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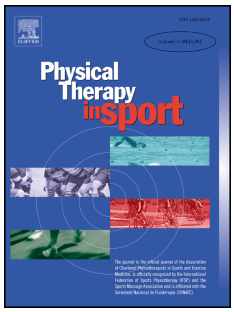

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Sally L. Coburn, Christian J. Barton, Stephanie R. Filbay, Harvi F. Hart, Michael S. Rathleff, Kay M. Crossley

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TITLE PAGE

Quality of Life in Individuals with Patellofemoral Pain: A Systematic Review Including Meta-analysis.

Sally L. Coburn, PT, MSc[1], Christian J. Barton, PT, PhD[1], Stephanie R. Filbay, PT, PhD[2], Harvi F. Hart, PhD[1,] Michael S. Rathleff, MD, PhD[3,4], Kay M. Crossley, PT PhD[1].

[1]La Trobe Sport and Exercise Medicine Research Centre, School of Allied Health, La Trobe University, Bundoora, Victoria, Australia.

[2]Arthritis Research UK Centre for Sport, Exercise and Osteoarthritis, Nuffield Department of Orthopaedics, Rheumatology & Musculoskeletal Science, Botnar Research Centre, University of Oxford, Oxford, England.

[3]Research Unit for General Practice in Aalborg, Department of Clinical Medicine, Aalborg University, Denmark.

[4]Department of Occupational therapy and Physiotherapy, Aalborg University Hospital, Denmark.

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ADDRESS FOR CORRESPONDENCE

Kay M Crossley

La Trobe Sport and Exercise Medicine Research Centre

School of Allied Health, College of Science, Health and Engineering

La Trobe University, Bundoora Vic. 3086 Australia

Tel: +61 3 9479 3902 Fax: +61 3 9479 5768

E-mail: k.crossley@latrobe.edu.au

ANONYMOUS TITLE PAGE

Quality of Life in Individuals with Patellofemoral Pain: A Systematic Review Including Meta-analysis.

ABSTRACT

Objective: The aim of this systematic review is to describe QoL in individuals with PFP, and determine the impact of PFP interventions on QoL.

Methods: Five databases were searched for studies reporting QoL in individuals with PFP, with mean age under 50 years. Data were pooled based on QoL tool (e.g. Knee Injury and Osteoarthritis Outcome Score [KOOS] QoL subscale, Short-Form 36 item health survey [SF-36]) using random-effects models, or through narrative synthesis where inadequate data were available.

Results: Individuals with PFP, had worse KOOS-QOL scores (pooled mean: 47[95% CI: 34 to 61] and health-related QoL (pooled SF-36 PCS and MCS: 47[95% CI: 41 to 53] and 54[95% CI: 47 to 62], respectively) compared with pain-free controls and population norms. Physical interventions were associated with improvements in knee- and health- related QoL in individuals with PFP in repeated measures studies. However, the effect of physical interventions compared to a control treatment was conflicting.

Conclusion: Individuals with PFP aged under 50 years, have markedly reduced knee- and health-related QoL compared to pain-free controls and population norms. Knee- and health-related QoL may improve following intervention, but it is unclear if these improvements are greater than that which occur in a control group.

Keywords: anterior knee pain**,** patellofemoral pain syndrome**,** KOOS**,** SF-36**,** intervention

1. INTRODUCTION

Patellofemoral pain (PFP) is a common disorder of the knee,[55] prevalent in adolescent[31] and adult populations,[62] and particularly prevalent in physically active individuals.[35] PFP is a chronic, painful condition predominantly of insidious onset, which often persists despite provision of evidence-based treatments.[37] Research suggests that 57% of individuals with

PFP may experience persistent symptoms and unfavourable outcomes 5-8 years after enrolment in a clinical trial.[28] Moreover, symptom severity may remain unchanged or progress in 50% of affected individuals,[7] often restricting an individual's participation in physical activity[40] and potentially reducing quality of life (QoL).

Health-related QoL is a multi-dimensional concept, encompassing physical, psychological and social aspects associated with a disease or its treatment.[19] Disease-specific and generic health-related QoL measures are used to evaluate patient experience of a musculoskeletal condition and the benefit of therapeutic interventions.[46] The patients' perspective and experience should be paramount when evaluating the impact of a condition or the efficacy of an intervention.[45] The use of QoL instruments recognizes that patient perceptions do not always match with knee pathology[50] or findings from a clinical examination of the knee.[24] Although rarely the primary outcome of interest, knee- and health- related QoL outcomes have been reported in a number of studies investigating individuals with PFP, and have been used to evaluate intervention efficacy for this condition. Synthesis of this evidence will provide a better understanding of the impact of PFP and the influence of specific treatment strategies on QoL.

This systematic review aims to: (i) describe QoL in individuals with PFP compared to pain-free controls and population norms; (2) evaluate whether intervention is associated with improved QoL in individuals with PFP; and (3) identify factors associated with QoL in individuals with PFP.

2. METHODS

This systematic review followed the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines,[30] with the protocol prospectively registered on PROSPERO (http://www.crd.york.ac.uk/PROSPERO/; CRD 42016026307, 12 April 2016). There were no peer-reviewed literature reviews of this topic at the time.

2.1 Literature Search Strategy

A comprehensive search strategy was devised for the following electronic databases: (i) AMED, (ii) CINAHL via EBSCO, (iii) Cochrane Central Register of Controlled Trials, (iv) EMBASE via OVID, and (v) MEDLINE via OVID. Diagnostic search terms from a Cochrane systematic review of exercise interventions for individuals with PFP were used to identify PFP literature;[54] and combined with terms for QoL measurement tools, similar to the strategy used by Filbay et al, 2014.[17] The search strategy for MEDLINE is presented in Appendix 1, and was adjusted to suit other databases. All potentially eligible papers were imported into EndNote X7.2.1 (Thomson Reuters, Carlsbad, California, USA) and duplicates were removed. The search was conducted in April, 2016. Two reviewers (X and Y) independently screened the titles and abstracts of all articles using a checklist based on the eligibility criteria. Papers with insufficient information in title and abstract to determine eligibility were retained for full-text evaluation using the same checklist. Reference lists of all publications considered for inclusion were hand-searched and citation tracking was completed using Google Scholar. The final lists of eligible articles were compared between the two reviewers, with a third reviewer available to resolve any disagreement (Z).

2.2 Selection Criteria

All studies reporting QoL in individuals with PFP were included, regardless of study design methodology. Participants in the studies were required to be experiencing PFP/retropatellar

knee pain/anterior knee pain or be diagnosed with chondromalacia patella. Studies were excluded if participants had other knee conditions (such as a ligament or meniscal injury, patellar tendinopathy, recurrent patella subluxation, diagnosed radiographic osteoarthritis or were preoperative patients awaiting surgery for their PFP). No other treatment intervention was excluded. To reduce the likelihood that a proportion of study participants may have undiagnosed patellofemoral osteoarthritis (PFOA) studies of participants with mean age of greater than 50 years were excluded from this systematic review.[21] Studies not published in English, French, German or Danish were ineligible. In the case of multiple studies using the same cohort, the study reporting QoL outcomes for the largest sample size was included.

2.3 Assessment of Reported Methodological Quality

Two independent reviewers (X, W) rated the reported methodological quality of included studies using two separate scales. The first scale was a checklist adapted from the 21-item Downs and Black checklist which is suitable for randomised and non-randomised studies (Appendix 2)[15]. Items were scored according to the method used by Downs and Black (1998): 'Yes' (score=1), 'No' (score=0), or 'Not Applicable' (items removed from scoring), except for Item 5 (i.e. description of principle confounders clearly described) which was scored 'Yes' (score=2), 'Partially' (score=1) or 'No' (score=0). Items considered not applicable to assess intervention studies were removed, resulting in a modified checklist of 15 items. One of the 15 items, concerning follow-up, was not applicable to cross-sectional studies and 6 items were not applicable to validity and reliability studies so were removed from scoring, leaving 14 and 8 items, respectively. Therefore a percentage score was calculated from relevant items for the three different study designs. The median value was identified to assign a level of methodological quality. Studies were classified as higher reported quality (study

score equal to or greater than the median value) and lower reported quality (study score less than the median value).[38]

The second scale used was The Cochrane Risk of Bias Tool.[22] This tool is specifically used for controlled intervention studies to provide explicit assessment of each component risk of bias.[58] The additional quality assessment tool provided more comprehensive evaluation of intervention study outcomes to inform the second aim of this review. The Cochrane Risk of Bias Tool is comprised of a 7 domain checklist to assess selection bias (2 domains), performance bias (1 domain), detection bias (1 domain), attrition bias (1 domain), reporting bias (1 domain), and other bias (1 domain). Domains were recorded as low or high risk of bias or risk of bias unclear. Risk of bias within studies was summarised as low risk (low risk of bias for all domains), unclear risk (low or unclear risk of bias for all domains), or high risk (high risk of bias for one or more domain).[22] Any inter-rater disagreement was discussed in a consensus meeting and unresolved items were taken to a third reviewer (Z) for consensus. A level of evidence was assigned for intervention study data using the statistical outcomes and methodological quality of included studies, based on recommendations by van Tulder.[56]

2.4 Data Management and Statistical Analyses

Participant (e.g. sex, age, BMI) and study (e.g. study design) characteristics, QoL, and type of treatment for intervention studies, were independently extracted (X). If sufficient data were not reported in the published article or supplementary material provided, the corresponding author was contacted to request further information. Data were cross-checked by a second reviewer (V). When intervention studies reported QoL data at multiple time points post-treatment for PFP, data from the first follow-up after treatment were extracted. If BMI data were not reported, then it was estimated from mean height and mass data.

Normative QoL data were obtained from previously published population studies. Studies with QoL data available from the largest number of participants of a comparable age were selected.[9,23,29,33] Pain-free control data were obtained from included studies.[5,36,39,42]

Data were analyzed based on QoL instrument. Knee-related QoL was measured with the Knee injury and Osteoarthritis Outcome Score QoL subscale (KOOS-QoL). Health-related QoL was measured with: i) the 36-Item Short Form Survey (SF-36) reported as 8 domain scores and/or physical and mental component summary scores (PCS and MCS respectively), (ii) the 8-Item Short Form Survey (SF-8) reported as 8 domain scores, or (iii) the European QoL-5 Dimension (EQ-5D) index score. To address the first aim of this review, pooled mean [95% CI] QoL data from individuals with PFP, pain-free controls, and normative populations are presented. Baseline mean QoL scores from intervention studies were pooled with QoL data from all other studies. To address the second aim of this review, random effects meta-analyses were used to compare QoL between pre- and post-treatment for repeated measure design intervention studies and to compare QoL outcomes between treatment and control groups for controlled intervention studies (Review Manager Version 5.3). Pooled findings of intervention studies were considered heterogeneous if I^2 >50% was statistically significant ($p<0.05$). Standardized mean differences (SMD) [95% CI] are reported. The magnitude of the pooled SMD was interpreted based on Cohen's criteria, where SMD ≥0.8 was interpreted as a large effect, >0.5 and <0.8 a moderate effect, and >0.2 and <0.5 a small effect.[18]

2.5 Deviations from study protocol

Initially, we were interested in exploring the association between secondary outcomes (i.e. body mass index [BMI], age, pain) and QoL through a meta-regression analysis (ie. Aim 3).

However, due to a low number of included case-control studies for each QoL instrument, a meta-analysis comparing QoL and secondary outcomes was not possible. Considering at least 10 studies should be included in a meta-analysis for each covariate in order for a meta-regression analysis to be meaningful, it was not possible to conduct the planned meta-regression analysis[8]. Additionally, the Cochrane risk of bias tool[22] was added to enhance examination of the risk of bias of included randomized controlled trials (RCT).

3.0 RESULTS

3.1 Search Strategy, Methodological Quality, and Risk of Bias

The comprehensive search strategy identified 1573 titles, with 1304 titles and abstracts evaluated after removal of duplicates. The full-text of 93 articles were retrieved and assessed for eligibility. Two additional papers were identified by citation tracking, and four were identified in an updated search performed prior to final data analysis using the same search strategy, in January, 2017. Twenty-one studies met the selection criteria (Figure 1).

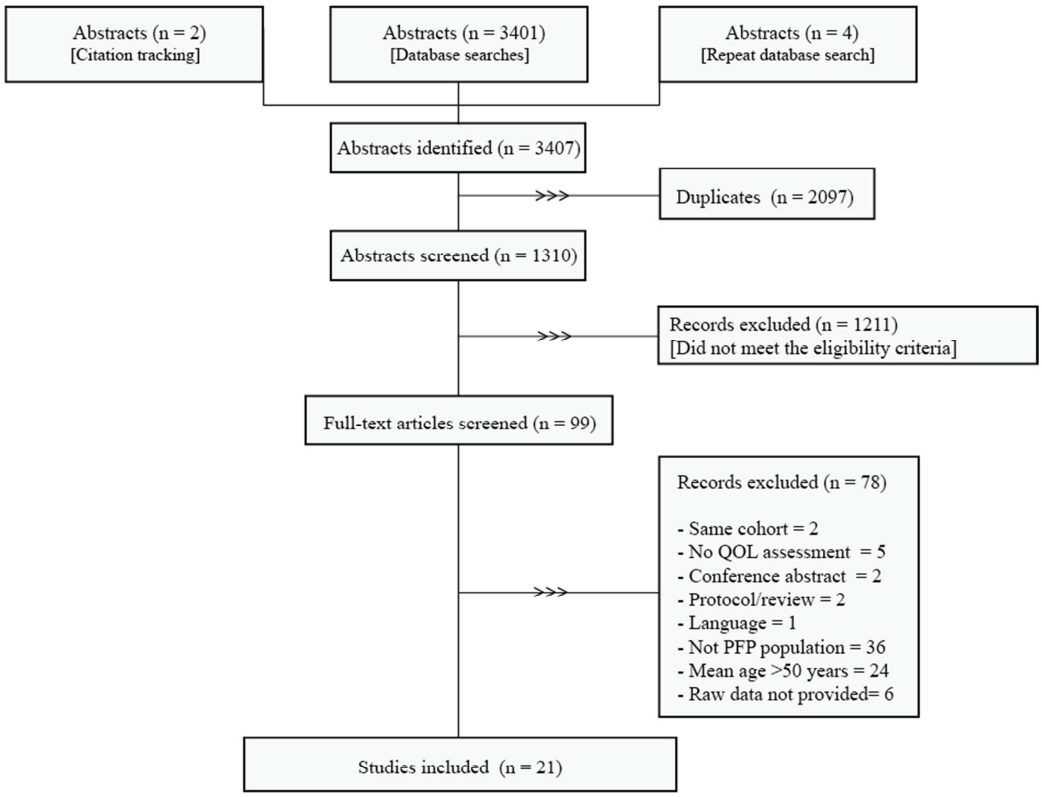

FIGURE 1: *Flow chart of the study selection process.*

Thirteen authors (for 15 studies) were contacted to obtain raw data, 10 responded and of these, 8 supplied data for 9 studies[4,11,14,32,34,36,41,47,57]. QoL data were extracted for 1111 individuals with PFP and 100 pain-free controls. Characteristics of included studies are presented in Table 1.

181 **TABLE 1:** *Characteristics of the included studies.*

Study	PFP participants	Control participants	Aim/Comparison/ Intervention	Rx Duration	QOL measure(s)	Domain	PFP	Comparator
Cross-sectional								
Assa 2015 (Israel)	n = 157 Age = 30 (5) BMI = 24 (3) W = 42%	n = 31, Pain-free Age = 32 (4) BMI = 23 (3) W = 45%	PFP compared to control		SF-36	PF RP BP GH V SF RE MH PCS MCS	65 [62 to 68] 40 [34 to 45] 50 [47 to 54] 65 [62 to 68] 54 [51 to 57] 77 [73 to 80] 65 [58 to 71] 69 [67 to 72] 55 [52 to 57] 66 [63 to 69]	97 [96 to 99] 97 [93 to101] 92 [88 to 96] 82 [88 to 96] 72 [67 to 75] 97 [95 to 100] 98 [95 to 101] 79 [76 to 83] 88 [86 to 90] 86 [83 to 88]
Rathleff CR 2013 (Denmark)	n = 20 Age = 15 (1) BMI = 20 (3) W = 80%	n = 20, Healthy Age = 15 (1) BMI = 19 (1) W = 80%	PFP compared to control		KOOS-QOL EQ-5D (index)		54 [49 to 60] 0.72 [0.68 to 0.78]	98 [95 to 101] 1.0 [1.0 to 1.0]
Rathleff MS 2013 (Denmark)	n = 57^ Age = 17 (1) BMI = 21 (2) W = 100%	n = 29, Pain-free Age = 17 (1) BMI = 21 (3) W = 100%	PFP compared to control		KOOS-QOL		54† [50 to 58]	99 [98 to 100]
Rathleff MS 2016 (Denmark)	n = 20^ Age = 20 (20-21) BMI =22* (NR) W = 100%	n = 20, Pain-free Age = 21 (19-21) BMI =22* (NR) W = 100%	PFP compared to control		KOOS-QOL		55† [47 to 63]	97 [94 to 100]
Study	**PFP**	**Control**	**Aim/Comparison/ Intervention**	**Rx Duration**	**QOL measures**	**Domain**	**PFP**	**Comparator**
Cheung 2013	*Amateur athletes*		Amateur compared to		SF-36	PF	88 [80 to 96]	

(China)	n = 19 Age = 23 (1) BMI = 20* (NR) W = NR	professional athletes with PFP		RP BP GH V SF RE MH PF	78 [59 to 96] 63 [54 to 72] 66 [56 to 74] 63 [55 to 72] 83 [72 to 93] 67 [45 to 88] 74 [66 to 81] 75 [67 to 82]
	Professional athletes n = 19 Age = 21 (2) BMI = 20* (NR) W = NR			RP BP GH V SF RE MH	42 [23 to 61] 51 [54 to 72] 65 [56 to 74] 55 [44 to 65] 78 [71 to 86] 58 [37 to 79] 65 [58 to 71]
Silva 2016 (Brazil)	*Non-athletes* n = 34 Age = 15 (1) BMI = 22* (NR) W = 32%	Non-athletes compared to athletes with with PFP	KOOS-QOL		68 [62 to 74]
	Athletes n = 22 Age = 14 (1) BMI = 22 ( ) W = 36%				78 [70 to 86]
Vincent 2010 (Australia)	n=33 Age = NR BMI = NR W = NR	Knee pain (PFP subgroup obtained from author)	SF-8	PF RP BP GH V SF	49 [46 to 52] 39 [36 to 42] 35 [30 to 39] 43 [41 to 46] 51 [48 to 53] 46 [43 to 49]

						RE	51 [49 to 54]	
Study	**PFP**	**Control**	**Aim/Comparison/ Intervention**	**Rx Duration**	**QOL measures**	**Domain**	**PFP**	**Comparator**
Vincent 2010 (Australia) *(Continued)*	n=33 Age = NR BMI = NR W = NR		Knee pain (PFP subgroup obtained from author)		SF-8	MH PCS MCS	48 [46 to 51] 40 [36 to 44] 54 [51 to 57]	
Validity and reliability								
Apivatgaroon 2016 (Thailand)	n = 49 Age = 47 (11) BMI = 25 (5) W = 80%		Testing validity & reliability of Kujala in PFP		SF-36	PF RP BP GH V SF RE MH PCS MCS	33 [26 to 39] 54 [48 to 60] 42 [37 to 47] 47 [41 to 54] 52 [47 to 57] 54 [49 to 59] 55 [49 to 62] 59 [53 to 64] 46 [41 to 50] 53 [49 to 58]	
Cheung 2012 (China)	n = 64 Age = 30 (6) BMI = 22* (NR) W = 41%		Testing validity & reliability Kujala in PFP		SF-36	PF RP BP GH V SF RE MH	88 [85 to 91] 76 [68 to 84] 58 [52 to 63] 64 [60 to 69] 62 [58 to 66] 84 [79 to 89] 79 [70 to 88] 73 [69 to 76]	
Negahban 2013 (Iran)	n = 100 Age = 25 (7) BMI = 23* (NR) W = 71%		Validity & reliability of Functional Index Questionnaire & Modified Functional Index Questionnaire in individuals with PFP		SF-36	PF RP BP GH V SF RE	65 [60 to 70] 48 [40 to 55] 51 [47 to 55] 54 [50 to 57] 58 [56 to 61] 66 [62 to 70] 45 [36 to 54]	

						MH	64 [61 to 67]	
						PCS	55 [52 to 58]	
						MCS	58 [54 to 61]	
Study	**PFP**	**Control**	**Comparison or Intervention**	**Rx Duration**	**QOL measures**	**Domain**	**PFP**	**Comparator**
Controlled intervention studies								
Crossley 2002 (Australia)	*Treatment* n = 36 Age = 29 (8) BMI = 24 (4) W = 64%		Randomized controlled trial comparing change in QOL after active MMP in PFP vs. change after placebo intervention in PFP	6 weeks	SF-36	PF RP BP GH V SF RE MH	64 [57 to 71] 59 [47 to 72] 52 [45 to 59] 71 [64 to 76] 55 [49 to 61] 67 [60 to74] 81 [69 to 93] 72 [67 to 77]	79 [73 to 85] 80 [70 to 91] 77 [71 to 83] 78 [72 to 84] 64 [58 to 70] 75 [69 to 81] 85 [75 to 95] 82 [78 to 86]
		Placebo N = 34 Age = 26 (8) BMI = 25 (4) W = 66%		6 weeks		PF RP BP GH V SF RE MH	64 [58 to 70] 57 [40 to 68] 52 [44 to 58] 71 [64 to 78] 56 [51 to 63] 69 [63 to 76] 73 [60 to 86] 75 [70 to 81]	82 [78 to 86] 79 [68 to 90] 72 [65 to 79] 77 [72 to 83] 63 [57 to 69] 80 [73 to 87] 89 [82 to 96] 81 [77 to 85]
Petersen 2016 (Germany)	*MMP & brace* n = 78 Age = 28 (9) BMI = 23 (2) W = 51%		Randomized trial comparing change in QOL following MMP & brace intervention vs. MMP alone	6 weeks	KOOS-QOL		40 [37 to 44]	69 [65 to 72]
	MMP n = 78 Age = 28 (8)			6 weeks			43 [40 to 45]	60 [55 to 65]

	BMI = 23 (1) W = 61%							
Study	**PFP**	**Control**	**Comparison or Intervention**	**Rx Duration**	**QOL measures**	**Domain**	**PFP**	**Comparator**
Rathleff MS 2014 (Denmark)	*Physiotherapy + Education* n = 62 Age = 17 (1) BMI = 21 (3) W = 74%		Cluster randomized trial comparing change in QOL following supervised physiotherapy + education vs. education alone	12 weeks	KOOS-QOL		57 [52 to 61]	62 [54 to 71]
	Education n = 59 Age = 17 (1) BMI = 22 (3) W = 86%			12 weeks			53 [49 to 57]	54 [52 to 57]
Syme 2011 (UK)	*VMO training* n = 23 Age = 29 (8) BMI = 26 (1) W = 57%		Randomized controlled trial comparing change in QOL following vastus medialis oblique selective training vs. general quadriceps strengthening	8 weeks	SF-36	PCS MCS	45 [42 to 48] 45 [42 to 48]	53 [49 to 58] 46 [42 to 51]
	Quadriceps strengthening n = 23 Age = 27 (8) BMI = 26 (1) W = 57%			8 weeks		PCS MCS	47 [43 to 50] 47 [43 to 50]	54 [49 to 60] 50 [47 to 54]
		No treatment n = 23		8 weeks		PCS MCS	47 [43 to 50] 47 [43 to 50]	40 [32 to 48] 49 [44 to 54]

Age = 29 (6)
BMI = 26 (1)
W = 65%

Study	PFP	Control	Comparison or Intervention	Rx Duration	QOL measures	Domain	PFP	Comparator
Repeated measure intervention studies								
Akkurt 2010 (Turkey)	n = 22 Age = 35 (8) BMI = NR W = 100%		Repeated measures study of QOL following isokinetic exercise	6 weeks	SF-36	PCS MCS	40 [31 to 49] 51 [41 to 60]	63 [55 to 72] 67 [59 to 75]
Banan 2016 (Iran)	n = 25 Age = 35 (10) BMI = 25 (7) W = 80%		Repeated measures study of QOL following rigid taping	4 weeks	KOOS-QOL		12 [8 to 15]	13 [9 to 17]
Eapen 2011 (India)	n = 20 Age = 28 (7) BMI = NR W = 60%		Repeated measures study of QOL following eccentric exercise	2 weeks	SF-36	BP PCS MCS	45 [40 to 51] 37 [35 to 39] 42 [39 to 45]	75 [69 to 80] 48 [46 to 49] 44 [43 to 46]
Haim 2013 (Israel)	n = 48 Age = 31 (7) BMI = 24 W = 44%		Repeated measures study of QOL following use of biomechanical device in shoe	26 weeks	SF-36	PF RP BP GH V SF RE MH PCS MCS	61 [55 to 66] 42 [30 to 53] 51 [44 to 57] 60 [55 to 66] 50 [44 to 56] 76 [69 to 83] 69 [57 to 82] 68 [64 to 73] 53 [47 to 58] 65 [59 to 71]	64 [58 to 70] 54 [43 to 65] 58 [53 to 64] 65 [59 to 70] 54 [48 to 59] 81 [74 to 88] 73 [61 to 85] 68 [63 to 73] 59 [54 to 64] 68 [63 to 73]
Kuru 2012 (Turkey)	*Kinesio tape & exercise* n = 15 Age = 33 (12) BMI = 24 (5)		Repeated measures study of QOL following Kinesio tape & exercise vs. Electrical stimulation	6 weeks	SF-36	PF RP BP GH V	41 [37 to 45] 34 [29 to 39] 40 [36 to 44] 40 [36 to 45] 46 [42 to 49]	49 [45 to 52] 45 [41 to 50] 50 [47 to 53] 44 [40 to 48] 51 [47 to 54]

	W = 80%		+exercise			SF	42 [38 to 47]	47 [44 to 50]
						RE	39 [32 to 47]	50 [46 to 55]
						MH	40 [35 to 45]	44 [41 to 47]
Study	**PFP**	**Control**	**Comparison or Intervention**	**Rx Duration**	**QOL measures**	**Domain**	**PFP**	**Comparator**
Kuru 2012 (Turkey) *(Continued)*	*Electrical stimulation & exercise* n = 15 Age = 41 (11) BMI = 27 (4) W = 93%			6 weeks	SF-36	PF	39 [33 to 45]	48 [43 to 53]
						RP	43 [35 to 50]	53 [49 to 57]
						BP	43 [38 to 49]	52 [49 to 54]
						GH	43 [37 to 49]	46 [41 to 51]
						V	44 [38 to 49]	48 [42 to 53]
						SF	44 [39 to 49]	49 [44 to 54]
						RE	43 [34 to 51]	53 [48 to 57]
						MH	40 [33 to 46]	46 [41 to 50]
Sinclair 2016 (UK)	n = 20 Age = NR BMI = NR W = 45%		Repeated measures study of QOL following brace use	2 weeks	KOOS-QOL		53 [47 to 58]	68 [60 to 76]
Tsai 2015 (USA)	n = 12 Age = 39 (NR) BMI = 23 (NR) W = 75%		Repeated measures study of QOL following off-axis elliptical training	6 weeks	KOOS-QOL		49 [36 to 62]	61 [48 to 74]

*Note. Demographic data are presented as mean (standard deviation), unless otherwise stated. Quality of life data are presented as mean [95% confidence interval]. Abbreviations as follows: PFP, patellofemoral pain; Rx, treatment; QOL, quality of life; BMI, body mass index (kg/m^2); W, women; NR, not reported; KOOS, Knee Injury and Osteoarthritis Outcome Score; SF-36, Short-Form 36-Item Health Survey; PF, physical function; RP, role physical; BP, bodily pain; GH, general health; V, vitality; SF-social function; RE, role emotional; MH, mental health; SF-8, Short-Form 8-Item Health Survey; MMP, multi-modal physiotherapy; * symbol denotes BMI not reported but estimated from height and mass; † is PFP participant data derived from participants included in largest cohort reported in 2014 paper*

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Eleven studies investigated the effect of a treatment intervention on QoL in PFP individuals. Interventions included single treatment and multi-modal physical therapy, shoe inserts, braces and elliptical training. The methodological quality scores ranged from 31-100%, with a median score of 67% (Table 2). There were 12 studies of higher quality and nine studies of lower quality. Of the four controlled intervention studies, there was one low risk of bias study, one unclear, and two high risk of bias studies (Table 3).

TABLE 2. *Reported methodological quality of the included studies.*

Author	1	2	3	5	6	7	10	11	12	15	18	20	25	26	27	Score	Total	%	Quality
QOL in PFP (cross-section studies compared to control)																			
Assa 2013	1	1	1	1	1	1	1	0	0	1	1	1	0	N/A	1	11	15	73	Higher
Rathleff CR 2013	1	1	1	2	1	1	1	1	0	1	1	1	1	N/A	0	13	15	87	Higher
Rathleff MS 2013	1	1	1	2	1	0	1	1	0	0	1	0	1	N/A	0	10	15	67	Higher
Rathleff MS 2016	1	1	1	2	1	1	1	1	0	1	1	1	1	N/A	1	14	15	93	Higher
QOL in PFP (cross-section & validity studies)																			
Apivatgaroon 2016	1	1	1	N/A	1	1	N/A	0	0	N/A	N/A	1	N/A	N/A	N/A	6	8	75	Higher
Cheung 2012	1	1	1	N/A	1	0	N/A	0	0	N/A	N/A	1	N/A	N/A	N/A	5	8	63	Lower
Cheung 2013	1	1	1	2	1	1	1	0	0	0	0	1	1	N/A	1	11	15	73	Higher
Negahban 2013	1	1	1	N/A	1	1	N/A	0	0	N/A	N/A	1	N/A	N/A	N/A	6	8	75	Higher
Silva 2016	1	1	1	2	1	1	1	1	0	0	1	1	1	N/A	1	13	15	87	Higher
Vincent 2010	1	1	0	2	1	0	1	0	0	0	1	1	1	N/A	1	10	15	67	Higher
Effect of intervention on QOL for PFP (randomised controlled studies)																			
Crossley 2002	1	1	1	2	1	1	1	1	0	1	1	1	1	1	1	15	16	94	Higher
Petersen 2016	1	1	1	1	1	0	0	1	0	0	1	1	1	0	1	10	16	63	Lower
Rathleff 2014	1	1	1	2	1	1	0	1	1	1	1	1	1	1	1	15	16	94	Higher
Syme 2009	1	1	1	2	1	1	0	1	1	1	1	1	1	1	1	15	16	94	Higher
Effect of intervention on QOL for PFP (repeated measures studies)																			
Akkurt 2010	1	1	1	0	1	1	1	0	0	0	0	0	0	0	0	6	16	38	Lower
Banan 2016	1	1	1	1	1	1	1	0	0	0	0	1	0	0	0	8	16	50	Lower
Eapen 2011	1	1	1	0	1	1	1	0	0	0	1	0	0	0	1	8	16	50	Lower
Haim 2013	1	1	1	1	1	1	1	0	0	0	1	0	0	N/A	1	9	15	60	Lower
Kuru 2012	1	1	1	1	1	1	1	0	0	0	0	0	0	1	0	8	16	50	Lower
Sinclair 2016	1	1	0	0	1	1	0	0	0	0	1	0	0	0	0	5	16	31	Lower
Tsai 2015	1	1	0	0	1	1	0	0	0	0	1	0	0	1	1	7	16	44	Lower

Note. N/A is not applicable. Higher quality is median score (67%) or above and lower quality is below median (<67%)

TABLE 3: *Risk of bias of included controlled intervention studies.*

Study	Random sequence generation	Allocation concealment	Blinding of participants & personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Risk of bias within trial
Crossley 2002	Low	Low	Low	Low	Low	Low	Low	Low risk
Petersen 2016	High	High	High	High	Unclear	Unclear	High	High risk
Rathleff 2014	Low	Low	Unclear	Low	Low	Low	Low	Unclear risk
Syme 2009	Low	Low	High	Low	Low	Low	High	High risk

Low *risk of bias (bias if present is unlikely to alter the results seriously);*

Unclear *risk of bias (a risk of bias that raises some doubt about the results);*

High *risk of bias (bias may alter the results seriously)*

3.3 QoL in Individuals with PFP

Knee-related QoL in individuals with PFP

Seven studies reported knee-related QoL (KOOS-QoL) in individuals with PFP.[6,34,36,41,47,48,51] The pooled mean KOOS-QoL score from 7 studies (3 higher quality and 4 lower quality) in individuals with PFP was 47 [95% CI: 34 to 61] (Figure 2).

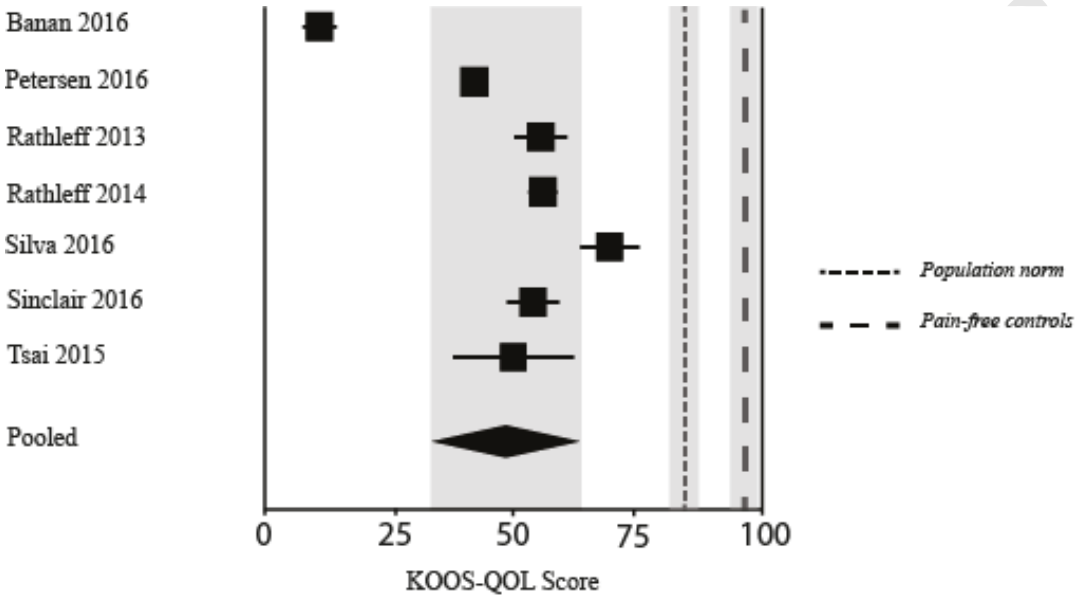


FIGURE 2: *Knee-related quality of life in individuals with patellofemoral pain.*

One study considered an outlier (i.e. mean KOOS-QoL score (11) was outside the 95% CI for the pooled mean),[6] when excluded from the analysis, resulted in a pooled mean KOOS-QoL score of 53 [95% CI: 45 to 61]. A single study reported knee-related QoL in athletes with PFP (KOOS-QoL score, 78 [95% CI: 70 to 86]) (Table 4).[47]

TABLE 4. *Quality of life in athletes with PFP compared to active population norms.*

	Included studies			Active Population Norm	Mean difference	
	PFP-Pooled	**Silva 2016 PFP-Athletes**		**Cameron 2013**	**PFP Athletes v Active Norm**	
KOOS-QoL	47 [34 to 61]	78 [70 to 86]		92 (12)	14	
SF-36	**PFP-Pooled**	**Cheung 2013**		**Huffman 2008**	**Mean difference**	
		PFP-Amateur athletes	**PFP-Professional athletes**		**PFP Amateur athletes v Active Norm**	**PFP Professional athletes v Active Norm**
PF	59 [45 to 74]	88 [80 to 96]	75 [67 to 82]	99 [98 to 100]	11	24
RP	50 (41 to 60]	78 [59 to 96]	42 [23 to 62]	96 [94 to 98]	18	54
BP	49 [45 to 53]	63 [54 to72]	51 [41 to 62]	89 [87 to 91]	26	38
GH	57 [50 to 66]	66 [56 to 76]	65 [56 to 74]	86 [85 to 88]	20	21
V	54 [49 to 58]	63 [55 to72]	55 [44 to 65]	71 [69 to 73]	8	16
SF	67 [55 to 79]	83 [72 to 93]	78 [71 to 86]	96 [95 to 98]	13	18
RE	61 [50 to 73]	67 [45 to 88]	58 [37 to 79]	98 [97 to 99]	31	40
MH	64 [55 to 72]	74 [66 to 80]	65 [58 to 71]	83 [82 to 85]	9	18

All data reported as mean, [95%CI].
Active population norm reported in groups with no history of injury

Knee-related QoL in individuals with PFP compared to population norms

The previously reported mean KOOS-QoL score from a general population sample of young adults was 84 [95% CI: 81 to 88][33]. Based on the pooled scores, individuals with PFP had worse knee-related QoL relative to this general population sample (mean difference: 37; [KOOS-QOL 95% CI: 34 to 61]). The previously published mean KOOS-QoL score from active individuals (with no history of knee injury) was 92 [95% CI: 92 to 93].[9] Based on this data, athletes with PFP had worse knee-related QoL relative to norms from an active population (mean difference: 14; [KOOS-QOL 95% CI: 70 to 86]).

Knee-related QoL in individuals with PFP compared to pain-free controls

Three included studies[36,39,42] provided KOOS-QoL data from three different groups of pain-free individuals (i.e. 69 females) and the pooled mean KOOS-QoL score was 98 [95% CI: 97 to 100]. Based on the pooled scores, individuals with PFP had worse knee-related QoL relative to pain-free controls (mean difference: 51).

Health-related QoL in individuals with PFP

Fourteen studies reported health-related QoL in individuals with PFP using SF-36, SF-8, and EQ-5D measures. Eleven studies reported on QoL using the SF-36; eight of these studies reported SF-36 domain scores,[4,5,11,12,14,20,27,32] seven studies reported SF-36 summary scores[2,4,5,16,20,32,49] and four reported both domain and summary scores.[4,5,20,32] One paper used the SF-8[57] and two studies used the EQ-5D[36,41] (one study used a youth version (EQ-5D-Y)).[36]

Pooled SF-36 domain scores from 7 studies (4 higher quality[4,5,14,32] and 3 lower quality[11,20,27]) in individuals with PFP were: physical function 59 [95% CI: 45 to 74], role physical 50 [95% CI: 41 to 60], bodily pain 49 [95% CI: 45 to 53], general health 57 [95% CI: 50 to 66], vitality 54 [95% CI: 49 to 58], social function 67 [95% CI: 55 to 79], role emotional 61 [95% CI: 50 to 73] and mental health 64 [95% CI: 55 to 72]. A single study reported health-related QoL (SF-36 domains) in amateur and professional athletes with PFP[12] (Table 4). Pooled SF-36 PCS and MCS scores from 7 studies (4 higher quality[4,5,32,49] and 3 lower quality[2,16,20]) were 47 [95% CI: 41 to 53] and 54 [95% CI: 47 to 62] respectively.

A PFP subgroup from a single study[57] of individuals with knee pain-related diagnoses reported health-related QoL measured with SF-8 (physical function 49 [95% CI: 46 to 52], role physical 39 [95% CI: 36 to 42], bodily pain 35 [95% CI: 30 to 39], general health 43

[95% CI: 41 to 46], vitality 51 [95% CI: 48 to 53], social function 46 [95% CI: 43 to 49], role emotional 51 [95% CI: 49 to 54] and mental health 48 [95% CI: 46 to 51]).

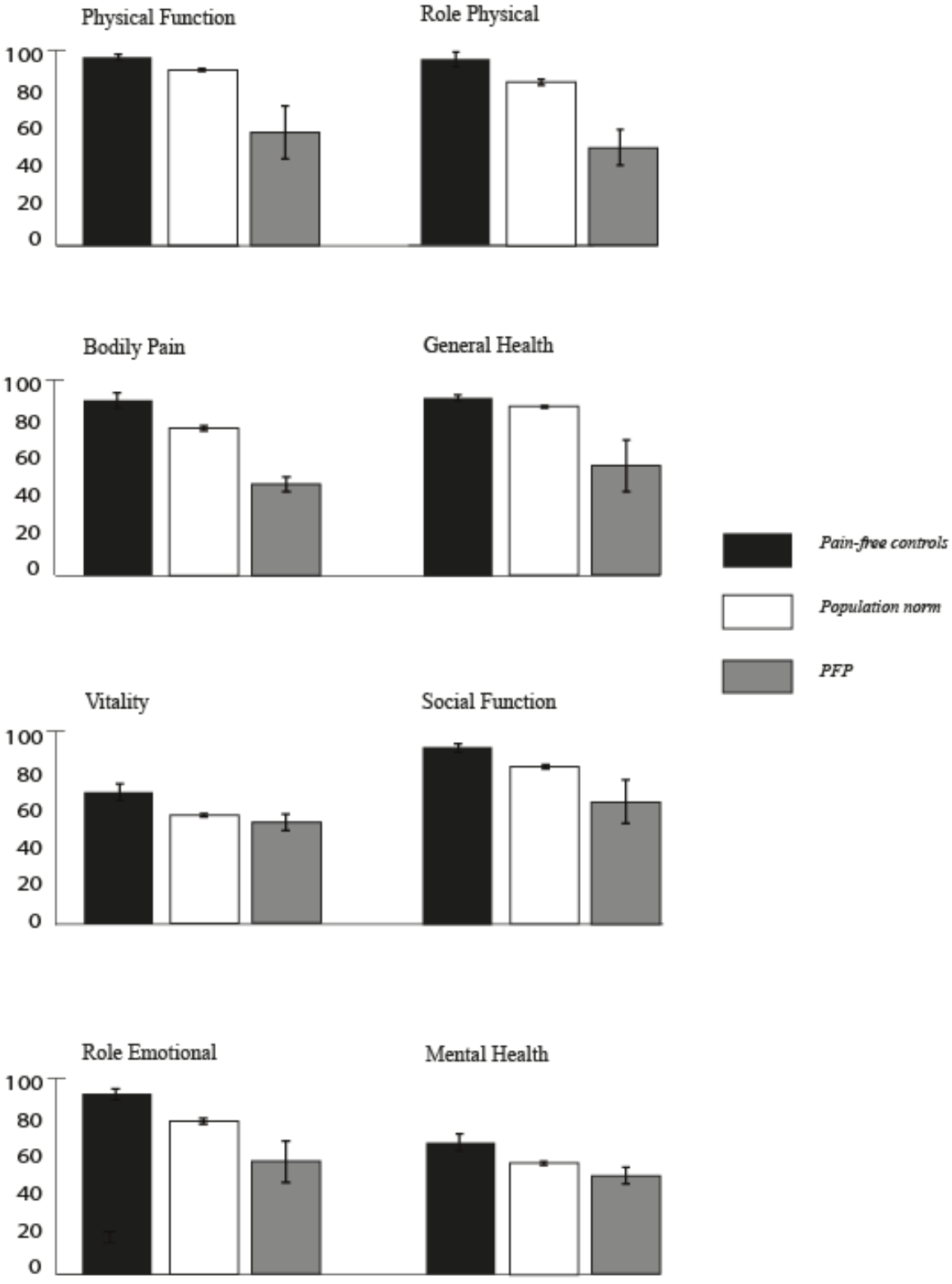
Two studies reported health-related QoL in individuals with PFP measured with EQ-5D,[36,41] but were unable to be pooled as they used different versions of the EQ-5D and one study[36] reported median score rather than mean. Scores from these 2 studies were mean 0.75 [standard deviation (SD)=0.12][41] and median 0.72 [interquartile range 0.68-0.78].[36]

Health-related QoL in indiviudals with PFP compared to population norms

Relative to previously reported mean SF-36 domain scores from a general population sample,[29] individuals with PFP had worse health-related QoL (mean difference: physical function=34, role physical=36, bodily pain=30, general health=24, vitality=6, social function=20, role emotional=23 and mental health=14). Additionally, amateur and professional athletes with PFP from a single study, also had worse health-related QoL when compared to previously published SF-36 scores from an active general population sample (Table 4).[23]

Health-related QoL in individuals with PFP compared to pain-free controls

Compared to mean SF-36 domain scores in pain-free controls,[5] individuals with PFP had worse health-related QoL (mean difference: physical function=38, role physical=47, bodily pain=43, general health=25, vitality=18, social function=30, role emotional=37 and mental health=16) (Figure 3).



288 **FIGURE 3:** *Health-related quality of life in individuals with patellofemoral pain.*

289

290 Individuals with PFP also had worse health-related QoL based on SF-36 PCS and MCS when
291 compared to data from pain-free controls[5] (mean difference: PCS=41, MCS=32) (Table 1).

Only one study reported EQ-5D scores in individuals with PFP (median score: 0.72) compared to pain-free controls (median score: 1.00).[36]

3.4 Effects of PFP Intervention on QoL

Knee-related QoL

Two RCTs reported conflicting evidence for the effect of intervention on KOOS-QoL.[34,41] A lower-quality and high risk of bias study showed that the combined treatment of a knee brace and multi-modal physical therapy, compared to multi-modal physical therapy alone significantly improved knee-related QoL (SMD=0.45 [95% CI: 0.13 to 0.77]).[34] A higher-quality and unclear risk of bias study reported no statistically significant differences in knee-related QoL between individuals with PFP receiving physical-therapist supervised neuromuscular retraining and home exercise with an education session, and those receiving an education session alone (SMD=0.31 [95% CI: -0.05 to 0.67]) (Figure 4).[41]

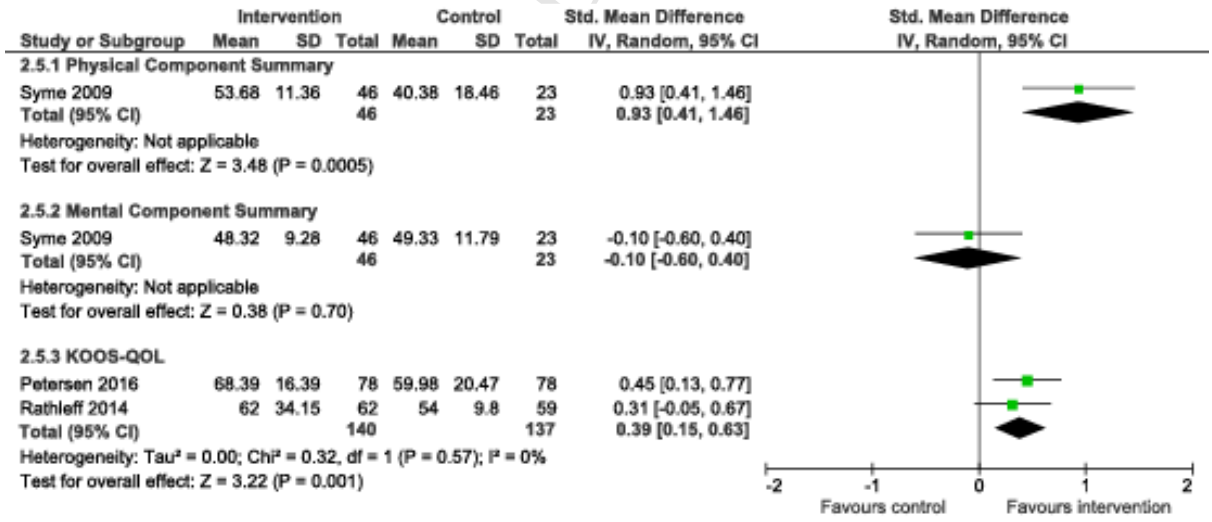


FIGURE 4: *Effect of intervention on quality of life in controlled studies.*

Pooled data from three lower-quality repeated measures design studies[6,48,51] provided limited evidence of moderate improvement in knee-related QoL post-intervention (interventions

consisted of brace, off-axis elliptical trainer and tape) compared to pre-intervention (SMD=0.54 [95% CI: 0.04 to 1.04], I^2=41%, p=0.03) (Figure 5).

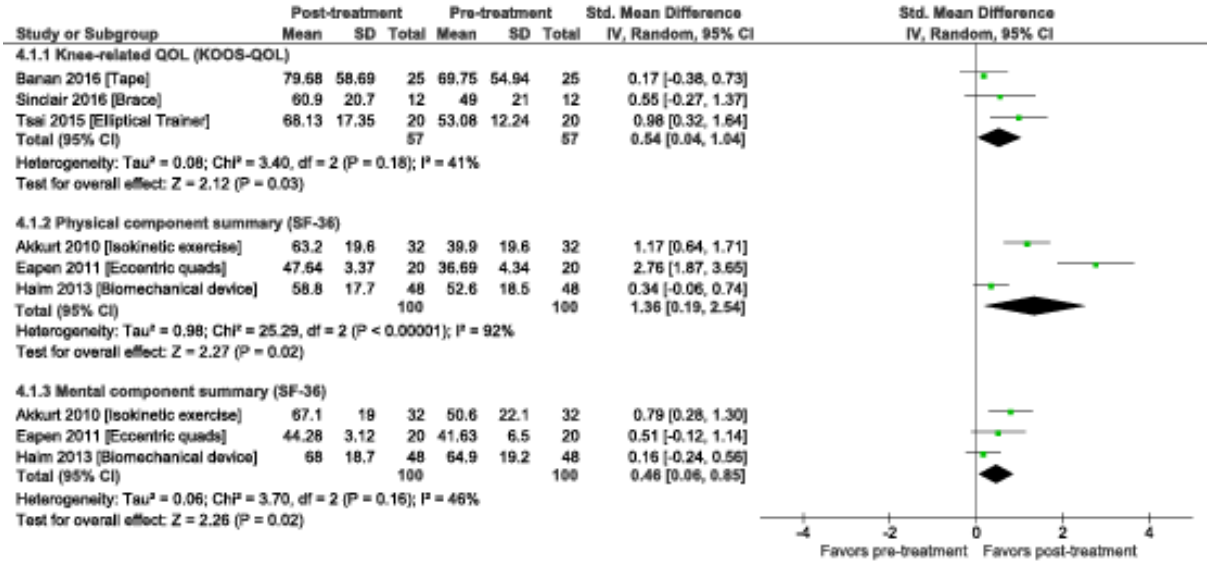


FIGURE 5: *Effect of intervention on quality of life in repeated measures studies.*

Health-related QoL

Two RCTs reported conflicting evidence of the effect of intervention on SF-36 scores.[14,49] A higher-quality and low risk of bias study investigated the effect of multi-modal physical therapy compared to a placebo intervention and found no significant differences between the domain scores of the two groups (Tables 1 and 2).[14] Another higher-quality but high risk of bias study investigated the effects of two multi-modal physical therapy treatments; one based on McConnell taping and selective vastus medialis obliquus exercise (VMO), and the other comprised of sling taping and quadriceps strengthening.[49] QoL outcomes were compared to a (no treatment) control group. Large improvements were observed following analysis of combined mean PCS scores following multi-modal physical therapy for all treated individuals (SMD=0.93 [95% CI: 0.41 to 1.46]) relative to the control group. There was no significant difference in PCS or MCS scores between intervention groups. Large PCS score

improvements were observed following analysis of each intervention group compared to no intervention; McConnell taping plus VMO exercise group (SMD=0.84 [95% CI: 0.23 to 1.44]) and the sling taping plus quadriceps strengthening group (SMD=0.87 [95% CI: 0.26 to 1.48]) (Figure 4).[49]

Four repeated measures design studies reported health-related QoL pre- and post-intervention.[2,16,20,27] Pooled SF-36 summary scores from three lower-quality studies[2,16,20] provided limited evidence of large improvements in health-related QoL (PCS SMD=1.36 [95% CI: 0.19 to 2.54], I^2=92%, p=0.02, MCS SMD=0.46 [95% CI: 0.06 to 0.85], I^2=46%, p=0.02) post-intervention (strengthening, biomechanical foot-worn device) relative to pre-intervention (Figure 5). A lower-quality study investigated two intervention for PFP: (i) Kinesio taping plus exercise program, and (ii) electrical stimulation of VMO plus exercise program.[27] Compared to pre-intervention, both interventions resulted in significant improvements in SF-36 domain scores, except for vitality.[27]

3.5 Factors associated with QoL in Individuals with PFP

Due to the very limited number of controlled studies, random effects meta-analysis to determine factors related to QoL outcomes in individuals with PFP could not be performed.

4.0 DISCUSSION

4.1 QoL in Individuals with PFP

This systematic review revealed that individuals with PFP had substantially worse knee- and health-related QoL relative to pain-free controls (KOOS-QoL mean difference: 51, SF-36 domains mean difference range: 16-47) and population norms (KOOS-QoL mean difference: 37, SF-36 domains mean difference range: 14-36). Impairments in knee- and health-related

QoL, were highlighted by the fact that pooled PFP mean 95% CI upper limits were all lower than the 95% CI lower limits for pain-free and normative QoL group means. Impairments in SF-36 PCS scores in individuals with PFP compared to the reference group, were greater than MCS scores, suggesting an emphasis on addressing physical impairments is needed to improve QoL in individuals with PFP.

Recent systematic reviews indicate similar impairments in KOOS-QoL for a range of other knee conditions, including knee osteoarthritis (pooled mean=35)[13], anterior cruciate ligament (ACL) injury (pooled mean=44)[13], and 5-16 years following ACL reconstruction (pooled mean=74)[17]. Our findings indicate that the impact of PFP (pooled mean=47) on knee-related QoL approaches that of knee osteoarthritis. Additionally, knee-related QoL impairment in people with PFP is similar or greater than QoL impairment following ACL injury, which is considered to be a life-changing event with substantial physical and psychological impacts.[25,43]

Our findings indicate athletetic cohorts with PFP (e.g. KOOS-QoL = 78)[12,47] have better knee- and health-related QoL compared to pooled findings of PFP cohorts without inclusion based on athletic status (e.g. KOOS-QoL = 47). This finding is not surprising considering athletes generally have an increased perception of their health in comparison with age-matched peers.[9,23,47] However, when compared to QoL norms measured in active populations, our findings indicate both knee- and health-related QoL was impaired in athletes with PFP.

4.2 Effects of PFP Intervention on QoL

Findings from repeated measure intervention studies indicate that knee- and health-related QoL improved following interventions for PFP including bracing, taping and exercise

therapy. Importantly, these improvements are greater than the minimal clinically important improvement (MCII) reported for KOOS-QoL (8-10 points)[44] and the SF-36 PCS and MCS (5-7 points).[60,61] However, less improvement was observed in SF-36 MCS scores (mean difference improvement: 6 points), perhaps reflecting the greater impairment in PCS compared with MCS at baseline. Significant improvements in knee- and health- related QoL following intervention in these repeated measure studies should be interpreted with caution. Importantly, a lack of control or comparison group means it is unclear if these improvements were the result of the intervention, placebo, physical-therapist interaction, natural history, or a combination of these factors.[53] Unfortunately, there are currently very few RCTs to provide further insight.

Very limited evidence from one RCT, indicated that despite significant improvements in pain and function, knee-related QoL did not improve more following physical-therapy intervention (i.e., patellofemoral soft tissue mobilisation, strength exercises, neuromuscular training) plus education in comparison to education alone. It is possible that the KOOS-QoL subscale (assessing lifestyle modification, knee awareness, knee confidence and knee difficulties) may not be sensitive to changes in knee pain and function. Similarly, two RCTs reported significant improvements in pain and function for individuals that received multi-modal physical therapy compared to controls, but the impact of intervention on health-related QoL was conflicting. Physical interventions may need to be specifically developed in order to target improvements in knee- and health-related QoL. Further research is needed to determine the most effective interventions for improving QoL in individuals with PFP.

Interestingly, Rathleff et al 2014, was the only RCT to encourage ongoing self management and exercise in the longer term (i.e. 12 months) and was also the only controlled study

without a high risk of bias to report significant improvements in knee-related QoL at longer-term follow up (i.e. 12 months), specifically in adolescents. This may indicate that improving QoL in individuals with PFP requires longer-term physical interventions and follow up (e.g. beyond the common 6-12 week clinical trial period), although further research is needed to confirm this, particularly in adults.

4.3 Limitations and Recommendations for Future Research

Firstly, all relevant studies were included regardless of methodological quality due to the paucity of research in this area. Therefore, low-quality studies may bias the findings. To account for this, the levels of evidence reported in this review involve consideration of study homogeneity, quality and quantity.

Previously published normative QoL data from Norway[29] and Sweden[33] were used for comparison as these were the largest published normative samples. However the comparison between Scandinavian normative QoL data and pooled QoL data from individuals with PFP from many different countries, may have biased these results.[1] Although chronic musculoskeletal conditions have been shown to have a similar impact on health-related QoL measured by the SF-36 in eight (Western) countries[3], comparison with non-Western cultures is complex[52] and such analysis is beyond the scope of this review.

Pain-free control group QoL data was very limited (i.e., 4 studies) which may bias pooled mean knee- and health-related QoL comparisons against individuals with PFP. Additionally, three of the four control groups were comprised of adolescent and adult women and lower health-related QoL scores have been reported in women compared to men.[10,26] However, due to the small number of included studies reporting QoL data for men and women, sex-based

analyses were not conducted. Given sex-based differences associated with PFP, future research should consider reporting data for men and women separately.

Most intervention studies included in this systematic review measured knee- or health-related QoL as a secondary outcome, and hence may be underpowered to detect changes in QoL.[59] Considering we found markedly impaired QoL in individuals with PFP, future research should consider QoL measures as a primary intervention target and power participant recruitment accordingly. We were unable to determine whether other participant or methodological factors are associated with QoL in individuals with PFP, due to the small number of controlled studies published.

5.0 CONCLUSION

Individuals with PFP aged under 50 years, have impaired knee- and health-related QoL compared to the general population and pain-free individuals. Based on current evidence, including a paucity of high quality randomised controlled trials, it is unclear whether common interventions provided to individuals with PFP have any beneficial effect on knee- and health-related QoL when compared to a control group. Developing treatments to target knee-related and health-realted QoL in individuals with PFP and evaluating their efficacy in longer-term, high-quality randomized controlled trials is urgently needed.

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APPENDIX 1: *Search Strategy for MEDLINE*

CONCEPT	KEYWORDS	MESH HEADING	
Patellofemoral pain	1. anterior knee pain.mp. 2. patella* or femoropatell* or retropatell* or patellofemoral or patello-femoral *adj2* pain or syndrome or dysfunction.mp 3. lateral compression or lateral facet or lateral pressure or odd facet *adj2* syndrome.mp 4. chondromalac* or chondropath* or chondrosis *adj2* patell* or femoropatell* or retropatell* or femoro-patell*.mp.	5. Patella/ or Knee joint/ or Knee/ AND Pain/ or Arthralgia/ 6. Patellofemoral pain syndrome/ 7. Chondromalacia Patellae/	8. OR/1-7
Quality of life	9. Knee Injury and Osteoarthritis Outcome Score or KOOS.mp. 10. Short?form 36 OR SF?36 OR Short?form 12 OR SF?12 OR Short Form Health Survey.mp. 11. EQ5D OR EQ-5D*.mp. 12. QOL OR AQOL OR Health related quality of life or HRQOL.mp. 13. lower extremity activity profile or leap.mp	14. Quality of life/	15. OR/9-14
			16. 8. AND 15.

APPENDIX 2. *Modified Downs & Black checklist for methodological quality appraisal.*

Item	Title	Description by Downs& Black	Yes	No/Unable to determine	Partially	Inter-vention	Cross-section	Validity
1	Aim	Is the hypothesis/aim/objective clearly described?	1	0				
2	Outcomes	Are the main outcomes to be measured clearly described in the Introduction or Methods section?	1	0				
3	Participants	Are the characteristics of the patients included in the study clearly described?	1	0				
5	Confounders	Are distributions of principal confounders in each group of subjects to be compared clearly described?	2	0	1			N/A
6	Findings	Are the main findings of the study clearly described?	1	0				
7	Random variability	Does the study provide estimates of the random variability in the data for the main outcomes	1	0				
10	Probability	Have actual probability values been reported for the main outcomes except where the probability value in less than 0.001?	1	0				N/A
11	External validity	Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	1	0				
12	External validity	Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	1	0				
15	Blinding	Was an attempt made to blind those measuring the main outcomes of the intervention?	1	0				N/A
18	Statistical tests	Were the statistical tests used to assess the main outcomes appropriate?	1	0				N/A
20	Accurate outcomes	Were the main outcome measures used accurate (valid and reliable)?	1	0				
25	Confounding adjustment	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	1	0				N/A
26	Loss to follow-up	Were losses of patients to follow-up taken into account?	1	0			N/A	N/A
27	Power	Did the study have sufficient power to detect a clinically important effect where probability value for difference being due to chance is < 5%	1	0				N/A
	Max score		**16**			**16**	**15**	**8**

Note. N/A is not applicable

HIGHLIGHTS

People with patellofemoral pain have impaired quality of life

Quality of life is worse than the general population

Quality of life is worse than pain-free people

Physical therapy may improve quality of life