HHS Public Access

Author manuscript

Am J Sports Med. Author manuscript; available in PMC 2023 February 08.

Published in final edited form as:

Am J Sports Med. 2021 February ; 49(2): 538–551. doi:10.1177/0363546520926448.

A Word of Caution for Future Studies in Patellofemoral Pain: A Systematic Review With Meta-analysis

Camila Grant, PhD[*], **Cameron N. Fick, MD MS**[*], **Judith Welsh, BSN, MLS**[†], **Jenny McConnell, PT, PhD**[‡], **Frances T. Sheehan, PhD**[*,§]

[*]Department of Rehabilitation Medicine, National Institutes of Health, Bethesda, Maryland, USA

[†]National Institutes of Health Library, Office of Research Services, National Institutes of Health, Bethesda, Maryland, USA

[‡]Centre for Health Exercise and Sports Medicine, University of Melbourne, Melbourne, Australia

Abstract

Background: Patellar maltracking is widely accepted as an underlying mechanism of patellofemoral pain. However, methodological differences in the literature hinder our ability to generate a universal quantitative definition of pathological patellofemoral kinematics (patellar maltracking) in patellofemoral pain, leaving us unable to determine the etiology of patellofemoral pain.

Purpose: Systematically review the literature to provide evidence regarding the influence of confounding variables on patellofemoral kinematics.

Study Design: Systematic review and random effects meta-analysis of control-case studies.

Methods: A literature search of case-control studies that evaluated patellofemoral kinematics at or near full extension and were written in English was conducted using Embase, PubMed, Scopus, and Web of Science up to September 2019. Cases were defined as patients with patellofemoral pain. Studies were eliminated if they lacked quantitative findings; had a primary aim to assess therapy efficacy; or included participants with osteoarthritis and/or previous trauma, pathology, or surgery. A quality assessment checklist was employed to evaluate each study. Meta-analyses were conducted to determine the influence of confounding variables on measures of patellofemoral kinematics.

Results: Forty studies met the selection criteria, with quality scores ranging from 13% to 81%. Demographic characteristics, data acquisition, and measurement methods were the primary sources of methodological variability. Active quadriceps significantly increased lateral shift (standardized mean difference $[SMD]_{shift} = 0.33$, $P = .0102$) and lateral tilt ($SMD_{tilt} = 0.43$, $P = .006$) maltracking. Individuals with pain secondary to dislocation had greater effect sizes for lateral maltracking than those with isolated patellofemoral pain ($\Delta SMD_{shift} = 0.71$, $P = .0071$; $\Delta SMD_{tilt} = 1.38$, $P = .0055$).

[§]Address correspondence to Frances T. Sheehan, PhD, Department of Rehabilitation Medicine, National Institutes of Health, 6707 Democracy Blvd, Suite 856. Bethesda, MD 20817, USA (gavellif@cc.nih.gov).

Conclusion: This review exposes large methodological variability across the literature, which not only hinders the generalization of results, but ultimately mitigates our understanding of the underlying mechanism of patellofemoral pain. Although our meta-analyses support the diagnostic value of maltracking in patellofemoral pain, the numerous distinct methods for measuring maltracking and the limited control for cofounding variables across the literature prohibit defining a single quantitative profile. Compliance with specific standards for anatomic and outcome measures must be addressed by the scientific and clinical community to establish methodological uniformity in this field.

Keywords

patellofemoral joint; maltracking; kinematics; dislocation

INTRODUCTION

Patellofemoral pain (PFP) is a common condition encountered in orthopaedic practice,[10] with an annual prevalence in the general population of 23% in adults and 29% in adolescents.[63] In the absence of structural injury or previous trauma, this anterior knee pain appears related to neuromechanical factors within the patellofemoral joint.[16] One widely accepted hypothesis is that a force imbalance around the knee leads to abnormal patellofemoral position (malalignment) and pathological patellofemoral kinematics (patellar maltracking) during functional activities.[52,56] This maltracking leads to elevated mechanical stress on the subchondral bone through altered patellofemoral contact, thereby causing pain.[17] Although maltracking in patients with PFP has been extensively studied, conflicting results have raised doubt regarding maltracking's role in the etiology of PFP.[5,7,18,38]

The divergent patellar maltracking results likely arise from methodological differences across studies,[30,79] including differences in patient characteristics (eg, age, comorbidities, sex), activities studied (eg, open vs closed chain exercise), image analysis techniques (eg, dynamic magnetic resonance imaging, static radiographs), and outcome measures selected to represent patellofemoral kinematics (eg, congruence angle vs lateral patellar displacement). Based on these differences, comparisons among studies are typically confined to general qualitative discussions, leaving us unable to generate a universal quantitative definition of patellar maltracking in PFP. The few studies exploring the influence of covariates in the assessment of patellofemoral maltracking (eg, patient position,[1] muscle participation,[3] knee angle[6,58,74]) suggested that the experimental paradigm employed influences the study conclusions. For example, Becher and colleagues[1] demonstrated an increased patellar tilt angle (patient group only) and an increase in bisect offset (patient and control cohorts) when comparing measures acquired in an upright posture with active quadriceps but not when measured in a supine position with relaxed musculature. The authors attributed the differences to the posture. However, the effect of quadriceps activity was not explored. By not controlling for potential confounding variables, such studies add confusion in regard to which factors are indeed influencing patellofemoral maltracking. The methodological differences within and across studies diminish the potential diagnostic value of maltracking in PFP.

We conducted this systematic review to provide a comprehensive understanding of the influence that confounding variables have on quantifying patellar maltracking patterns in individuals with PFP. This systematic review used meta-analysis and meta-regression to provide evidence of the confounding variables' influence on axial measures of patellofemoral position/kinematics across studies. In doing so, we hoped to support the development of a standard framework for the assessment of the patellar alignment/kinematics. We asked 3 primary questions: (1) Does quadriceps activity increase the ability to detect maltracking? (2) Are patients with isolated PFP (PFP_iso) kinematically unique from patients with PFP secondary to dislocation (PFP_dis)? (3) Do other variables (eg, patient position, activities studied, image techniques) influence the measured values of maltracking? Integral to our meta-analysis exploring the influence of confounding variable was the following overarching question: Is patellar maltracking associated with PFP? The purpose of the study was not to determine whether one methodology, imaging modality, or outcome variable is superior when investigating patellofemoral alignment/tracking but to explore the sources of variability across the literature in an attempt to provide clarity and unity for future studies.

METHODS

Search Strategy and Eligibility Criteria

This review followed the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-analyses). The search string was developed by 1 author (J.W.), a clinical informationist at the National Institutes of Health Library with 14 years of experience, using input from all authors. The search of the literature was conducted in July 2018 and then updated in September 2019 with the following databases: Embase, PubMed, Scopus, and Web of Science. The search strategy included 3 keyword strings and their associated range of terms (Appendix Table A1, available in the online version of this article). We included all studies irrespective of publication year, but limited inclusion to full-text English-language publications. The updated search was limited to publications published after 2017 that were not included in the original search.

This preliminary database was screened per the predetermined eligibility criteria. A study was included into the final review only if (1) it evaluated patellofemoral alignment and/or tracking in individuals with idiopathic PFP or pain secondary to subluxation, dislocation of the patella, or recurrent patellofemoral instability and (2) the results were reported at or near full extension (≤10° of knee flexion). A study was eliminated if (1) its participants had previous leg trauma, pathology, or surgery or displayed signs of osteoarthritis; (2) it did not quantitatively report the main findings or evaluate controls; and (3) its primary aim was to assess the therapy or treatment efficacy. Two reviewers (C.G. and C.N.F.) independently screened titles and abstracts to identify the initial study database. Finally, full-text manuscripts were screened according to the inclusion and exclusion criteria for final inclusion. A third reviewer (J.M.) was consulted when a consensus could not be reached.

Data Extraction and Quality Assessment

Data from all studies in the final database were extracted and tabulated. The potential sources of intra- and inter-study variability[30,79] were identified during data extraction. These sources fell into 3 main categories: demographics, study design, and outcome measurement techniques. As the influence of knee angle on the patellar position is well established,[6,58,74] this source of variability was not explored. Instead, for each included study, outcomes for patellofemoral shift and tilt were extracted for the patient (case) and asymptomatic (control) groups with the knee in full extension (≤10°). As part of the extraction process, the patient cohort was defined as PFP_iso, PFP_dis, or mixed (PFP_mix). A patient group was defined as being PFP_iso if the recruitment criteria clearly excluded individuals with history of dislocation, instability, or subluxation. If a study recruited only individuals with history of patellofemoral instability (primary dislocation, recurrent dislocation, subluxation, or signs of instability), then the patient group was defined as PFP_dis. Last, the patient group was defined as PFP_mix if neither of the aforementioned 2 criteria was met or if indications within the study demonstrated the partial presence of individuals with instability, dislocation, or history of subluxation.

A quality assessment checklist of 15 questions adopted from a validated quality assessment tool by Downs and Black[12] was employed to evaluate each study (Appendix Table A2, available online). Questions were rated 1 point for yes and 0 for no or unable to assess, except Q4, which was given a value of 2 for yes, 1 for partial, and 0 for no. Scores were converted to percentage of the maximum score (16 points).

Statistical Analysis

A separate meta-analysis for muscle effect was performed first to determine whether to include all the studies in the meta-analysis or only those that required the active quadriceps. Next, using subgroup meta-analysis, we explored whether the maltracking profile was unique in studies focused solely on individuals with PFP_iso, relative to studies that focused on individuals with PFP_dis. Following this, if possible, the other covariates of interest were explored with a meta-regression (Figure 1).

All meta-analyses were conducted in R (v 3.6.0; RStudio)[46,48] with the functions *meta*[53] and *metafor*.[72] As there were 2 primary outcome variables (patellofemoral shift and tilt), 2 independent meta-analyses were run for each study question. When a single study reported patellofemoral shift and/or tilt with >1 outcome measure,[6,47] the outcome measure with the lowest effect size was used. For multiple studies from the same research group that included or potentially shared the same population, the most recent study was used for comparison across studies. Because studies used different metrics/scales to measure patellar shift or tilt, calculation of effect size for each study was performed through standardized mean difference (SMD). SMD was calculated with Hedges *g*,[26] defined as the mean difference between groups in each study divided by the study's pooled standard deviation, producing a unitless index enabling comparison across studies (Equation 1):

$$\text{Hedges } g = (M_1 - M_2)/SD_{\text{pooled}}, \quad \text{Equation 1}$$

where M_1 = mean value for patients (group$_1$), M_2 = mean value for controls (group$_2$), and SD_{pooled} = pooled standard deviation of group$_1$ and group$_2$ (Equation 2):

$$SD_{pooled} = \sqrt{\frac{(n_1 - 1)^* SD_1 + (n_1 - 1)^* SD_2}{(n_1 + n_2 - 2)}}, \quad \text{Equation 2}$$

where n_1 = cohort size for group$_1$, n_2 = cohort size for group$_2$, SD_1 = standard deviation for group$_1$, and SD_2 = standard deviation for group$_2$.

The SMD was entered into the meta-analysis weighted by the inverse inter-study variance (Sidik-Jonkman estimator for tau-squared).[62] I^2 identified the percentage of variation across studies attributed to heterogeneity rather than chance.[27] Outcomes were reported as the SMD and 95% CI. An influential analysis based on a leave-one-out design was undertaken to identify if a single influential study significantly altered the heterogeneity. If such an influencer was found, this study was removed, and the meta-analysis was rerun.

We conducted the meta-analysis with random effects to explore whether quadriceps activity during patellofemoral alignment/tracking acquisition enhances the ability to diagnose malalignment/maltracking in patients with PFP (PFP_iso, PFP_dis, and PFP_mixed).[52] This separate meta-analysis of muscle effect on patellar profile included only studies that assessed the same individuals with and without participation of the quadriceps musculature for both cases and controls. Based on equation 1, M_1 and M_2 were the difference in shift/tilt between states (active vs passive quadriceps) for the control group (group$_1$) and the patient group (group$_2$), whereas SD_1 and SD_2 were the pooled standard deviation of the active and passive states for each group. If this analysis revealed that muscle activity influenced patellar maltracking, we moved forward with the main analysis using only studies that required active quadriceps. If this was not the case, we moved forward using all studies (Figure 1).

Next, we explored if PFP_iso has a distinct pathomechanism from PFP_dis,[9] by adding a subgroup analysis to a meta-analysis with random effects. For this analysis, M_1 and M_2 (equation 1) were the mean values for shit/tilt for the control (group$_1$) and patient cohort (group$_2$). In addition, this analysis tested if maltracking was significant in each patient population. If a significant distinction in effect size (SMD) between populations was found, meta-regression analyses were performed separately for studies of PFP_iso versus PFP_dis, with the PFP_mix studies being removed at this juncture. These final meta-regressions were run only if a minimum of 10 studies were available for analysis (the smallest number of studies recommended for meta-regression)[27] and significant heterogeneity remained (I^2).

RESULTS

After removal of duplicates, 4204 publications remained, with 487 belonging to the updated search (Figure 2). Applying the study selection criteria removed 4155 articles, leaving 49 for inclusion. During the data extraction process, 9 additional studies were excluded because of the presence of osteoarthritis in the study population that was not previously recognized. Thus, in total, the 2 searches produced 40 articles for the review.

Quality Assessment and Study Characteristics

The study quality mean score ± SD was 52% ± 18%, with a range of 13% to 81% (Appendix Table A2, available online). No study received a score of 2 (yes) for Q4, as the distribution of principal confounders was not fully described. Thirty studies received a score of 1 (partial) for Q4[1, 4, 6–8, 14, 15, 18, 19, 21, 24, 25, 28, 33, 35, 38, 42– 44, 47, 49, 50, 56, 57, 65, 67– 69, 73, 77]. Unable to assess (U) was frequently indicated for questions regarding the main outcome measures' accuracy (Q11) and the recruitment timeline (Q12), as they were scored affirmatively for 13 (27%)[1, 4, 21, 33, 35, 38, 42, 44, 49, 50, 56, 71, 73] and 4 (10%)[41,47,49,77]studies, respectively. An attempt to blind researchers measuring the primary outcomes (Q14) was mentioned in only 4 studies (10%).[14, 15, 21, 57]

The survey of the literature revealed 9 main sources of methodological variability in the 3 main categories (Table 1): demographic characteristics (age, sex, study case [PFP_iso, PFP_dis, PFP_mix]), data acquisition (imaging modality and condition [static vs dynamic], muscle activity, contraction intensity, patient position), and measurement methods (outcome measurement to quantify patellofemoral shift and tilt and analysis dimensionality: 2- vs 3-dimensional [3D]). As knee angle influences patellofemoral kinematics,[6,58,74] we reported information regarding whether a study cited an anatomic definition of knee angle. Height, weight, and body mass index were not listed in the extraction table, because they were often not provided. The mean cohort age ranged across studies from 13 to 36 years old. The majority of studies focused on adult populations, with only 2 studies focused solely on adolescents.[7,47] Several studies used a mixed or potentially mixed population of adolescent and adults. As for sex, the majority of studies excluded males. Only 1 study focused on males in isolation.[38] Differences between sexes were assessed by only 2 studies,[28,42] with conflicting results. Out of the 40 studies included in this review, 21 evaluated PFP_iso[4, 7, 8, 14, 15, 18, 19, 21, 23, 25, 35, 38, 42–44, 52, 65, 68, 69, 73, 74]; 10 evaluated PFP_dis (ie, history of dislocation, "instability," or "subluxation")[1, 6, 28, 33, 41, 45, 47, 51, 75, 76]; 1 study included 2 isolated patient populations;[67] and 8 allowed for a patient cohort of mixed diagnoses (PFP_iso and PFP_dis). [3,24,49,50,56,57,71,77] As highlighted by the quality assessment (Appendix Table A1, Q11, available online), two-thirds of the studies did not effectively describe the kinematic measures used. Surprisingly, knee angle was the measurement most often neglected, with only 10 studies[7, 8, 15, 21, 42, 43, 56, 57, 73, 74] providing an anatomic definition for it. Four studies[6,44,47,77] did not measure it; 10 studies[1, 18, 19, 33, 49–51, 65, 67, 68] used a locating device or goniometer to measure knee angle, but did not provide an anatomic definition; and the remaining 16[3, 4, 14, 23–25, 28, 35, 38, 41, 45, 52, 69, 71, 75, 76] failed to report how the knee angle was measured.

For the patellofemoral alignment and tracking outcome measures, 22 distinct methods were found for measuring medial-lateral (ML) shift, defined as patellar displacement relative to the femur (Figure 3). For example, patellar ML shift was reported as a pure length measurement (lateral patellar displacement, axial linear patellar displacement), as an index (bisect offset index, patella–lateral condyle index), or with proxies (congruence angle, patella offset position). Similarly, 11 distinct methods for measuring patellar ML tilt were reported (Figure 4). Although many studies used the same nomenclature, the actual

measurement differed across studies because of differences in referential landmarks. In 23 studies,[3, 4, 14, 18, 19, 23–25, 28, 33, 41–44, 47, 49–52, 65, 67, 68, 74] a single axial image was used to measure patellar position. The use of multiple axial slices was adopted by 5 other studies,[1,6,21,45,77] while 10 studies[7, 8, 15, 35, 38, 56, 57, 73, 75, 76] adopted 3-dimensional techniques for consistency in bony reference landmarks (Table 1).[69,71]

Statistical Analyses

Active quadriceps during data acquisition significantly increased lateral maltracking for shift and tilt (SMD_{shift} = 0.33, P = .0102; SMD_{tilt} = 0.43, P = .006), based on 12[1, 6, 14, 15, 21, 24, 25, 41, 51, 67, 74, 77] and 11[1, 6, 14, 15, 21, 24, 25, 51, 67, 74, 77] of the 40 studies, respectively, within the review. No single study was found to influence the results (Figure 5). Thus, in subsequent analyses, only studies with active quadriceps were included.

A total of 21 studies[1, 6–8, 14, 15, 18, 24, 25, 38, 41, 43, 44, 47, 50, 51, 65, 67, 68, 73, 74] were suitable for the subgroup meta-analysis based on patient cohort, as these were the only studies requiring active quadriceps participation. One of these 21 studies[67] had 2 case groups (PFP_iso and PFP_dis), and another[41] did not evaluate patellar tilt. Thus, 22 and 21 comparisons were used in the meta-analysis for shift and tilt maltracking (Figures 6 and 7). Significant differences among groups (PFP_iso, PFP_dis, and PFP_mix) were found in both subgroup analyses (ML shift, P = .024; ML tilt, P = .027). A post hoc analysis revealed that individuals with PFP_dis have a distinctively greater effect size for lateral maltracking than those with PFP_iso (ΔSMD_{shift} = 0.71, P = .0071; ΔSMD_{tilt} = 1.38, P = .0055). Comparisons between studies with PFP_mix and those with PFP_dis revealed significant differences in effect size for lateral tilt (ΔSMD_{tilt} = 1.19, P = .029), but not for shift (ΔSMD_{shift} = −0.21, P = .80). No differences in effect size for lateral maltracking were found between PFP_mix and PFP_iso (ΔSMD_{shift} = 0.51, P = .52; ΔSMD_{tilt} = 0.14, P = .59).

When the estimates of shift and tilt were then explored separately, as stratified by patient cohort and by removing studies with PFP_mix populations,[24,50] lateral shift maltracking and lateral tilt maltracking were significantly associated with PFP in both subgroups (Figures 6 and 7). No single study significantly influenced the overall lateral tilt results within any subgroup (PFP_iso or PFP_dis). However, a single study[65] significantly influenced the overall estimates for lateral shift maltracking in the subgroup of studies of PFP_iso. After this study was removed, the adjusted effect size was attenuated, but remained significant (SMD_{shift}, 0.62; 95% CI, 0.41-0.83; P < .0001).

Meta-regression analyses investigating covariate influence in estimates of lateral maltracking in shift and tilt were not performed after grouping of studies by patient cohort and subsequent removal of influential studies, as the resultant heterogeneity among studies with iso_PFP became nonsignificant[70] (I^2 = 0%, P = .95, for ML shift; I^2 = 16%, P = .27, for ML tilt). Furthermore, the subgroup of studies focused on PFP_dis fell below 10 studies.[27] Thus, the influence of other covariates (eg, patient position, activities studied, image techniques) identified by this review could not be investigated.

DISCUSSION

This systematic review expands our clinical and research understanding of the etiology of PFP by providing quantitative evidence of the specific confounding variables' influence, or lack thereof, on our ability to distinguish patellofemoral kinematics measured in patients with PFP from the kinematics measured in asymptomatic controls. This sets it apart from past reviews that attempted to generate a normative patellofemoral kinematic profile across studies[30,79] or sought to define which factors are most associated with patellofemoral pain (eg, sulcus angle, tibiofemoral alignment, bisect offset).[13,33] Irrespective of inter-study differences, this review presents strong evidence that lateral patellar shift and tilt maltracking are significantly associated with PFP_iso and PFP_dis. Furthermore, it provides quantitative evidence that assessing patellar maltracking during activities requiring active quadriceps improves our ability to diagnose maltracking. Last, this review adds much-needed quantitative evidence supporting a clear clinical distinction between patients with PFP_iso and those with PFP_dis. This not only fosters an evidence-based rationale for future study design, but exposes key clinical issues. Although our significant findings do not prove cause and effect, they do support the hypothesis that altered muscle forces leading to maltracking are integral to the etiology of PFP. The findings highlight the necessity to treat PFP_iso and PFP_dis as distinct pathologies and to advance interventions uniquely targeted for each patient cohort. Most important, this review clearly demonstrates the need to develop reporting standards for patellar maltracking.

Based on 12 studies[1, 6, 14, 15, 21, 24, 25, 41, 51, 67, 74, 77] representing 225 patients and 220 controls, evaluating patellofemoral kinematics with active quadriceps enhances our ability to detect patellar maltracking. Active quadriceps increased lateral tracking in patients and controls, but this increase was significantly larger in the patient cohorts.[51] The larger effect of quadriceps activity on maltracking in all patients, irrespective of population cohort, demonstrates the importance of controlling for this variable in future studies. For example, Becher et al[1] and Kim et al[31] attributed increased lateral tracking in controls and patients to the upright, relative to the supine, position. Based on the current results, the difference in quadriceps (active-upright vs passive-supine) likely accounted for this variability. Clinically, the finding of increased maltracking with active quadriceps activity emphasizes the role of imbalanced muscle forces in the etiology of PFP[55] and the importance of evaluating patellofemoral kinematics under active quadriceps conditions.

Although the tendency to evaluate patellofemoral kinematics during active quadriceps is supported by the current results, the type (static or dynamic) and intensity (maximal and submaximal voluntary contractions) of muscle contraction vary considerably between and within studies.[1,49] Vasti muscle stiffness changes at different rates in response to increments in contraction intensity.[2] Thus, while submaximal intensities may reveal imbalanced forces between the vasti, maximal isometric contraction may not. Consequently, the exercise intensity during assessment may influence the resultant patellar profile, and this parameter should be explored as a potential confounding variable in future studies.

The quantitative distinction in maltracking between individuals with PFP_iso (260 patients and 240 controls) and patients with PFP_dis (106 patients and 85 controls)

clearly demonstrates that future research must carefully control for comorbidity (ie, any concomitant condition other than idiopathic PFP). Although the presence of comorbidities is typically controlled for in PFP research, mixed populations were used as recently as 5 years ago,[50] and dislocation history is not often clearly defined as an inclusion/exclusion criterion. Thus, future study designs must include clear comorbidity inclusion/exclusion criteria that are fully explained in the manuscript. Furthermore, most studies including patients with a dislocation history do not distinguish if this history is a single traumatic event or a recurrent event. Patients with these 2 unique histories likely have distinct kinematic profiles, but this meta-analysis is unable to tease this out, owing to a lack of clarity in the literature. Clinically, the distinction in kinematics based on the specific patellofemoral pathological condition has implications regarding the selection of the most appropriate treatment intervention. Further stratification of the patient populations could arise from investigation of homogeneous subgroups with shared characteristics. The presence of subgroups with the PFP_iso and PFP_dis cohorts could explain the large variability found within studies for estimates of lateral maltracking (Figures 4 and 5). In addition, patients within unique subgroups may have distinct etiologies for PFP,[54,55] which would suggest the need to stratify interventional strategies based on subgrouping patients.

In agreement with previous reviews,[13,30] this study identifies several sources of methodological variability, beyond muscle activity and patient cohort, ranging from demographic characteristics to data acquisition to measurement methods. Given the lack of statistical heterogeneity (ie, inter-study differences in effect size) across studies, once these first 2 variables are controlled, the remaining sources cannot be explored with meta-regression. This is not to say that these remaining variables do not influence the estimates of maltracking.[29] Instead, the likely intertwined interaction among the numerous sources of methodological variability potentially masks their influence on maltracking estimates. Thus, expanded work is needed not only to understand how these factors influence PFP, but more important, to understand if and how treatment needs to be tailored on the basis of patient demographics.

The stark inter-study lateral maltracking differences in individuals with PFP, purely based on the metric used, create blind spots in our ability to establish a universal definition of normative and pathological tracking. On average, for every 2 studies, there is a unique measure of shift. Furthermore, use of a single axial image (typically, a mid-patellar image; 23 of 40 studies) (Table 1) to quantify patellar position results in unwanted variance and bias across cohorts owing to inter- and intra-individual differences in the femoral level captured.[61] For some studies,[45,65,76] the definition of shift is altered if alta and/or dysplasia is present, resulting in one measure being used primarily for the control group (Figure 3, BSO2) and another for the patient group (Figure 3, BSO1). For studies using only the mid-patellar image for analysis, the femoral reference changes for every knee angle evaluated. Thus, changes in metrics with knee angle may also be due to alterations in the bony references used.[60,61] This illustrates the importance of using 3D coordinates to identify referential landmarks to foster consistency within and across patients.[76] Last, with no common bony landmarks to offset differences among kinematic metrics, generalization across studies becomes impossible. To highlight these points, patellar position was measured in 3 individuals via 3 patellofemoral shift metrics (Figure 8). P3 has the most lateralized

patella with BSO2*, but the most medialized patella with PFD*, resulting from the long lateral patellar nose.[20] Similarly, P2 has the most lateralized patella with PFD*, but the most medialized patella with BSO2* given the small symmetric patella. The interpretation of ML shift changes across metrics owing to LPD2* and BSO2* sensitivity to bone shape size and shape. Recent work demonstrated a larger patella in patients with PFP_iso[64] and a smaller patella in patients with PFP_dis.[78] This would indicate that a measure such as LPD2* would be more lateral in the PFP_dis cohort, as compared with the PFP_iso cohort, even if the congruence (PFD*) was identical.

Although the purpose of this study was not to determine whether one methodology is superior for investigating patellofemoral alignment/tracking, the numerous distinct methods for measuring patellar shift and tilt (Figures 3 and 4) inhibit our understanding of PFP. As such, for the field to move forward, standardized metrics are needed. This review clearly demonstrates that metrics of ML shift and ML tilt must be acquired via a multiplane method (ie, landmarks defined with 3D coordinates). This will improve accuracy and precision relative to identifying the referential landmarks in a single axial image.[61] In terms of specific metrics, we recommend using PFD* or 3Dshift1*, as both relate to the congruency of the joint and are insensitive to alterations in patellofemoral shape and size. For tilt, PTA1* holds no distinct advantage over PTA2*, and both enable comparison with previous literature.

This review's greatest strength is its thorough examination of the literature with quantitative analyses focused on how variability in study recruitment, design, and methods affects assessing patellar maltracking. The reasonably large number of studies included within these meta-analyses attests to the validity of the conclusions drawn. Nonetheless, this review is not without limitations. As mentioned earlier, because of the varying study designs and assessment protocols within and across studies, the influence of certain potential confounders could not be teased out. As such, further evidence is needed to address the potential moderating influence of demographic characteristics (eg, age, sex, weight, physical activity), study design (eg, static vs dynamic, upright vs supine), and type of muscle activity (eg, maximum isometric vs isokinetic) on patellofemoral kinematics. Sixty-five percent (26 of 40) of the included studies had at least 1 cohort with <20 participants. Although studies with such small population sizes potentially introduce publication bias, we chose not to restrict manuscript selection based on cohort size, in an effort to represent the field as broadly as possibly. Thus, future research can be improved by defining demographic characteristics within the methods, including larger cohorts, and by blinding the researchers to the participant's cohort. In addition, study measures need to be precisely defined within the article for clarity. For example, "full knee extension" can have unique definitions across studies, and kinematic metrics (eg, lateral patellar displacement and bisect offset) often have varying definitions across the literature (Figure 3).

In conclusion, this review exposes large methodological variability across the literature, which not only hinders the generalization of results, but ultimately mitigates our understanding of the underlying mechanism of PFP. Although our meta-analyses support the diagnostic value of maltracking in PFP, the numerous distinct methods for measuring maltracking prohibit a single quantitative maltracking profile from being defined. Requiring active quadriceps during assessment clearly enhances our ability to diagnose patellar

maltracking. The meta-analyses highlight the importance of study participant selection by exposing statistically unique maltracking profiles between individuals with PFP_iso and those with PFP_dis. However, intrastudy variability in maltracking estimates supports the need for further subgrouping of these 2 patient populations. This will not only provide further explanation regarding the etiology of PFP_iso and PFP_dis, but also guide treatment intervention development. Finally, compliance with specific standards for anatomic and outcome measures must be addressed by the scientific and clinical community to establish methodological uniformity in this field.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

All data for the current study were collected at the Clinical Center of the National Institutes of Health. The authors thank the National Institutes of Health Clinical Center Radiology Department for its technical support this work. C.N.F. acknowledges funding support through the NIH Medical Research Scholars Program, a public-private partnership supported jointly by the NIH, and generous contributions from the Doris Duke Charitable Foundation, Genentech, American Association for Dental Research, the Colgate-Palmolive Company, Elsevier, alumni of student research programs, and other individual supporters via the Foundation for the National Institutes of Health. For a complete list, visit https://fnih.org/what-we-do/current-education-and-training-programs/mrsp. AOSSM checks author disclosures against the Open Payments Database (OPD). AOSSM has not conducted an independent investigation on the OPD and disclaims any liability or responsibility relating thereto.

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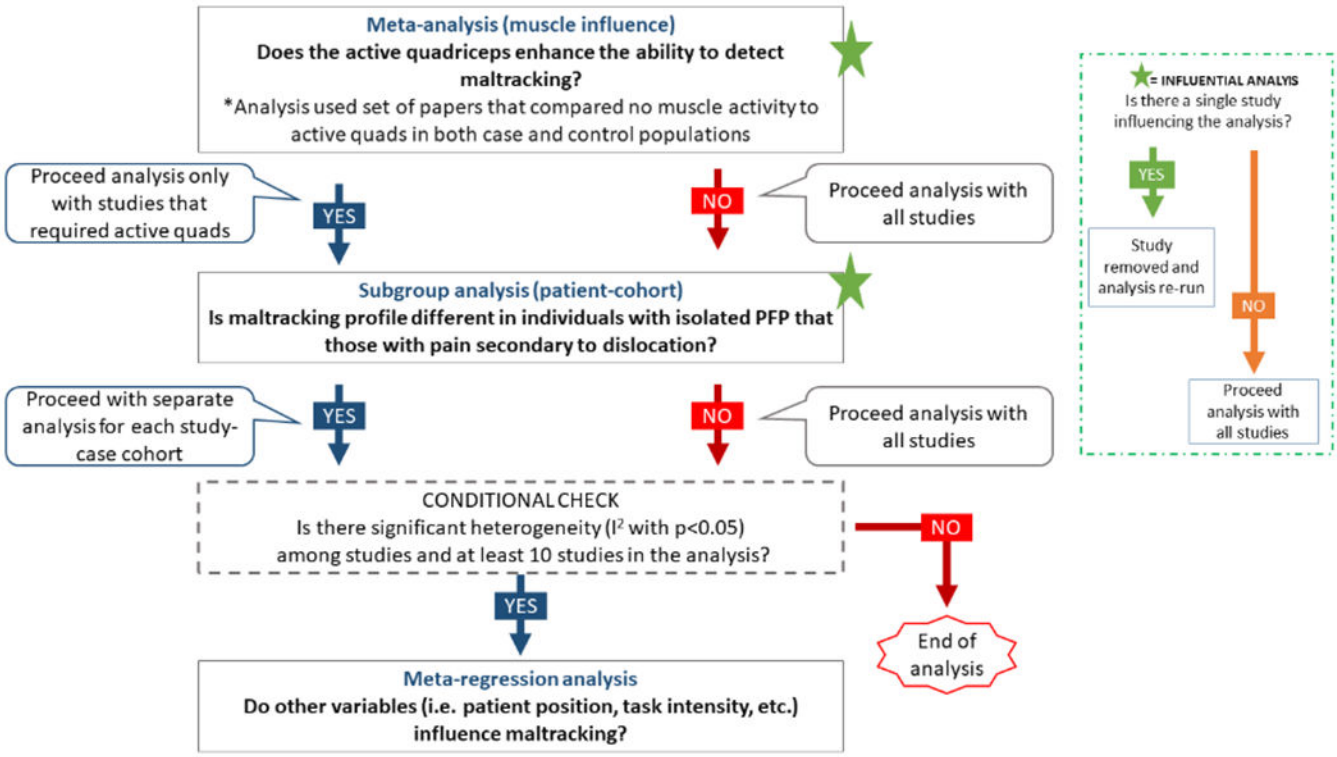

Figure 1.

Schematic representation of the statistical analysis pathway. The research questions are shown in bold letters and placed at the stage in which the statistical analysis would provide answers to them.

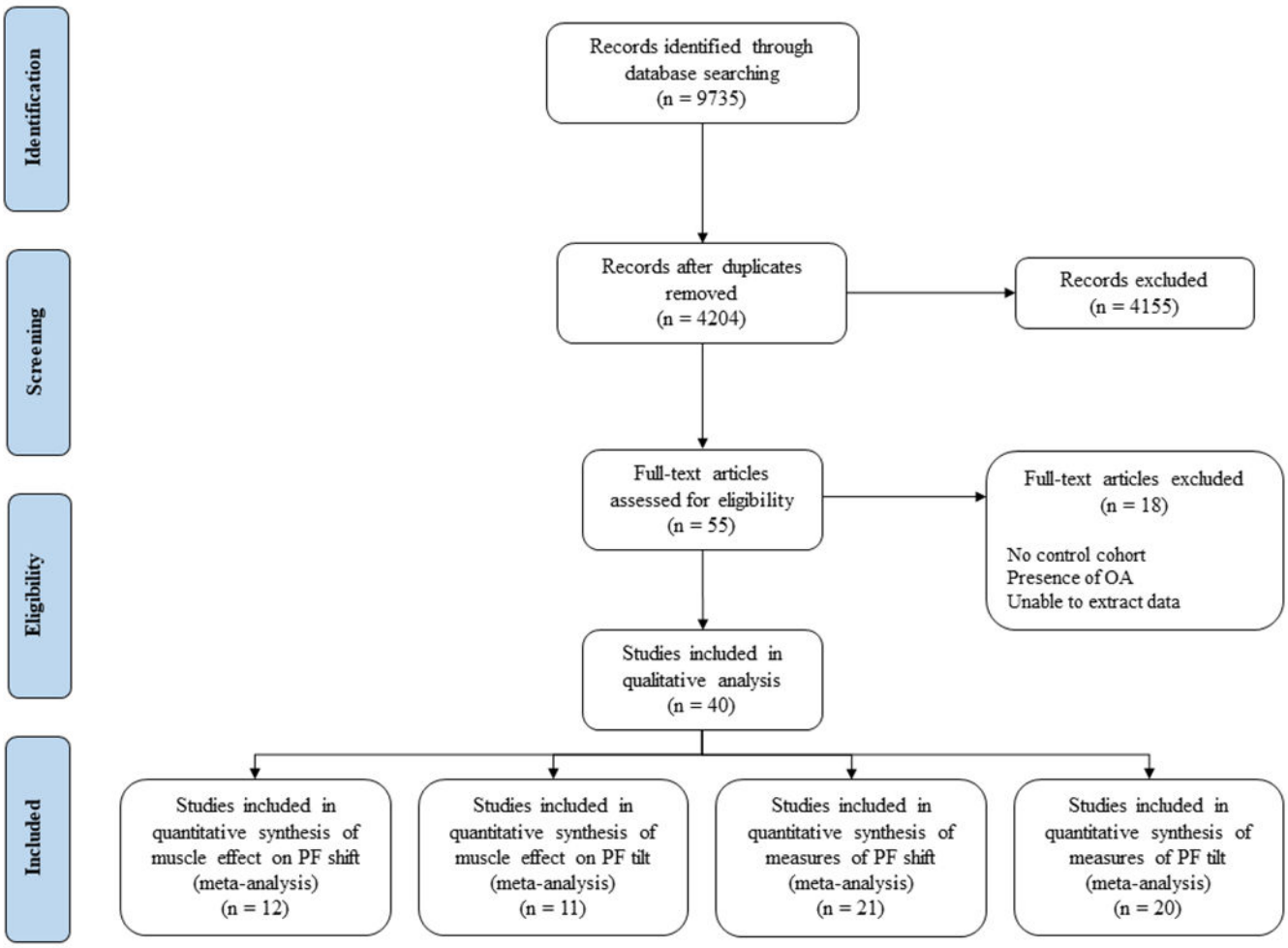

Figure 2.
Study selection process for the systematic review and meta-analysis. OA, osteoarthritis; PF, patellofemoral.

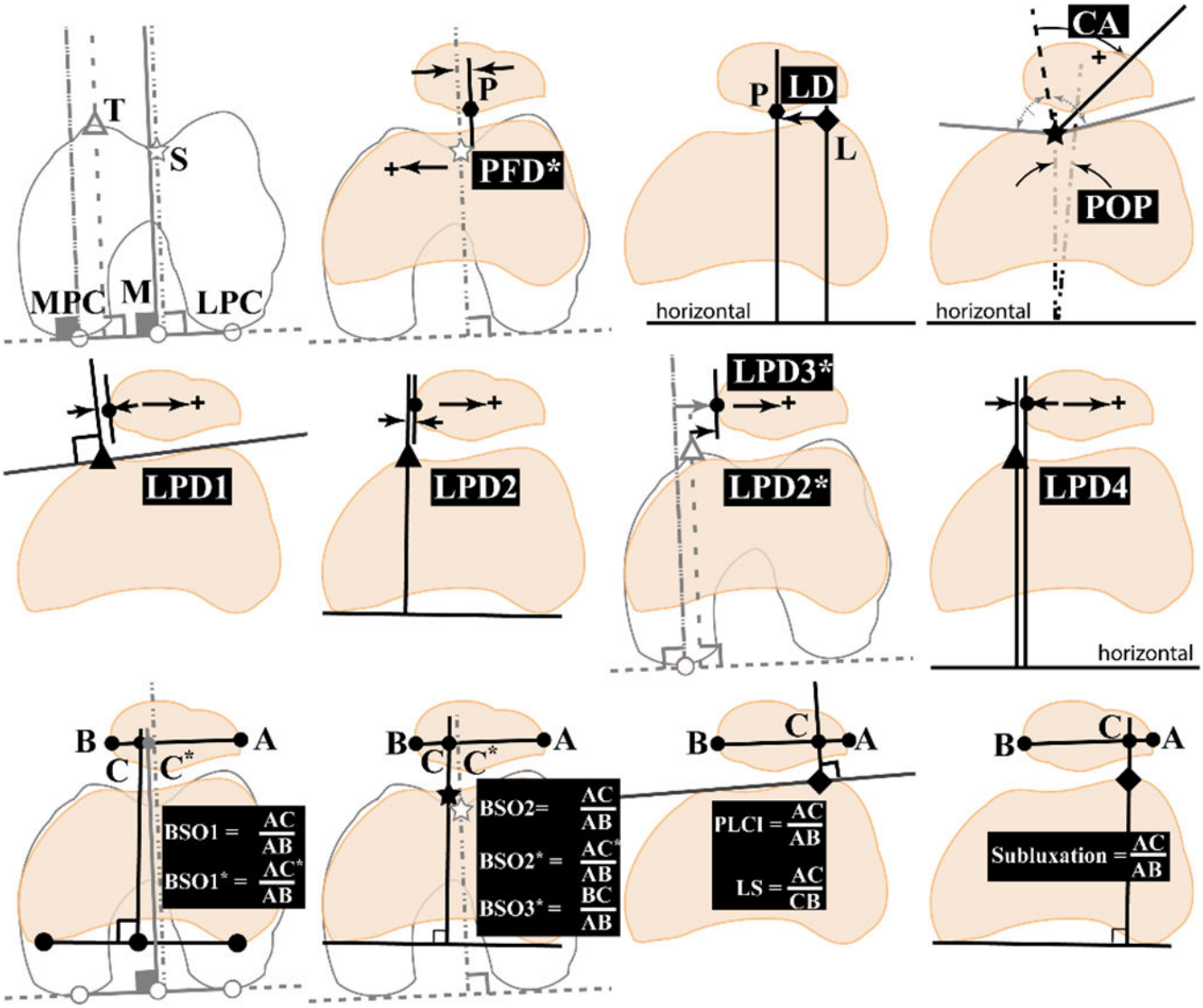

Figure 3.

Twenty-two patellar shift outcome metrics from studies within the review. Metrics: BSO, bisect offset (BSO1,[66] BSO1*,[1] BSO2,[44] BSO2*,[6] BSO3*[21]); CA, congruence angle[40]; LD, lateral displacement[41]; LPD, lateral patellar displacement (LPD1,[36] LPD2,[48] LPD2*,[6] LPD3*,[77] LPD4[14]); LS, lateral shift[51]; PFD*, patellar femoral displacement[56]; PLCI, patella–lateral condyle index[32]; POP, patella offset position[4]; subluxation.[69] The five 3-dimensional (3D) model metrics are not included (3D Shift1,[38] 3D Shift2,[73] 3D Shift3,[35] 3D Shift4,[76] 3D Shift5[14]). Top and middle rows: metrics measuring linear distance between patellofemoral bony landmarks, with the exception of CA and POP, which are measured in degrees. Bottom row: metrics with ratios. Referential landmarks: white symbols and gray lines are obtained at the widest femoral section. Solid symbols and black lines depict references obtained at the mid-patellar image. First row image 1: M, the bisect of line MPC-LPC; MPC/LPC, the medial/lateral femoral posterior condyles; S (star), the deepest point in femoral sulcus; T (triangle), the most anterior aspect of the medial trochlea. First

row image 2: L (diamond), the most anterior aspect of the lateral trochlea; P, the most posterior point of the patella. Bottom row: B/A, the most medial/lateral points on the patella; C, the point where vertical reference line crosses line B-A. The citation associated with each metric is the earliest published definition of that metric. The asterisk (*) denotes the use of multiplane reference points. A number is added to the metric if multiple studies defined the same metric name through different anatomic landmarks. A written description of all metrics is provided (Appendix Table A3, available online).

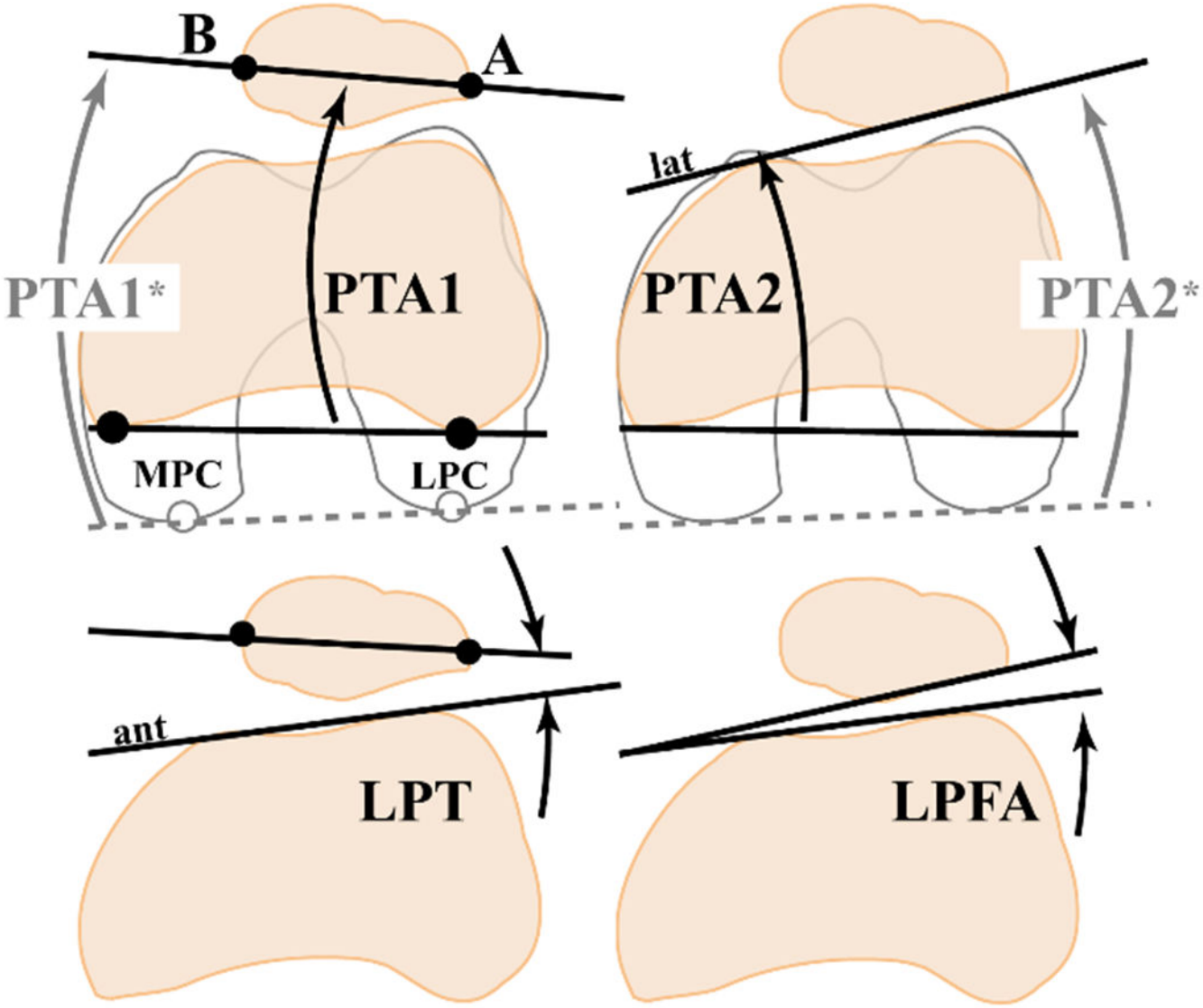

Figure 4.

Eleven patellar tilt outcome measurements from studies within the review. Metrics: LPFA, lateral patellofemoral angle[37]; LPT, lateral patellar tilt[11]; PTA, patella tilt angle (PTA1,[22] PTA1*,[1] PTA2,[39] PTA2*[59]). The five 3-dimensional (3D) methods (3D Tilt1,[38] 3D Tilt2,[73] 3D Tilt3,[35] 3D Tilt4,[76] 3D Tilt5[15]) are not included. Referential landmarks: Solid lines and symbols are obtained at the mid-patellar image, while the dashed gray line is obtained at the widest femoral section. MPC/LPC, the medial/lateral femoral posterior condyles. A and B, the most lateral and medial patellar points. Ant, the line connecting the 2 most anterior points of the femoral condyle. Lat, the lateral posterior patellar edge. The reference associated with each metric is the earliest published definition of that metric. The asterisk (*) denotes the use of multiplane reference points. A number is added to the metric if multiple studies defined the same metric name through different anatomic landmarks. A written description of all metrics is provided (Appendix Table A4, available online).

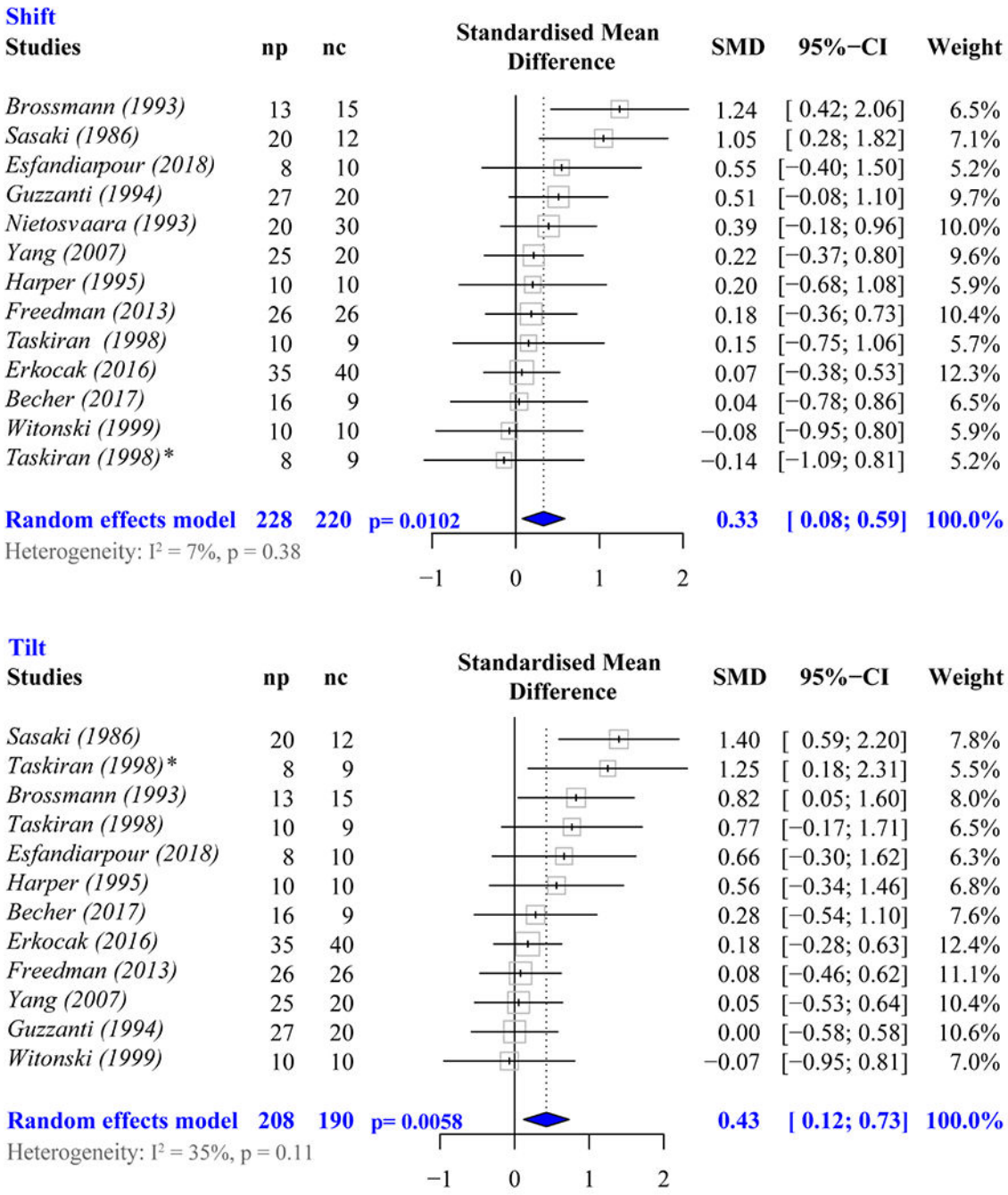

Figure 5.

Meta-analysis forest plots demonstrating the effect of the active muscle on measures of shift (top) and tilt (bottom). Diamonds represent the pooled effect size (standardized mean difference [SMD]) and 95% CI. nc, number in control cohort; np, number in patient cohort. *The study by Taskirin et al[67] evaluated 2 patient groups (isolated PFP and PFP secondary to instability. The asterisk (*) indicates the results comparing the control group to the latter patient group. The non-asterisk reference are the results comparing the group with isolated PFP to controls.

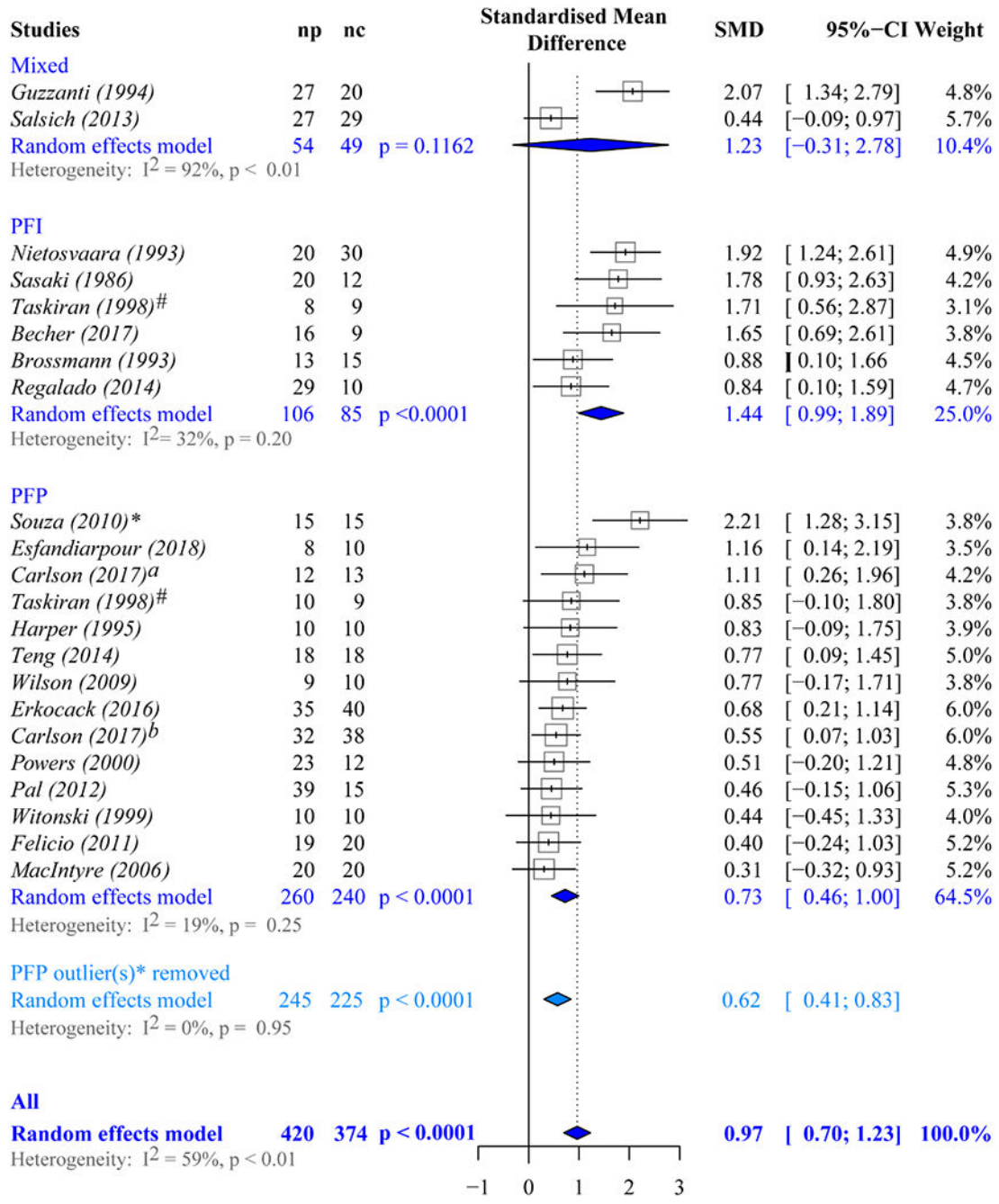

Figure 6.

Meta-analysis forest plots used to evaluate if lateral shift maltracking is significant in each cohort. Diamonds represent the pooled effect size (standardized mean difference [SMD]) and 95% CI. Mixed, studies in which the patient cohort contains individuals with patellofemoral pain and patellofemoral instability; nc, the number in the control cohort; np, the number in the patient cohort; PFI, studies in which the patient cohort contains only individuals with patellofemoral instability; PFP, studies in which the patient cohort contains only individuals with isolated patellofemoral pain. *The asterisk denotes the significant

single-study effect of the Souza et al65 study on the overall estimates for lateral shift maltracking for the PFP cohort. Thus, the random effects model results for the studies focused on PFP are listed twice. The first (dark grey) are based on all 14 PFP studies listed. The second (light grey) are based on the remaining 13 studies once the Souza et al study was removed. #The Taskirin et al[67] study is listed twice, as it evaluated patients with isolated PFP relative to controls, as well as patients with PFP secondary to instability relative to controls. [a]Carlson et al.[7] [b]Carlson et al.[8]

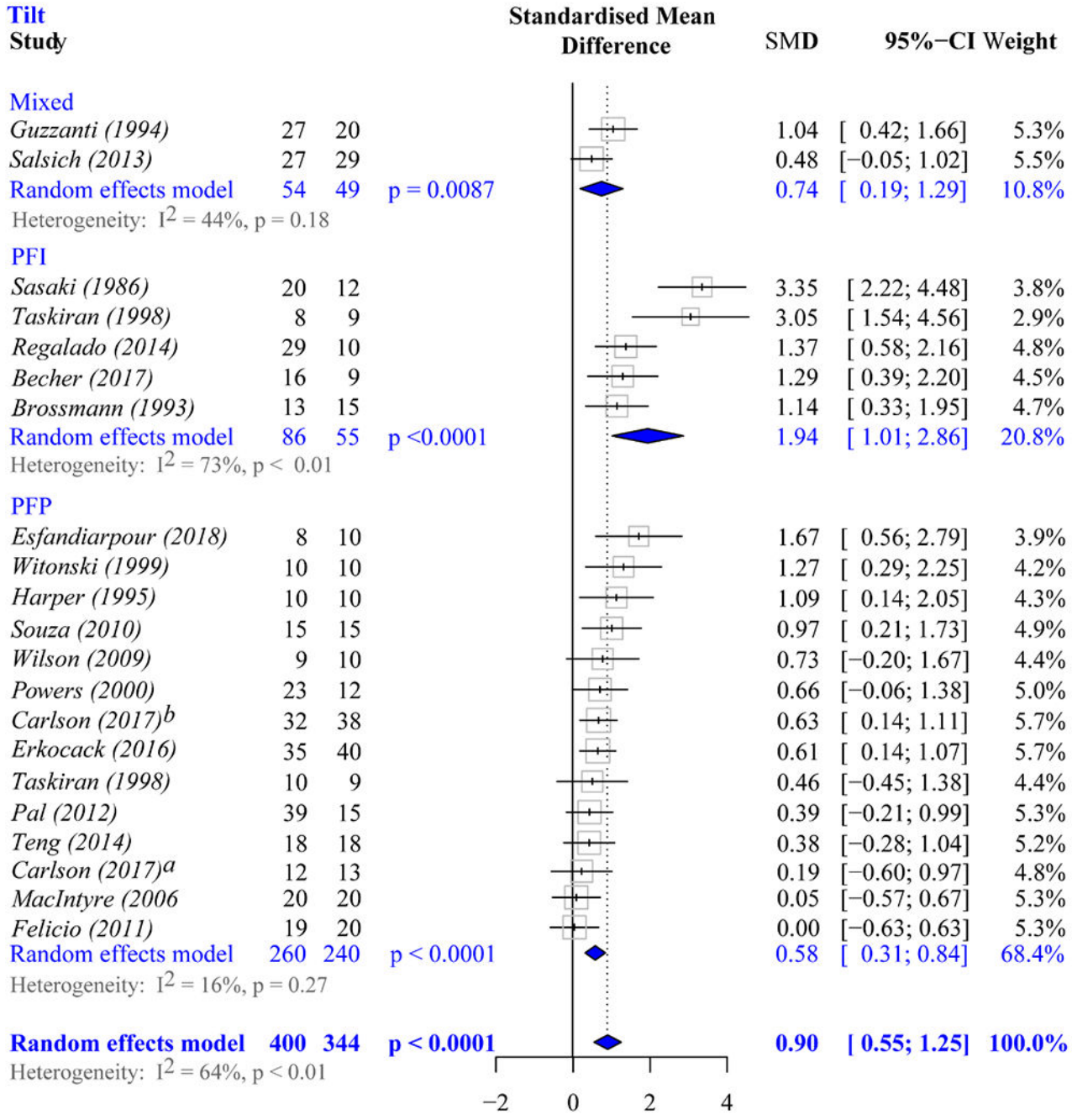

Figure 7.

Meta-analysis forest plots used to evaluate if lateral tilt maltracking is significant in each cohort. Diamonds represent the pooled effect size (standardized mean difference [SMD]) and 95% CI. Mixed, studies in which the patient cohort contains individuals with patellofemoral pain and patellofemoral instability; PFI, studies in which the patient cohort contains only individuals with patellofemoral instability; PFP, studies in which the patient cohort contains only individuals with isolated patellofemoral pain. [a]Carlson et al.[7] [b]Carlson et al.[8]

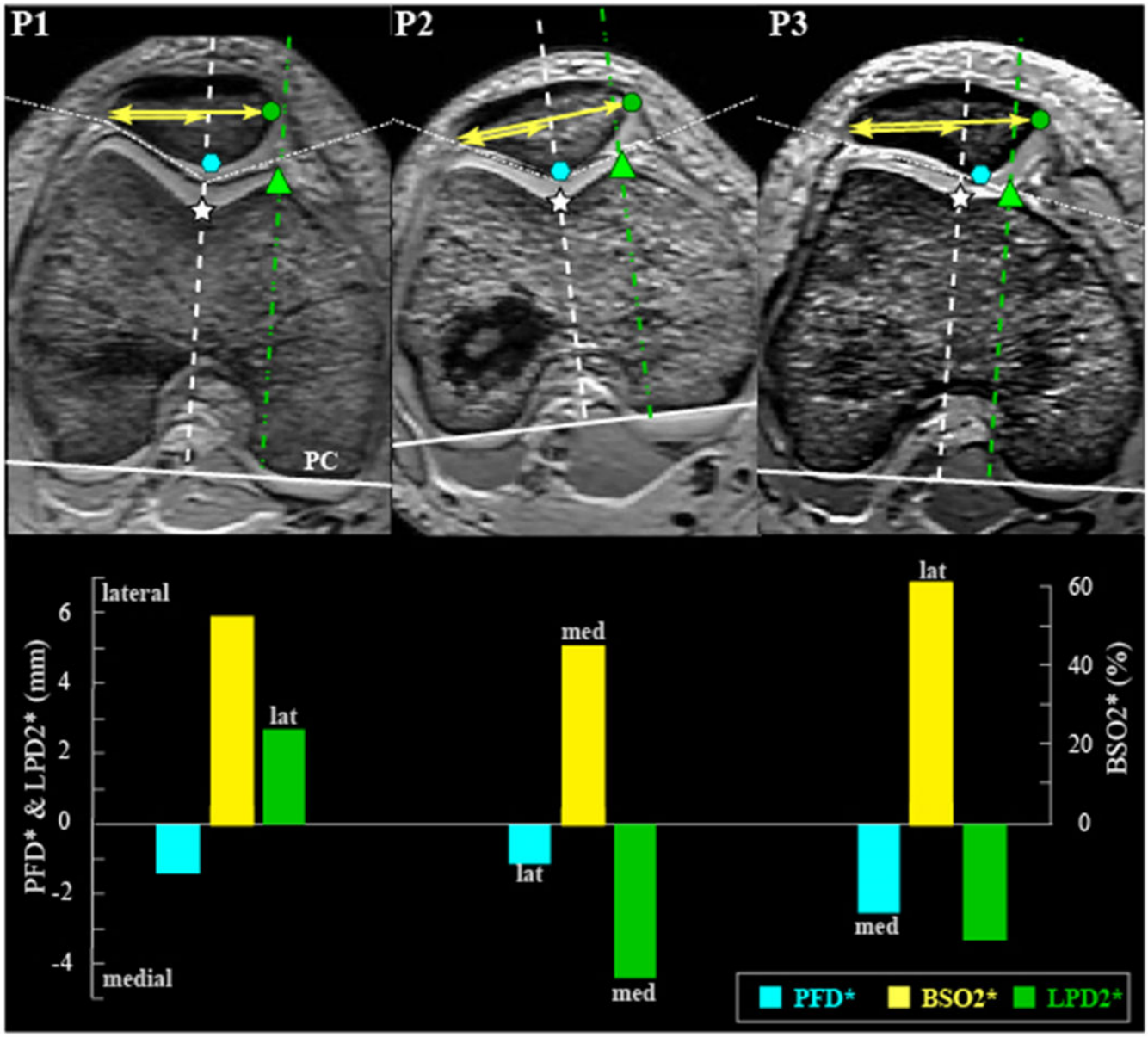

Figure 8.

Comparing 3 measurement methods for medial-lateral (ML) shift. Top row: Images for 3 control participants from our database (pixel size is not constant across participants). The images containing the femoral epicondylar width (widest femur) and the midpatella (defined as the inferior-to-superior midpoint of the posterior cartilage on the sagittal image containing the posterior ridge) were cropped together (white dotted line) without changing their relative medial-lateral or anterior-posterior position. The posterior condyle (PC) defines the lateral direction. For all 3 participants, the left side of the image is lateral. Bottom row: Graph of lateral shift for 3 participants per the metrics of PFD* (patellofemoral distance): distance from white star to blue octagon. BSO2* (bisect offset), ratio of the shorter to longer yellow

lines. LPD2* (lateral displacement), distance from green triangle to green circle (Appendix Table A3, available online).

TABLE 1:

Characteristics of Included Studies

	Demographics [a]						Data Acquisition [b]					Measurement Methods [c]			
	Control			Case			Imaging					Metrics			
Study: Author (Year)	**Patient Cohort**	**No.**	**Age, y**	**No.**	**Age. y**	**% Fem**	**Mode**	**Condition**	**Muscle Activity**	**Task Intensity**	**Patient Position**	**ML Shift**	**ML Tilt**	**2D/3D Analysis**	**Knee Angle**
Becher (2017)[1]	PFP_dis		22.3 ± 2.7	16	21.3 ± 2.7	9	MR	Static	Isom and Rel	UD	S&U	BSO1 *	PTA1 *	2D (m)	UD^
Biedert (1997)[3]	PFP_mix	8	NR	35	29.8	77.1	CT	Static	Isom and Rel	UD	S	LPD1, PLCI	LPFA	2D (s)	UD
Bolgla (2019)[4]	PFP_iso	12	24.3 ± 1.1	18	24.7 ± 3.4	100	US	Static	Rel		S	PPO	NA	2D (s)	UD
Brossmann (1993)[6]	PFP_dis	15	29.5	13	23.2	100	MR	Dynamic	Isok	LW	S	BSO2 *, LPD2 *	PTA2 *	2D (m)	NM
Carlson (2017)[7]	PFP_iso	13	14.2 ± 1.0	12	14.1 ± 1.1	100	MR	Dynamic	Isok	LW	S	PFD *	PTA2 *	3D	D
Carlson (2017)[8]	PFP_iso	38	27.4 ± 9.4	32	28.0 ± 7.9	75	MR	Dynamic	Isok	LW	S	PFD *	PTA2 *	3D	D
Erkocak (2016)[14]	PFP_iso	40	20-40	35	20-40	54.3	CT	Static	Isom and Rel	UD	S	LPD4	LPT	2D (s)	UD
Esfandiarpour (2018)[15]	PFP_iso	10	25.0 ± 7.7	8	29.7 ± 10.6	100	Fluoro	Dynamic	Isok and Rel	BW	Lunge	3D Shift5	3D Tilt5	3D	D
Felicio (2011)[18]	PFP_iso	20	21.5 ± 2.2	19	23.5 ± 3.2	100	MR	Static	Isom	MIVC	S	BSO2	PTA1	2D (s)	UD^
Felicio (2012)[19]	PFP_iso	20	21.5 ± 2.2	19	23.5 ± 3.2	100	MR	Static	Isom	MIVC	S	BSO2	PTA1	2D (s)	UD^
Freedman (2013)[21]	PFP_iso	26	25.3 ± 7.7	26	25.9 ± 11.1	73.1	MR	Dynamic	Isok and Rel	LW	S	BSO3 *, PFD *	PTA2 *	2D (m)	D
Grelsamer (2008)[23]	PFP_iso	51	NR	30	NR	NR	CT	Static	Rel		S	NA	PTA1	2D (s)	UD
Guzzanti (1994)[24]	PFP_mix	20	14	27	14	77.8	CT	Static	Isom and Rel	MIVC	S	CA	PTA2	2D (s)	UD
Harper (1995)[25]	PFP_iso	10	26	10	28	80	CT	Static	Isom and Rel	UD	S	CA	LPFA	2D (s)	UD
Inoue (1988)[28]	PFP_dis	30	22.7	50	19	86	CT	Static	Rel		S	CA	LPFA	2D (s)	UD

	Demographics [a]						Data Acquisition [b]					Measurement Methods [c]			
		Control		Case			Imaging					Metrics			
Study: Author (Year)	Patient Cohort	No.	Age, y	No.	Age. y	% Fem	Mode	Condition	Muscle Activity	Task Intensity	Patient Position	ML Shift	ML Tilt	2D/3D Analysis	Knee Angle
Kujala (1989)[33]	PFP_dis	10	24.5 ± 3.9	11	26.7 ± 6.0	100	MR	Static	Rel		S	CA, LPS	LPFA, LPT	2D (s)	UD^
Lau (2016)[35]	PFP_iso	6	28.6 ± 2.8	10	32.3 ± 5.2	80	MR	Static	Isom	25% BW	S	3D Shift3	3D Tilt3	3D	UD
MacIntyre (2006)[38]	PFP_iso	20	30.4 ± 8.4	20	36.0 ± 8.2	35	MR	Static	Isom	152 N	S	3D Shift1	3D Tilt1	3D	UD
Nietosvaara (1993)[41]	PFP_dis	30	12.9	20	13.9	75	US	Static	Isom	UD	S	LD	NA	2D (s)	UD
Pal (2011)[42]	PFP_iso	15	28.2 ± 3.9	40	28.9 ± 4.6	47.5	MR	Static	Isom	90% BW	U	BSO2	PTA1	2D (s)	D
Pal (2012)[43]	PFP_iso	15	28.4 ± 3.8	39	30.9 ± 5.8	53.8	MR	Static	Isom	90% BW	U	BSO2	PTA1	2D (s)	D
Powers (2000)[44]	PFP_iso	12	29.1 ± 5.0	23	26.8 ± 8.5	100	MR	Static	Isot	15% BW	P	BSO1 or BSO2	PTA1	2D (s)	NM
Prakash (2016)[45]	PFP_dis	87	25.6	48	23.4	73.8	CT	Static	Rel		S	BSO2 *, CA	LPFA, PTA1	2D (m)	UD
Regalado (2013)[47]	PFP_dis	10	13.0 ± 2.0	29	14.0 ± 1.0	75.9	MR	Static	Isom	LW	S	BSO2, LPD2	PTA2	2D (s)	NM
Salsich (2007)[49]	PFP_mix	21	23.2 ± 4.1	21	26.8 ± 7.7	76.2	MR	Static	Isom	UD	S	BSO2	PTA1	2D (s)	UD^
Salsich (2013)[50]	PFP_mix	29	24.2 ± 4.5	27	27.0 ± 7.1	77.8	MR	Static	Isom	UD	S	BSO2	PTA1	2D (s)	UD^
Sasaki (1986)[51]	PFP_dis	12	NR	20	20.0	NR	CT	Static	Isom and Rel	UD	S	LS	LPT	2D (s)	UD^
Schutzer (1986)[52]	PFP_iso	10	16-34	24	19	91.7	CT	Static	Isom and Rel	MVIC	LD	CA	PTA2	2D (s)	UD
Sheehan (2009)[56]	PFP_mix	20	26.7 ± 9.4	16	28.6 ± 10.3	81.3	MR	Static	Isok	LW	S	PFD *	PTA2 *	3D	D
Sheehan (2009)[57]	PFP_mix	28	26.3 ± 8.9	19	28.7 ± 11.4	84.2	MR	Static	Isok	LW	S	PFD *	PTA2 *	3D	D
Souza (2010)[65]	PFP_iso	15	30.8 ± 8.9	15	29.1 ± 4.2	100	MR	Static	Isom	BW	U	BSO1 or BSO2	PTA1	2D (s)	UD^
Taşkiran (1998)[67]	PFP_iso	9	23.0	10/8	31.0	100	CT	Static	Isom and Rel	MIVC	S	CA	PTA1	2D (s)	UD^

	Demographics [a]						Data Acquisition [b]					Measurement Methods [c]			
		Control		Case			Imaging					Metrics			
Study: Author (Year)	**Patient Cohort**	**No.**	**Age, y**	**No.**	**Age. y**	**% Fem**	**Mode**	**Condition**	**Muscle Activity**	**Task Intensity**	**Patient Position**	**ML Shift**	**ML Tilt**	**2D/3D Analysis**	**Knee Angle**
	PFP_dis			8	23.0	87.5									
Teng (2014)[68]	PFP_iso	18	26.2 ± 5.4	18	28.3 ± 6.9	100	MR	Static	Isom	25% BW	S	BSO2	PTA1	2D (s)	UD^
Thomeé (1995)[69]	PFP_iso	20	22.0 ± 3.0	40	20.0 ± 3.0	100	CT	Static	Rel		S	CA, subluxation	PTA2	2D (u)	UD
Türkmen (2018)[71]	PFP_mix	50	33.7 ± 7.1	54	34.5 ± 7.1	70.4	MR	Static	Rel		S		PTA2	2D (u)	UD
Wilson (2009)[73]	PFP_iso	10	26.7 ± 7.7	9	30.2 ± 12.5	77.8	MAS	Dynamic	Isok	BW	U	3D Shift2	3D Tilt2	3D	D
Witonski (1999)[74]	PFP_iso	10	19.4	10	18.8	100	MR	Static	Isom and Rel	UD	S	CA	PTA2	2D (s)	D
Yamada (2017)[76]	PFP_dis	10	24.0	56	22.0	83.9	MR	Static	Rel		S	BSO2 *, 3D Shift4	PTA1 *, 3D Tilt4	3D	UD
Yamada (2018)[75]	PFP_dis	10	24.0	56	22.0	83.9	MR	Static	Rel		S	BSO2 *, 3D Shift4	PTA1 *, 3D Tilt4	3D	UD
Yang (2007)[77]	PFP_mix	20	28.6 ± 4.7	23	22.3 ± 5.4	78.3	MR	Static	Isom and Rel	LW	S	BSO2 *, LPD3 *	PTA2 *	2D (m)	NM

[a] ***Patient cohort***: **PFP_dis**, history of patellofemoral instability (dislocation, subluxation, or signs of instability); **PFP_iso**, isolated patellofemoral pain; **PFP_mix**, mixed comorbidities in the PFP cohort. **No.**: number of participants in specified cohort. **Age**: reported as mean, mean ± SD, range, or not reported (NR). **% Fem**: percentage of females in the pain cohort.

[b] ***Mode***: **CT**, computed tomography; **MAS**, motion acquisition system; **MR**, magnetic resonance; **NR**, not reported; **US**, ultrasound. ***Muscle Activity***: **Isok**, isokinetic activation; **Isom**, isometric activation; **Isot**, isotonic activation; **Rel**, relaxed. ***Task intensity***: **BW**, body weight; **LW**, lower leg weight; **MVIC**, maximum voluntary isometric contraction; **N**, newton; **UD**, unable to determine. ***Patient position***: **LD**, lateral decubitus; **P**, prone; **S**, supine; **U**, upright.

[c] ***Metrics***: **3D Shift**, patellar shift defined with a 3-dimensional patellofemoral model; **3D Tilt**, patellar tilt defined with a 3-dimensional patellofemoral model; **BSO**, bisect offset; **CA**, congruence angle; **LD**, lateral distance; **LPD**, lateral patellar displacement; **LPFA**, lateral patellofemoral angle; **LPT**, lateral patellar tilt; **LS**, lateral shift; **NA**, not applicable; **PFD**, patellofemoral displacement; **PLCI**, patella–lateral condyle index; **PTA**, patellar tilt angle. A number is added to the metric if multiple studies defined the same metric name with different anatomic landmarks. 2D/3D analysis: **2D (m)**, metric uses multiple 2-dimensional images; **2D (s)**, metric is 2-dimensional with a single axial image; **3D**, a 3-dimensional model is used to define metric. ***Knee angle***: **D**, method defined; **NM**, not measured; **UD**, unable to determine; **UD^**, use of a measuring device (eg, goniometer) with no further description.

* Multiple images were used for measuring the outcome (Appendix Table A3, available online).