFP. The advanced 3D quantitative imaging analysis highlights the impact that inconsistent imaging position and mixed gender analysis may be having on these morphological findings. Aligning this structural knowledge to existing biomechanical and clinical features enabled the identification of four subgroups: ‘Strong’,’ Pronation & Malalignment’, ‘Weak’ and ‘Flexible’. At 12 months follow up, these subgroups showed a trend towards different odds of reporting a favourable outcome. This suggests that attention should be focused on identifying and targeting treatment at the subgroups less likely to improve or subgroups more amenable to a specific intervention. Targeting PFP subgroups as demonstrated in this work appears to be feasible in terms of conversion to consent, missing data, attrition and adherence. Now that novel subgroups have been identified and targeted treatment shown to be conceptually feasible; future research should aim to investigate this stratified approach within adequately powered multicentre clinical trials.

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