Risk factors for patellofemoral pain: a systematic review & meta-analysis

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ABSTRACT

Background: Patellofemoral pain (PFP) is a prevalent condition commencing at various points throughout life. We aimed to provide an evidence synthesis concerning predictive variables for PFP, to aid development of preventative interventions.

Methods: We searched Medline, Web of Science and SCOPUS until February 2017 for prospective studies investigating at least one potential risk factor for future PFP. Two independent reviewers appraised methodological quality using the Newcastle-Ottawa Scale. We conducted meta-analysis where appropriate, with standardised mean differences (SMD) and risk ratios calculated for continuous and nominal scaled data.

Results: This review included 18 studies involving 4818 participants, of whom 483 developed PFP (heterogeneous incidence 10%). Three distinct subgroups (military recruits, adolescents, recreational runners) were identified. Strong to moderate evidence indicates that age, height, weight, body mass index (BMI), body fat and Q-angle are not risk factors for future PFP. Moderate evidence indicates that quadriceps weakness is a risk factor for future PFP in the military, especially when normalised by BMI (SMD -0.69, CI -1.02, -0.35). Moderate evidence indicates that hip weakness is not a risk factor for future PFP (multiple pooled SMD's, range -0.09 to -0.20), but in adolescents, moderate evidence that higher hip abduction strength is a risk factor for future PFP (SMD 0.71, CI 0.39,1.04).

Conclusions: This review identifies multiple variables that do not predict future PFP, but identifies that quadriceps weakness in military recruits and higher hip strength in adolescents are risk factors for PFP. Identifying modifiable risk factors is an urgent priority to improve prevention and treatment outcomes.

Keywords: Patellofemoral Pain, Risk Factors, Incidence, Systematic Review.

INTRODUCTION

Patellofemoral pain (PFP) is characterised by diffuse retropatellar or peripatellar symptoms throughout activities that load the knee during flexion, such as running, stair descent or squatting.[1] PFP is a common pathology in both adolescents[2] and adults[3], with prevalence in the general population reported as 22.7%[4]. However, the factors associated with PFP development and the incidence of the condition across a variety of populations remains under-evaluated due to limited prospective data and the homogeneity of studied populations.[4,5] As PFP is reported to be common across the lifespan and may be the precursor to patellofemoral osteoarthritis,[6,7] an improved understanding of the factors associated with the development of PFP and its incidence in differing populations is essential to prevent symptoms.

With the incidence of PFP reported to be high[4] and symptoms persisting despite evidence based interventions,[8] further investigation is warranted to understand variables that are associated with PFP development and subsequently deliver evidence based preventative strategies. In 1992, Van Mechelen et al. presented a theoretical model described as the 'sequence of prevention' for sports injury (see figure 1) to guide injury prevention development.[9] With the incidence of PFP defined across populations[4] (stage one), an understanding of the aetiology (stage two) is required to identify the variables associated with the pathology development. A variable associated with future pathology should be manipulated as a preventative strategy within a randomised controlled trial (RCT) (stage 3). The effectiveness of the implemented strategy should then be appraised by re-examining the incidence within a specific population (stage 4).

In 2012, Lankhorst et al. completed a systematic review of risk factors for PFP,[10] which identified a clear association between low knee extension strength and subsequent risk of PFP irrespective of measurement method, but no associations with other investigated variables. This is likely due to the low number of included studies (n=7), high data heterogeneity and data pooling being possible for just 13 out of 137 identified variables, but was unexpected given the known crossectional

association between PFP and multiple pathomechanical variables such as muscle function and lower limb biomechanics.[11]

Additional risk factors for future PFP have been identified within other systematic reviews using data from single studies. Increased navicular drop in military recruits[12], greater peak hip adduction during running[13] and increased forces at foot level during both walking and running[14] all increase the risk of future PFP. Whilst these findings are statistically significant, the absence of data pooling and the small to moderate effect sizes limit the impact and clinical applicability. Given the number of subsequently published prospective studies, an updated systematic review on this topic is now appropriate.

The aim of this systematic review was to provide researchers and clinicians with evidence synthesis concerning predictive variables for PFP to aid the development of preventative interventions. The review was designed to synthesise the available evidence at stage two (aetiology) of the Van Mechelen model (see figure 1), and enable addressing stage three (preventative strategies). A secondary aim was to determine the incidence of PFP within the included studies, both as a heterogeneous condition and within specific homogenous cohorts. Specific objectives were to (i) establish prospective links between all investigated variables and future PFP (ii) identify risk factors and PFP incidence specific to individual homogenous cohorts and (iii) inform future studies on PFP prevention.

METHODS

This systematic review was completed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[15] and was registered with PROSPERO prior to completion of the initial search (registration number: CRD42016049327).

Search strategy

The search terms used by Lankhorst et al[10] were duplicated for the purpose of this review. The following terms were used for PFP: arthralgia AND knee joint OR anterior knee pain OR (patell* OR femoropatell* OR femoro-patell* OR retropatell*) AND (pain OR syndrome OR dysfunction). Key words used for risk factors were: risk factor OR association OR relative risk OR odds ratio. We searched MEDLINE, Web of Science and SCOPUS from inception until February 2017, limited to papers published in the English language involving human subjects. In addition, a citing reference search was undertaken using Google Scholar up to March 2018, as well as hand searching of the reference lists of identified papers.

Inclusion criteria

A single investigator (AR) exported all studies identified by the search strategy to Endnote X7 (Thomson Reuters, Philadelphia). Eligibility criteria were adapted from the original review of Lankhorst et al,[10]: (i) studies involving male or female subjects who developed subsequent PFP (synonyms including retropatella pain, chondromalacia or anterior knee pain); (ii) at least one variable investigated as a risk factor for PFP; and (iii) prospective study designs. Studies with less than 20 PFP subjects were excluded by the review of Lankhorst et al,[10] but were included in this review. Two independent authors (BN and NL) reviewed all abstracts to determine eligibility. Full texts were screened where eligibility could not be determined by the abstract alone and any discrepancies were resolved at a consensus meeting.

Quality assessment

Methodological quality and risk of bias of included studies was determined by combining the Newcastle-Ottawa scale[16] (NOS) and appraising the number of events per variable[17]. Eligible studies were independently rated by two authors blind to study authors and institutions (SL and NL), with discrepancies resolved at a consensus meeting. The NOS contains 8 categories relating to methodological quality and each study was given an eventual score out of a maximum of 8 points. A score of 0-3 points equated to a low quality (LQ) study, a score of 4-6 points equated to a moderate quality (MQ) study, with a score of 7-8 points required for a study to be given a score of high quality (HQ). In addition, HQ or MQ studies were reduced to either MQ or LQ respectively if they were determined to have a high risk of bias as a result of having less than 10 PFP participants for each investigated variable within their total sample.[17] Inter-rater reliability of the NOS was calculated using the percentage agreement method.

Data extraction

Data related to study characteristics were initially extracted from all included studies by one author (AR) and subsequently reviewed by a second author (BN). This included participant numbers (separating those who developed PFP and those who did not), characteristics of these groups (such as population), study duration and publication details (author and year). A second author (BSN) extracted all data pertaining to potential risk variables to be included in the meta-analysis. Means and standard deviations (SD) were extracted for variables of interest, which included (but were not limited to: anthropometrics and demographics (such as sex, body mass index (BMI)), biomechanical variables (such as kinematics and kinetics) and muscle function (such as strength or onset timing).

Statistical methods

Statistical analyses were undertaken using Review Manager 5.0 (The Cochrane Collaboration, Copenhagen, Denmark). Analyses were completed initially by one author (BSN) and subsequently reviewed by a second author (SDL). Means and SD's were extracted for continuous scaled variables and used to calculate a standardised mean difference (SMD) with 95% confidence intervals (CI's). Calculated individual or

pooled SMDs were categorised as small (0.59), medium (0.60–1.19) or large (1.20) [18]. For nominal scaled variables, raw counts of injured and uninjured participants (e.g. PFP incidence in males and females) were extracted and used to calculate risk ratios (RR) with 95% CI's, with a small effect indicated by a RR ≥ 2.0 and a large effect by a RR ≥ 4.0.[18]

Data were pooled and has been presented as both a heterogeneous PFP cohort and further pooled by specific homogeneous subgroup where possible. Where methodological approaches between studies were deemed to be adequately comparable a meta-analysis was performed and the level of statistical heterogeneity for pooled data were determined using I^2 statistics (heterogeneity defined as I^2 > 50%, $p < 0.05$). Random effects were used due to the variation in study methods and populations, and the typically low number of studies, therefore reducing the possibility of a type 1 error.[19]

Only outcomes incorporating data from a minimum of two studies are presented in the main body of the review, due to the risk of reporting inappropriate levels of evidence where data pooling were not possible.

Evidence based recommendations

Levels of evidence were assigned to each calculated variable (pooled or otherwise) as described by Van Tulder et al,[20] which incorporate both assigned methodological quality of included studies and statistical outcomes:

Strong evidence: Pooled results derived from three or more studies, including a minimum of two high quality studies that are statistically homogenous.

Moderate evidence: Pooled results derived from multiple studies, including at least one high quality study, that are statistically heterogeneous; or from multiple moderate or low quality studies which are statistically homogenous.

Limited evidence: Results from one high quality study or multiple moderate or low quality studies that are statistically heterogeneous.

Very limited evidence: Results from one moderate or low quality study.

RESULTS

Search results

The search resulted in 3044 titles and abstracts being identified for screening. Following the removal of duplicates and studies that did not meet the inclusion criteria of the review, 18 studies involving a total of 4818 participants were included (see figure 2),[21-38] 483 of whom went on to develop symptoms consistent with PFP. This is indicative of a heterogeneous PFP incidence of 10%. Extracted data relating to study characteristics are presented in table 1.

Table 1: study characteristics

Study	NOS Score	Risk of Bias	Cohort	PFP	Sample Size	Incidence	Study Duration (Months)
Boling (‘09) [21]	H	L	Military (USA)	40 (M=16, F=24)	1319	3%	30
Duvigneaud (‘08) [25]	H	L	Military (Belgium)	26 (F=26)	62	42%	1.5
Finnoff (‘11) [26]	MD	H	Adolescents (USA)	5 (M=2, F=3)	98	5%	9
Foss (’12) [22]	H	L	Adolescents (USA)	39 (F=39)	262	15%	24
Herbst (‘15) [27]	H	L	Adolescents (USA)	38 (F=38)	255	15%	12
Hetsroni (‘06) [28]	H	L	Military (Israel)	61 (M/F=?)	405	15%	4
Holden (‘15) [29]	MD	H	Adolescents (Ireland)	8 (F=8)	76	11%	24
Luedke (‘16) [30]	MD	H	Recreational Runners (USA)	3 (M=1, F=2)	57	5%	12
Milgrom (‘91) [23]	MD	L	Military (Israel)	60 (M=60)	390	15%	3.5
Myer (‘10) [31]	MD	H	Adolescents (USA)	14	145	10%	9

Noehren (‘13) [32]	MD	H	Recreational Runners (USA)	15 (F=15)	400	3%	24
Ramskov (‘15) [33]	H	L	Recreational Runners (Denmark)	24 (M=10, F=14)	629	4%	12
Thijs (‘07) [36]	H	L	Military (Belgium)	36 (M=25, F=11)	84	43%	1.5
Thijs (‘08) [34]	MD	H	Recreational Runners (Belgium)	17 (M=1, F=16)	102	17%	2.5
Thijs (‘11) [35]	MD	H	Recreational Runners (Belgium)	16 (F=16)	77	21%	2.5
Van Tiggelen (‘04) [37]	H	L	Military (Belgium)	31 (M=31)	96	32%	1.5
Van Tiggelen (‘09) [24]	H	L	Military (Belgium)	26 (M=26)	79	33%	1.5
Witvrouw (‘00) [38]	MD	H	Adolescents (Belgium)	24 (M=11, F=13)	282	9%	24

Key: H=high; MD=moderate; L=low; M=male; F=female, USA=United States of America

Subgroups and PFP incidence

Three distinct subgroups were identified during the data extraction process. There were a total of seven studies involving military recruits,[21,23-25,28,36,37] six studies involving adolescents[22,26,27,29,31,38] and five studies involving recreational runners.[30,32-35] Studies involving military recruits involved a total of 2435 participants, 280 of whom went on to develop PFP, reflective of an incidence of 11% (range 3%-43%). Studies involving adolescents involved a total of 1118 participants, 128 of whom went on to develop PFP, reflective of an incidence of 11%

(range 5%-15%). Studies involving recreational runners involved a total of 1265 participants, 75 of whom went on to develop PFP, reflective of an incidence of 6% (range 4%-21%).

Quality assessment

After evaluation of study quality and risk of bias,[16,17] a total of 9 HQ studies [21,22,24,25,27,28,33,36,37] and a further 9 MQ studies were identified.[23,26,29-32,34,35,38] Mean percentage agreement for the NOS was 95% (range 89%-100%), indicating high inter-rater reliability (see table 2). The questions with the lowest percentage agreement were question 5 (does the study control for any confounding variables) and question 7 (was follow up time clearly defined).

Table 2: individual study NOS scores and percentage agreement

Question	The cohort was truly or somewhat representative of a typical PFP cohort		Selection of the non-PFP cohort was from the same community as the PFP cohort		Ascertainment of PFP was made via secure record OR structured interview		Demonstration that outcome of interest was not present at start of study		Cohorts were comparable on the basis of the design OR confounders controlled for		Assessment of outcome was independent OR linked to medical records		Follow up time was clearly defined		Follow up was adequate (all subjects accounted for or ≤20% attrition)	
	R1	R2	R1	R2	R1	R2	R1	R2	R1	R2	R1	R2	R1	R2	R1	R2
Boling (‘09) [21]	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**N**	**N**	**Y**	**Y**
Duvigneaud (‘08) [25]	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**?**	**Y**	**Y**	**Y**	**N**	**Y**	**Y**
Finnoff (‘11) [26]	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Foss (‘12) [22]	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Herbst (‘15) [27]	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Hetsroni (‘06) [28]	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**N**	**N**	**N**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Holden (‘15) [29]	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**N**	**N**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Luedke (‘16) [30]	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**N**	**Y**	**Y**
Milgrom (‘91) [23]	**N**	**Y**	**N**	**Y**	**Y**	**Y**	**Y**	**Y**	**N**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Myer (‘10) [31]	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Noehren (‘13) [32]	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**N**	**?**
Ramskov (‘15) [33]	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Thijs (‘07) [36]	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Thijs (‘08) [34]	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**N**	**N**
Thijs (‘11) [35]	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Van Tiggelen (‘04) [37]	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**?**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Van Tiggelen (‘09) [24]	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Witvrouw (‘00) [38]	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**N**	**N**
Percentage Agreement	94%		94%		100%		100%		89%		100%		89%		94%	

Key: R=rater; Y=yes; N=no; ?=unable to determine

Anthropometrics and demographics

Data pooling were possible for seven individual variables (sex, height, weight, BMI, body fat percentage, age and limb length).

Sex

There is moderate evidence from three HQ[21,33,36] and four MQ[26,30,34,38] studies that sex is not a risk factor for future PFP (I^2=73%, RR 1.33, CI 0.76,2.34) (see figure 3). This outcome does not change when pooling data only for military subjects (moderate evidence, I^2=91%, RR 0.82, CI 0.25,2.74), adolescents (moderate evidence, I^2=0%, RR 1.23, CI 0.38,2.07) or recreational runners (moderate evidence, I^2=76%, RR 3.08, CI 0.59,15.99). Whilst subgroup data pooling were non-significant, six of the seven included studies that reported data on sex had a greater proportion of females in their PFP cohort,[21,26,30,33,36,38] the highest of which was observed in the recreational runner subgroup.

Height

There is strong evidence from five HQ[24,25,33,36,37] and seven MQ[23,26,29,31,34,35,38] studies that height is not a risk factor for future PFP (I^2=0%, SMD -0.08, CI -0.21,0.05) (see figure 4). This outcome does not change when pooling data for only military recruits (strong evidence, I^2=41%, SMD -0.15, CI -0.42,0.12), adolescents (moderate evidence, I^2=0%, SMD 0.06, CI -0.23,0.35) or recreational runners (moderate evidence, I^2=0%, SMD -0.15, CI -0.43,0.13).

Weight

There is strong evidence from five HQ[24,25,33,36,37] and seven MQ[23,26,29,31,34,35,38] studies that weight is not a risk factor for future PFP (I^2=0%, SMD 0.02, CI -0.11,0.16) (see figure 5). This outcome does not change when pooling data for only military recruits (strong evidence, I^2=0%, SMD 0.05, CI -0.12,0.23), adolescents (moderate evidence, I^2=28%, SMD -0.10, CI -0.46,0.25) or recreational runners (moderate evidence, I^2=0%, SMD 0.10, CI -0.18,0.37).

BMI

There is strong evidence from four HQ[22,25,33,37] and three MQ[26,34,35] studies that BMI is not a risk factor for future PFP (I^2=33%, SMD 0.10, CI -0.12,0.32) (see figure 6). This outcome does not change when pooling data for only military recruits (moderate evidence, I^2=65%, SMD 0.09, CI -0.48,0.65), adolescents (moderate evidence, I^2=75%, SMD 0.23, CI -0.72,1.18) or recreational runners (moderate evidence, I^2=0%, SMD 0.15, CI -0.13,0.43).

Body fat percentage

There is moderate evidence from one HQ study[22] and 1 MQ study[38] that body fat percentage is not a risk factor for future PFP in adolescents (I^2=0%, SMD -0.13, CI -0.40,0.13) (see figure 7). This variable was not investigated in either military recruits or recreational runners.

Age

There is strong evidence from three HQ[24,33,36] and five MQ studies[29,31,32,34,35] that age is not a risk factor for future PFP (I^2=13%, SMD 0.06, CI -0.13,0.25) (see figure 8). This outcome does not change when pooling data for only military recruits (moderate evidence, I^2=0%, SMD -0.05, CI -0.36,0.27), adolescents (limited evidence, I^2=80%, SMD 0.04, CI -0.98,1.07) or recreational runners (moderate evidence, I^2=0%, SMD 0.16, CI -0.09,0.40).

Limb length

There is limited evidence from two MQ studies[23,26] that limb length is not a risk factor for future PFP (I^2=0%, SMD -0.01, CI -0.28,0.25). This variable was not investigated in recreational runners and no data pooling were possible within any individual subgroups.

Lower limb alignment

Data pooling were only possible for static Q-angle. Limited evidence from one HQ[21] and one MQ study[35] indicates that Q-angle is not a risk factor for future

PFP (I^2=0%, SMD 0.06, CI -0.22,0.33) (see figure 9). No data pooling were possible for any identified subgroup.

Strength measures

Quadriceps strength

When pooling all available data for quadriceps strength, regardless of cohort or measurement method, there is strong evidence that quadriceps weakness is a risk factor for future PFP (moderate evidence, I^2=65%, small SMD -0.32, CI -0.42, -0.22).

Data pooling were only possible for the military subgroup for all quadriceps strength measures. There is moderate evidence from two HQ studies[25,37] that quadriceps weakness is a risk factor for future PFP when measured with an isokinetic dynamometer concentrically at 60˚/second (I^2=0%, moderate SMD -0.66, CI -0.99,-0.32) (see figure 10a) or concentrically at 240˚/second (I^2=17%, small SMD -0.49, CI -0.85,-0.12) (see figure 10b).

For normalised quadriceps strength measured with an isokinetic dynamometer, there is moderate evidence from two HQ studies[25,37] that quadriceps weakness is a risk factor for future PFP when normalised by body mass at 60˚/second (I^2=0%, moderate SMD -0.61, CI -0.94,-0.28) (see figure 10c) or at 240˚/second (I^2=0%, small SMD -0.53, CI -0.87,-0.20) (see figure 10d). When normalised by BMI, moderate evidence remains quadriceps weakness is a risk factor for future PFP when measured at both 60˚/second (I^2=0%, moderate SMD -0.69, CI -1.02,-0.35) (See figure 10e) and 240˚/second (I^2=0%, small SMD -0.51, CI -0.84,-0.18) (see figure 10f).

For quadriceps strength measured isometrically with a hand-held dynamometer (HHD), there is moderate evidence from one HQ[21] and one MQ study[23] that quadriceps strength is not a risk factor for future PFP (I^2=82%, small SMD -0.25, CI -0.74,0.25).

Hamstrings strength

There is moderate evidence from two HQ studies[25,37] that hamstring strength is not a risk factor for future PFP in the military when measured with an isokinetic dynamometer concentrically at 60˚/second (I^2=0%, SMD -0.09, CI -0.42,0.24) or 240˚/second (I^2=0%, SMD -0.10, CI -0.43,0.22). This variable was not investigated in either adolescents or recreational runners.

Hip strength

There is moderate evidence from one HQ[21] and two MQ studies[26,35] that hip extension (I^2=0%, SMD -0.18, CI -0.44,0.09) (see figure 11a), hip internal rotation (I^2=20%, SMD -0.09, CI -0.42,0.23) (see figure 11b) and hip external rotation (I2=0%, SMD -0.17, CI -0.43,0.10) (see figure 11c) strength, measured isometrically with a HHD, are not risk factors for future PFP. There is also limited evidence from two MQ studies[26,35] that both hip adduction strength (I^2=0%, SMD -0.20, CI -0.67,0.28) (see figure 11d) and hip flexion strength (I^2=52%, SMD -0.08, CI -0.82,0.67) (see figure 11e) are not risk factors for future PFP when measured with a HHD. No data pooling were possible for any identified subgroup for these strength measures.

There is moderate evidence from two HQ[21,27] and two MQ[26,35] that hip abduction strength is not a risk factor for future PFP (I^2=86%, SMD 0.25, CI -0.38,0.88) (see figure 12a) when measured isometrically with a HHD. When data were pooled for the adolescent cohort, there is moderate evidence from one HQ[27] and one MQ study[26] that increased hip abduction strength is a risk factor for future PFP (I^2=0%, SMD 0.71, CI 0.39,1.04) (see figure 12b) when measured with isometrically a HHD. Data pooling were not possible for the military or recreational runner subgroups.

Biomechanics

Dynamic knee valgus angle

Moderate evidence from one HQ study[21] and one MQ study[29] indicates that knee valgus angle during a jump land task is not a risk factor for future PFP (I^2=99%,

SMD 4.17, CI -4.19,12.53). No data pooling were possible for any identified subgroup.

Foot kinetics

One HQ study[36] and one MQ study[34] investigated foot kinetics during walking and running respectively. When these data were pooled, moderate evidence indicates no significant associations between time to peak force at any investigated region of the foot, which included the hallux, the metatarsal heads and the medial/lateral heel.

DISCUSSION

This systematic review aimed to provide a synthesis of the evidence concerning predictive variables for PFP development. Despite the inclusion of 11 additional prospective studies and 55 additional variables when compared to the previous review of Lankhorst et al,[10] high data heterogeneity and a limited ability to pool data remained. Just two predictive variables, lower isokinetic quadriceps strength in the military and higher isometric hip abduction strength in adolescents, were identified. Heterogeneous incidence of PFP was 10%, with incidence also identified within the specific homogenous cohorts of military recruits (11%), adolescents (11%) and recreational runners (6%).

Isokinetic quadriceps weakness is predictive of future PFP in a military cohort[25,37] and this is in agreement with the previous review of Lankhorst et al.[10] Unfortunately, the strength of this evidence has not changed, as no new prospective studies using an isokinetic dynamometer to measure quadriceps strength have been published since 2011. New data from two studies investigating isometric quadriceps strength in military cohorts,[21,23] not included by Lankhorst et al, demonstrated no significant association with future PFP. Whilst this could be interpreted as conflicting evidence, it could be that isometric muscle testing may not be sensitive enough to identify military recruits at risk of PFP. This limits the clinical applicability of these results, as isometric testing with a HHD is a more accessible tool for clinicians to use when measuring muscle strength.

Quadriceps weakness was not identified as a risk factor for future PFP in an adolescent group[27]. Whilst this further validates the importance of investigating risk factors within homogenous groups, it is also important to consider the implications of these findings in relation to risk modification interventions within differing populations. A similar disparity between adult and adolescent populations has been observed cross-sectionally, with no differences in hip or knee strength between adolescents with PFP and a group of asymptomatic controls matched for both age and sex[39], but significant strength deficits in adults with PFP compared to control groups.[40,41] These findings offer indications as to why rehabilitation

programmes have been shown to be of significant benefit in adults with PFP,[42,43] but are of only limited additional benefit to education alone in adolescents.[44]

In contrast to the quadriceps data, hip muscle weakness, regardless of test direction, was not a risk factor for future PFP in military recruits or recreational runners. However, higher baseline isometric hip abduction strength predicts future PFP in adolescents[26,27]. Herbst et al[27] make the suggestion that greater hip abduction strength could be the result of increased eccentric hip abductor demands due to increased peak hip adduction during dynamic tasks. When pooling data from both military and adolescent cohorts, dynamic knee valgus angle was also not a risk factor for future PFP. However, Holden et al[29] reported higher knee valgus displacement in adolescent females who develop PFP (mean difference 7.79˚). Despite these reported kinematic deficits, hip strength and altered kinematics during dynamic tasks are consistently negatively correlated,[45] contradicting this hypothesis.

A more plausible explanation for the association between increased isometric hip abduction strength and future PFP in young adolescents is a high level of physical activity, common within this age group.[46] The mean age of the Herbst et al[27] cohort is 12.7 years and may therefore have higher lower limb muscle strength as a consequence of high physical activity levels. It may be that lower limb muscle strength correlates with duration of symptoms in adolescents, with strength deficits presenting later in life when symptoms persist and if activity levels subsequently reduce.[39] As a result, it is sensible to question the role of increasing muscle strength in adolescent cohorts as a preventative measure. It is advised that future prospective studies both report and stratify for activity levels when investigating the association between strength variables and future PFP.

In 2011 Coppack et al[47] reported a significant reduction in PFP risk after completion of a quadriceps and gluteal strengthening programme when compared to a non-specific control group. It is surprising that an exercise intervention designed to increase quadriceps strength has not been investigated further, given both level one[10] and two[47] evidence identifying quadriceps weakness as a preventative

treatment target. Whilst increased baseline hip abduction strength increases the risk for future PFP in adolescents, this is potentially a surrogate indicator of activity level. Given the positive results of education and load management interventions in this population,[44] we suggest prioritising these interventions in future in order to reduce the incidence of PFP in adolescents.

Multiple variables often described as risk factors for future PFP, perhaps due to strong associations in cross-sectional studies, were not found to be so in this meta-analysis. Participant height, weight, BMI, body fat percentage, age and Q-angle did not predict future PFP in any cohort. The recent systematic review of Hart et al[48] reports a cross-sectional association between high BMI and both PFP and patellofemoral osteoarthritis (PFOA) in adults, again perhaps due to a reduction in activity levels after symptom development.[49] Higher BMI was not a risk factor for future PFP in either adults or adolescents, nor was a high BMI linked to intervention outcomes in participants with PFP.[48] Whilst these data question the biologically plausible suggestion that a high BMI contributes to PFP development, it remains plausible that high BMI may influence treatment outcomes and this suggestion requires further investigation.[48]

Using data from the work of Boling et al,[21] the previous 2012 review of Lankhorst et al[10] reported that females are at a higher risk of developing PFP within the military (odds ratio: 2.23, 95% CI 1.16,4.10). Our results are in conflict with this, with pooled data from 7 studies[21,26,30,33,34,36,38] identifying no significant links between the female sex and PFP development. Pooling data for the identified individual subgroups is also non-significant, but a greater proportion of females developing subsequent PFP was reported in six of the seven studies. The largest proportion of females occurs amongst the recreational runner subgroup and this is in fact statistically significant when a fixed-effects model is used for the meta-analysis, meaning observed results are most likely a result of selection bias in source studies. However, given the low number of studies (n=3) and high heterogeneity, a fixed-effects model is inappropriate and increases the chance of sustaining a type I error.[19] Given the absence of a causal association between the female sex and

future PFP, the frequent bias towards the female sex in trial sampling and the need to control for sex as a confounder may not be necessary.

The heterogeneous incidence of PFP was 10% in this review, demonstrating that PFP affects up to one in ten persons across multiple populations. The recent systematic review of PFP incidence and prevalence by Smith et al[4] identified a wide range of PFP incidence amongst military recruits (9.7-571.4 cases per 1000 person-years), which is similar to the incidence range identified by this review (3-43%). The variance is likely explained by the four studies[24,25,28,37] included in this review not included by Smith et al,[4] and the three studies included by Smith et al[4] not eligible for inclusion within this review.[47,50,51] The incidence range for PFP within adolescent cohorts are identical (5-15%), despite two studies from this review[22,29] not being included by Smith et al.[4]

Limitations and future research directions

This review is not without limitations, which must be considered when interpreting the results. There is currently no accepted method for determining study methodological quality or ascertaining risk of bias. Whilst the NOS is advocated by the Cochrane Group, it is possible that using a different quality appraisal tool may have yielded different levels of eventual evidence. It should also be considered that the NOS does not have a component pertaining to the reliability of exposure data collection, focussing more on the validity of outcome data. As per the PRISMA guidelines[15] three databases were searched, but is it also possible that increasing the number of databases searched may have yielded additional studies for inclusion. An attempt was made to mitigate this risk by completing a citing reference search in Google Scholar in addition to hand searching the reference lists of included studies. It must be stressed that incidence data has been calculated only from included studies, and the addition of other epidemiology studies that do not fit the inclusion criteria of this review would have affected the figures reported. It was also not possible to express incidence data relative to a timeframe given the high heterogeneity observed between included studies.

Some included studies provided data that were not suitable for inclusion in a meta-analysis (i.e. no mean/SD or raw counts) and efforts to obtain raw data directly from study authors were unsuccessful. Despite the addition of 11 new studies, ability to pool data were limited, which is partly attributable to the 116 individual variables investigated across the 18 included studies that could not be pooled. A total of 8 studies[26,29-32,34,35,38] failed to adhere to the rule of 10,[17] that is ensuring a minimum of 10 PFP events for each variable of interest, resulting in a high risk of bias and reduced methodological quality.

Given the lack of associations identified by this review (pooled data or otherwise), it is sensible to suggest that perhaps the current body of research is not placing appropriate focus on variables of interest. Altered hip and knee kinematics during running are known to have moderate to strong cross-sectional association with PFP,[13] yet there remains just one prospective investigation of these variables in female runners only.[32] There is also an emerging evidence base surrounding the association between psychological variables and PFP, with levels of anxiety, depression, catastrophising and fear of movement reported to be elevated in persons with PFP by a recent systematic review.[52]

The prospective studies included within this review have sought to detect an association between single variables and risk of PFP. The inherent limitation of this approach is the inability to consider interactions between multiple variables. Consequently, research needs to move towards a complex systems approach to better understand injury aetiology.[53] Rather than endeavouring to identify a singular causal factor, studies should be designed to investigate the interactions between a 'web of determinants' that are likely to be non-linear in nature.[54] This approach has significant methodological challenges and requires the use of a statistical learning approach such as a Bayesian network.[55] Examples of variables that could fit into a web of determinants for PFP from the published literature include muscle strength (quadriceps and gluteal), hip/knee kinematics, activity levels/sporting workload and psychosocial measures (see figure 13).

No variable included within this systematic review identified a link with future PFP in recreational runners. High peak hip adduction is known to be associated with future PFP in female runners,[32] and future studies should further explore the causal associations between lower limb kinematics and PFP. Whist not presented in a fashion that allowed for data pooling, increased eccentric hip abduction strength reduces the risk of future PFP in recreational runners[33]. The distinct limitation of this study design is that no guidance was given to the included runners regarding training frequency or intensity which is likely to be a significant confounder, as more aggressive run volume progressions increase the risk of injury development.[56]

CONCLUSION

Quadriceps weakness, measured using an isokinetic dynamometer and whether or not normalised to either bodyweight or BMI, is a risk factor for future PFP in military recruits and should be investigated as a preventative strategy in a future RCT. Whilst higher hip abduction strength is a risk factor for future PFP in adolescents, this may simply be a composite of activity level. Overall, our understanding of what contributes to the development of PFP is inadequate and requires further scientific exploration, though the relationship between given variables and PFP risk is likely to be both complex and individual.

Reference List

1. Crossley KM, Stefanik JJ, Selfe J, et al. 2016 Patellofemoral pain consensus statement from the 4th International Patellofemoral Pain Research Retreat, Manchester. Part 1: Terminology, definitions, clinical examination, natural history, patellofemoral osteoarthritis and patient-reported outcome measures. British journal of sports medicine 2016;**50**(14):839-43 doi: 10.1136/bjsports-2016-096384[published Online First: Epub Date]|.
2. Rathleff MS, Skuldbøl SK, Rasch MN, Roos EM, Rasmussen S, Olesen JL. Care-seeking behaviour of adolescents with knee pain: a population-based study among 504 adolescents. BMC musculoskeletal disorders 2013;**14**(1):225
3. Boling M, Padua D, Marshall S, Guskiewicz K, Pyne S, Beutler A. Gender differences in the incidence and prevalence of patellofemoral pain syndrome. Scandinavian journal of medicine & science in sports 2010;**20**(5):725-30
4. Smith BE, Selfe J, Thacker D, et al. Incidence and prevalence of patellofemoral pain: A systematic review and meta-analysis. PloS one 2018;**13**(1):e0190892 doi: 10.1371/journal.pone.0190892[published Online First: Epub Date]|.
5. Callaghan MJ, Selfe J. Has the incidence or prevalence of patellofemoral pain in the general population in the United Kingdom been properly evaluated? Physical therapy in Sport 2007;**8**(1):37-43
6. Thomas MJ, Wood L, Selfe J, Peat G. Anterior knee pain in younger adults as a precursor to subsequent patellofemoral osteoarthritis: a systematic review. BMC musculoskeletal disorders 2010;**11**:201 doi: 10.1186/1471-2474-11-201[published Online First: Epub Date]|.
7. Crossley KM. Is patellofemoral osteoarthritis a common sequela of patellofemoral pain? British journal of sports medicine 2014;**48**(6):409-10 doi: 10.1136/bjsports-2014-093445[published Online First: Epub Date]|.
8. Lankhorst NE, van Middelkoop M, Crossley KM, et al. Factors that predict a poor outcome 5-8 years after the diagnosis of patellofemoral pain: a multicentre observational analysis. British journal of sports medicine 2016;**50**(14):881-6 doi: 10.1136/bjsports-2015-094664[published Online First: Epub Date]|.
9. Van Mechelen W, Hlobil H, Kemper HC. Incidence, severity, aetiology and prevention of sports injuries. Sports medicine 1992;**14**(2):82-99
10. Lankhorst NE, Bierma-Zeinstra SM, van Middelkoop M. Risk factors for patellofemoral pain syndrome: a systematic review. The Journal of orthopaedic and sports physical therapy 2012;**42**(2):81-94 doi: 10.2519/jospt.2012.3803[published Online First: Epub Date]|.
11. Powers CM, Witvrouw E, Davis IS, Crossley KM. Evidence-based framework for a pathomechanical model of patellofemoral pain: 2017 patellofemoral pain consensus statement from the 4th International Patellofemoral Pain Research Retreat, Manchester, UK: part 3. British journal of sports

medicine 2017;**51**(24):1713-23 doi: 10.1136/bjsports-2017-098717[published Online First: Epub Date]|.
12. Neal BS, Griffiths IB, Dowling GJ, et al. Foot posture as a risk factor for lower limb overuse injury: a systematic review and meta-analysis. Journal of foot and ankle research 2014;**7**(1):55 doi: 10.1186/s13047-014-0055-4[published Online First: Epub Date]|.
13. Neal BS, Barton CJ, Gallie R, O'Halloran P, Morrissey D. Runners with patellofemoral pain have altered biomechanics which targeted interventions can modify: A systematic review and meta-analysis. Gait & posture 2016;**45**:69-82 doi: 10.1016/j.gaitpost.2015.11.018[published Online First: Epub Date]|.
14. Dowling GJ, Murley GS, Munteanu SE, et al. Dynamic foot function as a risk factor for lower limb overuse injury: a systematic review. Journal of foot and ankle research 2014;**7**(1):53 doi: 10.1186/s13047-014-0053-6[published Online First: Epub Date]|.
15. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Annals of internal medicine 2009;**151**(4):W65-94
16. Wells G, Shea B, O'connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: h ttp. ohri. ca/programs/clinical_epidemiology/oxford. asp (accessed June 2014) 2008
17. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. Journal of clinical epidemiology 1996;**49**(12):1373-79
18. Hume P, Hopkins W, Rome K, Maulder P, Coyle G, Nigg B. Effectiveness of foot orthoses for treatment and prevention of lower limb injuries : a review. Sports medicine (Auckland, N.Z.) 2008;**38**(9):759-79
19. Brockwell SE, Gordon IR. A comparison of statistical methods for meta‐analysis. Statistics in medicine 2001;**20**(6):825-40
20. van Tulder M, Furlan A, Bombardier C, Bouter L. Updated method guidelines for systematic reviews in the cochrane collaboration back review group. Spine 2003;**28**(12):1290-9 doi: 10.1097/01.brs.0000065484.95996.af[published Online First: Epub Date]|.
21. Boling MC, Padua DA, Marshall SW, Guskiewicz K, Pyne S, Beutler A. A prospective investigation of biomechanical risk factors for patellofemoral pain syndrome the joint undertaking to monitor and prevent ACL injury (JUMP-ACL) cohort. The American journal of sports medicine 2009;**37**(11):2108-16
22. Foss KDB, Hornsby M, Edwards NM, Myer GD, Hewett TE. Is body composition associated with an increased risk of developing anterior knee pain in adolescent female athletes? The Physician and sportsmedicine 2012;**40**(1):13-19
23. Milgrom C, Finestone A, Eldad A, Shlamkovitch N. Patellofemoral pain caused by overactivity. A prospective study of risk factors in infantry recruits. JBJS 1991;**73**(7):1041-43

24. Van Tiggelen D, Cowan S, Coorevits P, Duvigneaud N, Witvrouw E. Delayed vastus medialis obliquus to vastus lateralis onset timing contributes to the development of patellofemoral pain in previously healthy men: a prospective study. The American journal of sports medicine 2009;**37**(6):1099-105
25. Duvigneaud N, Bernard E, Stevens V, Witvrouw E, Van Tiggelen D. Isokinetic assessment of patellofemoral pain syndrome: a prospective study in female recruits. Isokinetics and Exercise Science 2008;**16**(4):213-19
26. Finnoff JT, Hall MM, Kyle K, Krause DA, Lai J, Smith J. Hip strength and knee pain in high school runners: a prospective study. PM & R : the journal of injury, function, and rehabilitation 2011;**3**(9):792-801 doi: 10.1016/j.pmrj.2011.04.007[published Online First: Epub Date]|.
27. Herbst KA, Barber Foss KD, Fader L, et al. Hip Strength Is Greater in Athletes Who Subsequently Develop Patellofemoral Pain. The American journal of sports medicine 2015;**43**(11):2747-52 doi: 10.1177/0363546515599628[published Online First: Epub Date]|.
28. Hetsroni I, Finestone A, Milgrom C, et al. A prospective biomechanical study of the association between foot pronation and the incidence of anterior knee pain among military recruits. The Journal of bone and joint surgery. British volume 2006;**88**(7):905-8 doi: 10.1302/0301-620x.88b7.17826[published Online First: Epub Date]|.
29. Holden S, Boreham C, Doherty C, Delahunt E. Two‐dimensional knee valgus displacement as a predictor of patellofemoral pain in adolescent females. Scandinavian journal of medicine & science in sports 2015
30. Luedke LE, Heiderscheit BC, Williams D, Rauh MJ. Influence of Step Rate on Shin Injury and Anterior Knee Pain in High School Runners. Medicine and science in sports and exercise 2016
31. Myer GD, Ford KR, Barber Foss KD, et al. The incidence and potential pathomechanics of patellofemoral pain in female athletes. Clinical biomechanics (Bristol, Avon) 2010;**25**(7):700-7 doi: 10.1016/j.clinbiomech.2010.04.001[published Online First: Epub Date]|.
32. Noehren B, Hamill J, Davis I. Prospective evidence for a hip etiology in patellofemoral pain. Medicine and science in sports and exercise 2013;**45**(6):1120-4 doi: 10.1249/MSS.0b013e31828249d2[published Online First: Epub Date]|.
33. Ramskov D, Barton C, Nielsen RO, Rasmussen S. High eccentric hip abduction strength reduces the risk of developing patellofemoral pain among novice runners initiating a self-structured running program: a 1-year observational study. The Journal of orthopaedic and sports physical therapy 2015;**45**(3):153-61 doi: 10.2519/jospt.2015.5091[published Online First: Epub Date]|.
34. Thijs Y, De Clercq D, Roosen P, Witvrouw E. Gait-related intrinsic risk factors for patellofemoral pain in novice recreational runners. British journal of sports medicine 2008;**42**(6):466-71 doi: 10.1136/bjsm.2008.046649[published Online First: Epub Date]|.
35. Thijs Y, Pattyn E, Van Tiggelen D, Rombaut L, Witvrouw E. Is hip muscle weakness a predisposing factor for patellofemoral pain in female novice runners? A prospective study. The American journal of sports medicine

2011;**39**(9):1877-82 doi: 10.1177/0363546511407617[published Online First: Epub Date]|.
36. Thijs Y, Van Tiggelen D, Roosen P, De Clercq D, Witvrouw E. A prospective study on gait-related intrinsic risk factors for patellofemoral pain. Clinical journal of sport medicine : official journal of the Canadian Academy of Sport Medicine 2007;**17**(6):437-45 doi: 10.1097/JSM.0b013e31815ac44f[published Online First: Epub Date]|.
37. Van Tiggelen D, Witvrouw E, Coorevits P, Croisier J-L, Roget P. Analysis of isokinetic parameters in the development of anterior knee pain syndrome: a prospective study in a military setting. Isokinetics and exercise science 2004;**12**(4):223-28
38. Witvrouw E, Lysens R, Bellemans J, Cambier D, Vanderstraeten G. Intrinsic risk factors for the development of anterior knee pain in an athletic population a two-year prospective study. The American journal of sports medicine 2000;**28**(4):480-89
39. Rathleff CR, Baird WN, Olesen JL, Roos EM, Rasmussen S, Rathleff MS. Hip and knee strength is not affected in 12-16 year old adolescents with patellofemoral pain--a cross-sectional population-based study. PloS one 2013;**8**(11):e79153 doi: 10.1371/journal.pone.0079153[published Online First: Epub Date]|.
40. Rathleff M, Rathleff C, Crossley K, Barton C. Is hip strength a risk factor for patellofemoral pain? A systematic review and meta-analysis. British journal of sports medicine 2014:bjsports-2013-093305
41. Lankhorst NE, Bierma-Zeinstra SM, van Middelkoop M. Factors associated with patellofemoral pain syndrome: a systematic review. British journal of sports medicine 2013;**47**(4):193-206 doi: 10.1136/bjsports-2011-090369[published Online First: Epub Date]|.
42. Fukuda TY, Melo WP, Zaffalon BM, et al. Hip posterolateral musculature strengthening in sedentary women with patellofemoral pain syndrome: a randomized controlled clinical trial with 1-year follow-up. The Journal of orthopaedic and sports physical therapy 2012;**42**(10):823-30 doi: 10.2519/jospt.2012.4184[published Online First: Epub Date]|.
43. van Linschoten R, van Middelkoop M, Berger MY, et al. Supervised exercise therapy versus usual care for patellofemoral pain syndrome: an open label randomised controlled trial. BMJ (Clinical research ed.) 2009;**339**:b4074
44. Rathleff MS, Roos E, Olesen J, Rasmussen S. Exercise during school hours when added to patient education improves outcome for 2 years in adolescent patellofemoral pain: a cluster randomised trial. British journal of sports medicine 2015;**49**(6):406-12
45. Hannigan JJ, Osternig LR, Chou LS. Sex-Specific Relationships between Hip Strength and Hip, Pelvis, and Trunk Kinematics in Healthy Runners. Journal of applied biomechanics 2017:1-22 doi: 10.1123/jab.2016-0333[published Online First: Epub Date]|.
46. Rathleff MS, Rathleff CR, Olesen JL, Rasmussen S, Roos EM. Is Knee Pain During Adolescence a Self-limiting Condition? Prognosis of Patellofemoral Pain and Other Types of Knee Pain. The American journal of sports medicine 2016;**44**(5):1165-71 doi: 10.1177/0363546515622456[published Online First: Epub Date]|.

47. Coppack RJ, Etherington J, Wills AK. The effects of exercise for the prevention of overuse anterior knee pain: a randomized controlled trial. The American journal of sports medicine 2011;**39**(5):940-8 doi: 10.1177/0363546510393269[published Online First: Epub Date]|.
48. Hart HF, Barton CJ, Khan KM, Riel H, Crossley KM. Is body mass index associated with patellofemoral pain and patellofemoral osteoarthritis? A systematic review and meta-regression and analysis. British journal of sports medicine 2017;**51**(10):781-90 doi: 10.1136/bjsports-2016-096768[published Online First: Epub Date]|.
49. Glaviano NR, Baellow A, Saliba S. Physical activity levels in individuals with and without patellofemoral pain. Physical therapy in sport : official journal of the Association of Chartered Physiotherapists in Sports Medicine 2017;**27**:12-16 doi: 10.1016/j.ptsp.2017.07.002[published Online First: Epub Date]|.
50. Wills AK, Ramasamy A, Ewins DJ, Etherington J. The incidence and occupational outcome of overuse anterior knee pain during army recruit training. Journal of the Royal Army Medical Corps 2004;**150**(4):264-9
51. Kaufman KR, Brodine SK, Shaffer RA, Johnson CW, Cullison TR. The effect of foot structure and range of motion on musculoskeletal overuse injuries. The American journal of sports medicine 1999;**27**(5):585-93 doi: 10.1177/03635465990270050701[published Online First: Epub Date]|.
52. Maclachlan LR, Collins NJ, Matthews ML, Hodges PW, Vicenzino B. The psychological features of patellofemoral pain: a systematic review. British journal of sports medicine 2017:bjsports-2016-096705
53. Bittencourt N, Meeuwisse W, Mendonça L, Nettel-Aguirre A, Ocarino J, Fonseca S. Complex systems approach for sports injuries: moving from risk factor identification to injury pattern recognition—narrative review and new concept. British journal of sports medicine 2016:bjsports-2015-095850
54. Philippe P, Mansi O. Nonlinearity in the epidemiology of complex health and disease processes. Theoretical medicine and bioethics 1998;**19**(6):591-607
55. Chipman HA, George EI, McCulloch RE. BART: Bayesian additive regression trees. The Annals of Applied Statistics 2010;**4**(1):266-98
56. Nielsen RO, Parner ET, Nohr EA, Sorensen H, Lind M, Rasmussen S. Excessive progression in weekly running distance and risk of running-related injuries: an association which varies according to type of injury. The Journal of orthopaedic and sports physical therapy 2014;**44**(10):739-47 doi: 10.2519/jospt.2014.5164[published Online First: Epub Date]|.

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Andrew Raye and Bradley Neal completed the search.

Bradley Neal and Nienke Lankhorst determined eligible papers for inclusion.

Simon Lack & Nienke Lankhorst completed the quality appraisal of included papers.

Bradley Neal and Andrew Raye completed the data extraction.

Bradley Neal, Simon Lack and Dylan Morrissey completed the meta-analysis.

All authors contributed to the writing of the final manuscript.

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Summary Box – What are the new findings?

- Heterogeneous incidence of PFP is 10%
- Higher baseline hip abduction strength predicts future PFP development in adolescents.
- Multiple variables (including sex, BMI and Q-angle) were no risk factors for future PFP development

FIGURE LEGENDS

Figure 1: the Van Mechelen model of injury prediction

Figure 2: PRISMA search flow chart

Figure 3: sex
Forrest plot detailing risk ratios for sex when comparing participants who developed PFP with controls. HQ – high quality; MQ – medium quality; LQ – low quality; M – military recruits; A – adolescents; R – recreational runners; SD – standard deviation; IV – inverse variance; CI – confidence intervals PFP – patellofemoral pain

Figure 4: height
Forrest plot detailing standardised mean differences for height when comparing participants who developed PFP with controls. HQ – high quality; MQ – medium quality; LQ – low quality; M – military recruits; A – adolescents; R – recreational runners; SD – standard deviation; IV – inverse variance; CI – confidence intervals PFP – patellofemoral pain

Figure 5: weight
Forrest plot detailing standardised mean differences for weight when comparing participants who developed PFP with controls. HQ – high quality; MQ – medium quality; LQ – low quality; M – military recruits; A – adolescents; R – recreational runners; SD – standard deviation; IV – inverse variance; CI – confidence intervals PFP – patellofemoral pain

Figure 6: BMI
Forrest plot detailing standardised mean differences for BMI when comparing participants who developed PFP with controls. HQ – high quality; MQ – medium quality; LQ – low quality; M – military recruits; A – adolescents; R – recreational runners; SD – standard deviation; IV – inverse variance; CI – confidence intervals PFP – patellofemoral pain; BMI – body mass index

Figure 7: body fat percentage
Forrest plot detailing standardised mean differences for body fat percentage when comparing adolescents who developed PFP with controls. HQ – high quality; MQ – medium quality; LQ – low quality; A – adolescents; SD – standard deviation; IV – inverse variance; CI – confidence intervals PFP – patellofemoral pain; % - percentage

Figure 8: age
Forrest plot detailing standardised mean differences for age when comparing participants who developed PFP with controls. HQ – high quality; MQ – medium quality; LQ – low quality; M – military recruits; A – adolescents; R – recreational runners; SD – standard deviation; IV – inverse variance; CI – confidence intervals PFP – patellofemoral pain;

Figure 9: Q-angle
Forrest plot detailing standardised mean differences for Q-angle when comparing participants who developed PFP with controls. HQ – high quality; MQ – medium quality; LQ – low quality; M – military recruits; R – recreational runners; SD – standard deviation; IV – inverse variance; CI – confidence intervals PFP – patellofemoral pain;

Figures 10a-f: Quadriceps strength
Forrest plot detailing standardised mean differences for Quadriceps strength when comparing military recruits who developed PFP with controls. HQ – high quality; MQ – medium quality; LQ – low quality; M – military recruits; SD – standard deviation; IV – inverse variance; CI – confidence intervals PFP – patellofemoral pain;

Figures 11a-e: Hip strength

Forrest plot detailing standardised mean differences for hip strength when comparing participants who developed PFP with controls. HQ – high quality; MQ – medium quality; LQ – low quality; M – military recruits; A – adolescents; R – recreational runners; SD – standard deviation; IV – inverse variance; CI – confidence intervals PFP – patellofemoral pain;

Figures 12a-b: Hip abduction strength

Forrest plot detailing standardised mean differences for hip abduction strength when comparing participants who developed PFP with controls. HQ – high quality; MQ – medium quality; LQ – low quality; M – military recruits; A – adolescents; R – recreational runners; SD – standard deviation; IV – inverse variance; CI – confidence intervals PFP – patellofemoral pain;

Figure 13: potential causal inference diagram for PFP