TITLE: Are there three main subgroups within the patellofemoral pain population? A detailed characterisation study of 127 patients to help develop targeted Intervention (TIPPs).

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ABSTRACT

- **Background**

Current multimodal approaches for the management of non-specific patellofemoral pain are not optimal, however, targeted intervention for subgroups could improve patient outcomes. This study explores whether subgrouping of non-specific patellofemoral pain patients, using a series of low cost simple clinical tests, is possible.

- **Method**

The exclusivity and clinical importance of potential subgroups was assessed by applying à priori test thresholds (1 SD) from seven clinical tests in a sample of adult patients with non-specific patellofemoral pain. Hierarchical clustering and latent profile analysis, were used to gain additional insights into subgroups using data from the same clinical tests.

- **Results**

One hundred and thirty participants were recruited, 127 had complete data: 84 (66%) female, mean age 26 years (SD 5.7) and mean BMI 25.4 (SD 5.83), median (IQR) time between onset of pain and assessment was 24 (7-60) months. Potential subgroups defined by the à priori test thresholds were not mutually exclusive and patients frequently fell into multiple subgroups. Using hierarchical clustering and latent profile analysis three subgroups were identified using 6 of the 7 clinical tests. These subgroups were given the following nomenclature: (i) 'strong', (ii) 'weak and tighter', and (iii) 'weak and pronated foot'.

- **Conclusions**

We conclude that three subgroups of patellofemoral patients may exist based on the results of six clinical tests which are feasible to perform in routine clinical practice. Further research is needed to validate these findings in other datasets and, if supported by external validation, to see if targeted interventions for these subgroups improve patient outcomes.

BACKGROUND

Non-specific patellofemoral pain (PFP) is a musculoskeletal disorder of the knee joint that causes significant pain and dysfunction around the patella leading to limitations in physical activities [1]. The condition is not self-limiting, 90% of PFP patients still have symptoms 4 years after diagnosis [2,3], and only 6% are symptom free at 16 years follow up [4].

PFP may be a risk factor for developing patellofemoral osteoarthritis (OA) [5, 6]. PFP has recently emerged as the 3rd highest ranked topic out of 185 in the Chartered Society of Physiotherapy (UK) Musculoskeletal Research Priority Project [7]. Expert consensus statements published following three International Patellofemoral Pain Research Retreats (IPFPRR) propose biomechanical risk factors for developing PFP described by anatomical location relative to the knee. These factors are: Proximal - upper femur, hip and trunk; Local - in and around the patella and the patellofemoral joint; Distal - lower leg foot and ankle [8,9,10]. These risk factors may guide in developing clinical subgroups.

Subgrouping approaches have proved fruitful to optimise management in other musculoskeletal conditions such as low back pain, in which psychosocial characteristics have also been incorporated into subgroup criteria [11, 12]. Previous authors have investigated subgroups within the PFP population using specialised high cost equipment not routinely seen in clinic e.g. radiographic examination and scintigraphy [13], dynamic MRI [14, 15], and six camera three dimensional motion analysis systems [16]. The translation of these results into routine practice in physiotherapy clinics is therefore likely to be limited. With the exception of Dierks et al [16] the focus of these studies has tended to be on local biomechanical factors, rather than adopting an holistic approach that also incorporates proximal and distal factors.

Recently Selhorst et al [17] reported on a pilot study of 21 paediatric PFP patients, mean age 14 years, where they defined a new PFP classification algorithm that contains four subgroups; elevated fear avoidance, decreased muscle flexibility, functional malalignment, decreased muscle strength. Unfortunately they provided no details are as to how the 4 groups were derived. Keays, Mason and Newcombe [18] also described four clinical PFP subgroups; hypermobility, hypomobility, faulty movement pattern, osteoarthritis. Interestingly they had a very wide age range in their sample from 13-82 years with only eight patients in the 20-40 year age range and each participant was required to have four X-rays of the knee. With the exception of gender [19] the main focus of most previous

studies of PFP has been on biomechanical rather than non-biomechanical factors [20]. Selhorst et al [17] highlight the necessity of addressing psychosocial factors in PFP and there is some evidence to suggest a relationship exists between patients with PFP and activity levels [8], weight [6], and pain mechanisms [21], these factors may be of relevance to subgrouping approaches in the management of patients suffering from PFP.

The present study is part of a larger programme of work exploring whether targeted management of PFP subgroups can optimise patient outcome.   Previously, seven clinical assessment tests have been proposed that may be useful in identifying clinical subgroups [22]. Further detail on these clinical assessment tests and à priori test thresholds can be found in the protocol for this study [22].

In the present paper, we aimed to explore whether subgrouping of patellofemoral pain patients, using a series of low cost simple clinical tests, was possible. Four objectives were identified:

> (1) to determine the relative frequency with which the patients fell into each of the potential subgroups defined by the à priori test thresholds;
> (2) to assess whether the potential subgroups defined by the à priori test thresholds were mutually exclusive or whether, and how frequently, patients fell into two or more subgroups;
> (3) to ascertain whether other approaches such as hierarchical clustering and latent profile analysis, offered additional insights into subgrouping of PFP patients using data from the same clinical assessment tests;
> (4) to report differences in patient-related characteristics (demographic, clinical and psychosocial) across subgroups.

METHODS

Design of the clinical study

A cross-sectional observational study design was used. Participants attended an assessment clinic on one occasion prior to physiotherapy treatment, at which a physiotherapist undertook the seven clinical assessment tests (Table 1). In addition, an assessment of demographic (e.g. age, gender and anthropometry), clinical (e.g. skin temperature index, time since onset), and psychosocial characteristics (e.g. physical activity, function, quality of life and pain levels) was completed (Table 2). No formal power calculation was undertaken given the exploratory nature of the study but a target sample of 150 was considered sufficient to estimate the proportion of participants who fell into different subgroups and for multiple group membership, with adequate precision [22].

The setting and type of participants

Four National Health Service (NHS) physiotherapy clinics, serving the general population, participated in this study; one in primary care, three in hospital settings. Between May 2012 and November 2013, patients aged between 18 and 40 years diagnosed with non-specific unilateral or bilateral PFP were approached to participate in this study (Figure 1). Eligibility criteria were based on criteria used in two previous studies [23, 24] where patients with specific pathologies such as ligamentous instability or patella subluxation were excluded, these are fully detailed in the protocol for this study [22]. Patients were included in this study if the duration of their pain was at least 3 months and they self-reported anterior or retropatellar pain on at least two of the following activities: prolonged sitting, ascending or descending stairs, squatting, running, kneeling, and hopping/jumping. Two of the following on clinical examination were also required: pain during resisted isometric quadriceps contraction, pain on palpation of the posterior facets of the patella, pain during squatting. When eligible patients agreed to participate, written informed consent was obtained.

Clinical assessment

There were seven clinical assessment tests 1) passive prone knee flexion (rectus femoris length), 2) passive knee extension in supine (hamstrings length), 3) calf flexibility standing method (gastrocnemius length) measured using inclinometry, 4) Hip abductor strength, 5) quadriceps strength measured using hand-held dynamometry, 6) Total patellar mobility (medial plus lateral glide) measured using the patellar glide test, and 7) foot pronation assessed by the Foot Posture Index (FPI). In the presence of bilateral PFP pain, assessment was undertaken on the most affected leg, as nominated by the patient. To ensure standardisation across the study centres, all therapists attended an initial, and three refresher, training days and were provided with a manual outlining the assessment procedures. Each site was visited by members of the research team (JS, JJ) on at least 3 occasions to monitor fidelity with assessment procedures.

Statistical methods

For each measure of muscle flexibility, the mean of three assessments, reported in degrees from the baseline position, was taken as the test score. For both measures of muscle strength, the maximum moment measured in Newton-metre (Nm) from 3 trials was taken as the test score. This was also

normalised to body mass, that is, Newton-metre per kilogram (Nm/Kg). For patellar mobility the total medial/lateral displacement in millimetres of the distal pole was taken as the test score. For the seven clinical assessment tests, and patient demographic, clinical, psychosocial and functional characteristics, summaries are presented using mean (SD), median (inter-quartile range) or frequency (%), as appropriate.

In this paper we report the findings of an exploratory analysis of the membership of predetermined subgroups using two approaches. Firstly the data were explored using à priori test thresholds, based on 1 SD from published norms (Table 3). The lower limb biarticular muscle tightness subgroup was defined by lack of flexibility in two of the three clinical assessment tests. For quadriceps and hip abductor muscle weakness subgroups, the test score was in Nm because of the lack of available population data normalised for weight. Percentages of participants falling into individual subgroups and into multiple subgroups were estimated, with 95%CIs calculated using exact binomial methods. Sensitivity analysis was undertaken using different standard deviations from the published population norms (1.5 SD, 2.0 SD, 2.5 SD).

Secondly the data were explored using two other approaches; hierarchical agglomerative cluster analysis (using SPSS) and latent profile analysis (using Latent Gold). Hierarchical agglomerative cluster analysis, a bottom-up approach to partitioning participants into subgroups based on the similarity (or distance) of the set of variables (e.g. clinical tests or measures), and latent profile analysis, a statistical method of estimating the probability of individuals' membership of latent (or unknown) classes (or subgroups) based on a set of variables (e.g. clinical tests or measures), in which it is assumed that the variables are independent, given the class membership. For the hierarchical agglomerative cluster analysis, Ward's method was used, Euclidean distance squared and standardised the data using the Z-scores. The number of subgroups was based on the number which could be supported within a clinical context [25].

For latent profile analysis, Akaike information criterion (AIC) and Bayesian information criterion (BIC) were computed for each model to aid the choice of model and hence the number of subgroups [26]. Both methods, hierarchical clustering and latent profile analysis were performed independently and parallel to each other by two separate authors of this paper. In these analyses data were used from each flexibility test separately and strength normalised for body mass (Nm/kg). The mean and standard deviation of test scores are reported for each subgroup in each approach and analysis of variance (ANOVA) was performed to test for significant differences in individual test scores between the groups. The differences between means of other patient characteristics were

also explored using ANOVA. In both sets of ANOVAs, when overall differences were statistically significant (p<0.05), multiple comparisons between subgroups were performed using Tukey's B (Wholly Significant Difference) test [27]; if observed subgroup variances differed substantially, the sensitivity to the equal variances assumption was assessed by also performing the Games-Howell test [28]. Comparisons between subgroups for gender and activity were made using χ^2-tests, with pairwise multiple comparisons using Bonferroni correction of P-values when overall differences were statistically significant (P<0.05).

Approvals, consent and licenses

The study received ethical approval from NRES Committee North West – Greater Manchester North, REC reference: 11/NW/0814 and University of Central Lancashire (UCLan) Built, Sport and Health (BuSH) Ethics Committee Reference Number: BuSH 025. R&D approval was also obtained from each participating NHS trust and licenses for the questionnaire instruments obtained, where required.

RESULTS

One hundred and thirty participants were recruited, three participants did not have a complete set of seven clinical test scores and were removed from further analyses (table 1). The study cohort was predominantly female and on average was slightly overweight, the mean age was 26 years (SD 5.7) (Table 2).

Table 1. Mean (sd) for the 7 clinical tests for 127 participants

Clinical assessment tests	Rectus Femoris Length test ^{0}	129.4 (20.05)
	Hamstring Length test ^{0}	151.4 (14.77)
	Gastrocnemius Length test ^{0}	27.8 (10.75)
	Maximum Quadriceps Strength Nm	73.7 (41.13)
	Maximum Quadriceps Strength normalised to body mass Nm/kg	1.0 (0.51)
	Maximum Hip Abductor Strength Nm	72.8 (38.85)
	Maximum Hip Abductor Strength normalised to body weight Nm/kg	1.0 (0.50)
	Total Patellar Mobility mm	12.2 (4.63)
	Foot Posture index	4.4 (4.44)

Table 2. Patient-related (demographic, clinical and psychosocial) characteristics for 127 participants

Demographic characteristics	Mean (SD) age in years	26 (5.7)
	Number (%) of females	84 (66%)
	Mean (SD) Height in m	1.7 (0.11)
	Mean (SD) Body Mass in kg	73.5 (18.3)
	Mean (SD) Body mass index in kg/m2	25.4 (5.83)
Clinical characteristics	Median (IQR) time since clinical onset in months***	24 (7 to 60)
	Number (%) with Bilateral pain	67 (52.8%)
	Number (%) with traumatic onset**	17 (13.4%)
	Mean (SD) patellar temperature index (Celsius) $^\$$*	4.7 (3.55)
Psychosocial characteristics	Mean (SD) Numerical Pain Rating Scale*	4.7 (1.95)
	Mean (SD) Self-completed Leeds Assessment of Neuropathic Symptoms and Signs pain scale (SLANSS)***	6.5 (5.84)
	Mean (SD) Short-form McGill Pain Questionnaire	
	Continuous pain	3.1 (1.95)
	Intermittent pain	2.4 (2.02)
	Neuropathic pain	0.8 (1.15)
	Affective descriptors	1.2 (1.76)
	Number (%) with low physical activity level – (IPAQ)****	19 (15.0%)
	Mean (SD) Modified Functional Index Questionnaire*	34.1 (16.97)
	Mean (SD) Hopkins Symptom Checklist	1.3 (0.42)
	Mean (SD) EQ-5D-5L	
	Index value*	0.7 (0.17)
	Visual Analogue Scale (VAS)	75.4 (16.56)
	Mean (SD) WHO Disability Assessment Scale II***	19.4 (7.04)
	Mean (SD) Movement Specific Reinvestment Scale	
	Movement self-consciousness subscale	13.3 (6.69)
	Conscious motor processing subscale	17.4 (5.75)

$^\$$ Difference in skin temperature between the patella and anterior tibialis;* 1 missing value;** 2 missing values; *** 3 missing values; **** 6 missing values

No participant met the à priori criteria for hypermobility, few for lower limb biarticular muscle tightness (27.6%, 95%CI 20.0% to 36.2%) or foot pronation (33.9%, 95% CI 25.7% to 42.8%) but most met the criteria for quadriceps weakness (98.4%, 95% CI 94.4% to 99.8%), patellar hypomobility (96.1%, 95% CI 91.1% to 98.7%) and hip abductor weakness (88.2%, 95% CI 81.3% to 93.2%). Consequently, most participants (89.8%, 95% CI 83.1% to 94.4%) met the criteria for at least 3 subgroups: 40.2% fell into 3 subgroups; 44.1% into 4 subgroups and 5.5% into 5 subgroups (figure 2).

Even when the most extreme values of 2.5 SD was considered, only 38.6% (n=49) fell into just one subgroup.

Table 3. Distribution of 127 participants into predetermined subgroups using different SD from population norms

		Standard deviation from published population norm			
	Published population norm	1 SD	1.5 SD	2 SD	2.5 SD
	Mean (sd)	n (%)	n (%)	n (%)	n (%)
Lower limb biarticular tightness		35 (27.6%)	12 (9.4%)	8 (6.3%)	3 (2.4%)
Quadriceps	132.21 (16.39)	33 (30.0%)	19 (15.5%)	12 (9.4%)	3 (2.4%)
Hamstrings	Male: 142.55 (6.85) Female: 153.66 (11.13)	31 (24.4%)	18 (14.2%)	9 (7.1%)	4 (3.1%)
Gastrocnemius	35.22 (6.59)	74 (58.3%)	46 (36.2%)	38 (29.1%)	24 (18.9%)
Hip abductor weakness	Male: Age<30: 185 (37.6) Age≥30: 163 (37.4) Female: Age<30: 114 (31.8) Age≥30: 102 (26.0)	112 (88.2%)	100 (78.7%)	66 (52.0%)	38 (29.9%)
Quadriceps weakness	Male: Age<30: 242 (55.8) Age≥30: 236 (43.8) Female: Age<30: 160 (26.4) Age≥30: 157 (41.9)	125 (98.4%)	119 (93.7%)	115 (90.6%)	104 (81.9%)
Patellar hypomobility	26.2 (5.8)	122 (96.1%)	111 (87.4%)	89 (70.1%)	63 (49.6%)
Patellar hypermobility	26.2 (5.8)	0	0	0	0
Foot pronation	4 (3)	43 (33.9%)	18 (14.2%)	17 (13.4%)	3 (2.4%)
No subgroup		0	1 (0.8%)	2 (1.6%)	7 (5.5%)

Preliminary analysis of both hierarchical cluster and latent profile analysis, showed a similar mean

hamstring length across subgroups, therefore this variable was excluded from the final analyses for

both approaches. For the latent profile analysis approach, the AIC and BIC suggested either a 3 or 5 cluster solution as the best fit to the data. Three subgroups were chosen, as this would be more feasible to implement in practice and partitioning into 5 subgroups did not offer any further insight into potential treatment regimens.

Both classification methods, hierarchical clustering and latent profile analysis, generated subgroups which, on interpretation of the mean test scores across the six clinical assessments, could be given the same nomenclature (table 4) : there was a 'strong' subgroup, a 'weak and tighter' subgroup, and a 'weak and pronated foot' subgroup. In both methods, the 'strong' subgroup exhibited the highest mean quadriceps and hip abductor strength with the most flexible rectus femoris and subgroup membership was highly consistent. The 'weak and tighter' subgroup, exhibited weak mean quadriceps and hip abductor strength and were less flexible (in one of the two assessments). The 'weak and pronated foot' subgroup exhibited the highest mean FPI, and in the hierarchical clustering method, this was also accompanied by the greatest patellar mobility.   However, only about half of the participants were consistently classified across the hierarchical cluster and latent profile analysis methods for these two subgroups (table 5).

Table 4. Mean test scores across the 3 subgroups generated by hierarchical cluster and latent profile analysis

Subgroup	WEAK and TIGHTER Mean (SD)	STRONG Mean (SD)	WEAK and PRONATED FOOT Mean (SD)	ANOVA
Hierarchical clustering	**N=49**	**N=29**	**N=49**	
Rectus Femoris Length^0	121.8 (19.48)	140.7 (17.06)**	130.4 (19.21)	F=9.26 P <0.001
Gastrocnemius Length^0	22.3 (9.71)*	28.0 (6.51)*	33.1 (11.21)*	F=14.98 p<0.001
Quadriceps Strength Nm/kg	0.84 (0.32)	1.65 (0.53)**	0.82 (0.32)	F=53.01 p<0.001
Abductor Strength Nm/kg	0.79 (0.30)	1.69 (0.46)**	0.83 (0.29)	F=75.11 p<0.001

Total Patellar Mobility mm	10.0 (3.55)	10.8 (3.03)	15.4 (4.61)**	F=27.12 p<0.001
Foot Posture index	3.3 (4.16)	3.0 (5.28)	6.3 (3.49)**	F=8.22 p<0.001
Latent profile analysis	**N=50**	**N=28**	**N=49**	
Rectus Femoris Length^{0}	119.1 (18.06)**	140.6 (16.91)	133.5 (18.99)	F=14.58, p<0.001
Gastrocnemius Length^{0}	28.7 (11.08)	28.2 (6.29)	26.6 (12.39)	F=0.53, p=0.59
Quadriceps Strength Nm/kg	0.62 (0.24)*	1.68 (0.52)*	1.04 (0.23)*	F=97.54, p<0.001
Abductor Strength Nm/kg	0.60 (0.18)*	1.73 (0.42)*	1.02 (0.21)*	F=167.69, p<0.001
Total Patellar Mobility mm	12.5 (3.77	10.5 (3.15)	12.8 (5.84)	F=2.55, p=0.083
Foot Posture index	2.80 (4.35)	3.71 (5.33)	6.37 (3.11)**	F=9.51, p<0.001

* all groups significantly different from each other (p<0.05)

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

Table 5: Comparison of subgroup membership between the two classification methods

Subgroups generated by		Latent profile analysis			Total
		'Weak and tight'	'Strong'	'Weak and pronated foot'	
Hierarchical cluster analysis	'Weak and tighter'	25	1	23	49
	'Strong'	1	26	2	29
	'Weak and pronated foot'	24	1	24	49
total		50	28	49	127

Table 6 shows the comparison of other patient related factors across the three subgroups generated by each of the methods. The 'strong' subgroup had more males, lower BMI and higher levels of physical activity; they also exhibited lower pain scores with significantly lower SLANSS; function as measured by the MFIQ was significantly better than the 'weak and tight' subgroup when classified by the latent profile analysis, and there was a trend towards better quality of life compared to the

other subgroups. The 'weak and tighter' subgroup had significantly higher BMI and worse MFIQ scores when classified by the latent profile analysis, and there was a trend towards low physical activity and longer duration of PFP, when classified by the hierarchical cluster analysis. The 'weak and pronated foot' subgroup was significantly younger at time of first assessment and had the shortest duration since the onset of their PFP according to both classification methods.

Table 6. Patient-related factors distributed across the 3 subgroups generated by the hierarchical cluster and latent profile analysis

Subgroup	WEAK and TIGHTER Mean (SD)	STRONG Mean (SD)	WEAK and PRONATED FOOT Mean (SD)	Test statistic and P-value
Hierarchical cluster analysis	**N=49**	**N=29**	**N=49**	
Age	26.9 (5.34)	28.3 (6.15)**	24.9 (5.36)**	F=3.85,p=0.024
Gender (% male)	13 (26.5%)	17 (53.6%)*	13 (26.5%)	χ^2 = 10.29, p=0.006
BMI	25.8 (5.37)	23.5 (4.44)	26.2 (6.77)	F=2.12, p=0.12
Physical activity level (low)	10 (20.8%)	2 (6.9%)	7 (15.2%)	χ^2 = 2.69, p=0.26
Movement specific reinvestment scale	31.4 (11.33)	29.0 (12.50)	30.9 (10.66)	F=0.418, p=0.66
Time from onset	58.0 (63.77)	45.2 (57.5)	34.1. (43.15)	F=2.22, P=0.11
HSCL (depression)	1.3 (0.38)	1.3 (0.57)	1.3 (0.36)	F=0.066, P=0.94
Pain (NPRS)	5.2 (1.88)	4.1 (1.68)	4.5 (2.08)	F=2.84, P=0.062
SLANSS (total)	8.1 (5.85)**	4.4 (5.58)**	6.1 (5.62)	F=3.98, P=0.021
EQ-5D-5L VAS	75.9 (14.40)	77.9 (17.23)	73.5 (18.22)	F=0.67, P=0.52
WHO Disability Assessment Scale II	20.9 (7.27)	17.5 (8.27)	19.2 (5.70)	F=2.24, P=0.11
Modified Functional Index Questionnaire	37.0 (16.99)	28.0 (15.45)	35.0 (17.21)	F=2.72 P=0.070
Latent profile analysis	**N=50**	**N=28**	**N=49**	
Age	27.1 (5.56)	28.1 (5.99)**	24.8 (5.26)**	F=3.74, p=0.026
Gender (% male)	8 (16.0%)**	17 (60.7%)**	18 (36.7%)	χ^2=16.32, p<0.001
BMI	28.3 (6.81)*	23.2 (4.60)	23.7 (3.89)	F=12.24, p<0.001
Physical activity level (low)	8 (16.7%)	2 (7.1%)	9 (19.1%)	χ^2=2.03, p=0.36
Movement specific reinvestment scale	30.6 (10.89)	28.6 (12.34)	31.9 (11.18)	F=0.77, p=0.47
Time from onset	46.7 (54.67)	47.2 (57.70)	44.5 (56.93)	F=0.03, p=0.97
HSCL (depression)	1.3 (0.37)	1.23 (0.45)	1.3 (0.46)	F=0.21, p=0.81
Pain (NPRS)	5.0 (2.03)	4.14 (1.76)	4.6 (1.93)	F=1.96, p=0.15
SLANSS (total)	6.5 (5.36)	4.14 (5.62)**	7.8 (6.11)**	F=3.56, p=0.031
EQ-5D-5L VAS	72.3 (18.54)	80.4 (15.61)	75.8 (14.40)	F=2.18, p=0.12

WHO Disability Assessment Scale II	20.4 (6.59)	16.8 (8.05)	20.0 (6.60)	F=2.59, p=0.079
Modified Functional Index Questionnaire	38.1 (16.98)**	28.3 (16.52)**	33.5 (16.46)	F=3.18, p=0.045

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

** subgroup pairs different (p<0.05)

DISCUSSION

The present findings suggest that three subgroups of PFP patients may be identified using six low cost, simple clinical assessment, tests that can be applied in routine practice. This study provides an important first step in deducing whether targeted intervention for patients with PFP may be a useful strategy that ultimately leads to improved outcomes for patients.   Previous work on subgrouping has mostly focussed on using imaging techniques [13, 14, 15, 16] rather than on clinical testing; the small number of studies which have had a greater clinical focus have been small scale with a total of just 71 patients across two studies [17, 18] these may be underpowered to detect subgroups. Although it was anticipated that separate subgroups would be identified by each of the clinical assessment tests, this was not the case. In part, this may be because of inadequately defined á priori diagnostic thresholds available in the literature, but even applying more extreme thresholds suggested most participants fell into more than one predetermined subgroup (Table 3). Multiple predetermined subgroup membership was confirmed by hierarchical cluster and latent profile analysis, which generated three novel subgroups based on a combination of test scores. A 'strong' subgroup had the highest hip abductor and quadriceps strength mean scores and greatest rectus femoris length, while a 'weak and tighter' group had low mean scores for hip abductor and quadriceps strength and evidence of less flexibility, Although the 'weak and pronated foot' subgroup appeared to be reliant on the results of just the FPI in the latent profile analysis, greater patellar mobility additionally appeared to be an important factor in the hierarchical cluster analysis (Table 4).   Using different populations to that reported in this paper previous researchers [17, 18] have proposed four rather than three clinical subgroups of PFP patients. However, in common with the results reported here both previous papers describe a tight or hypomobile group that included measurements of rectus femoris and gastrocnemius length. Both previous papers also describe a weak group where weakness in the quadriceps and hip muscles were identified by a combination of visual inspection and functional testing rather than through specific objective testing using dynamometry. It is interesting to note that three independent studies performed in different

countries USA [17], Australia [18], and the UK, each with a slightly different PFP population and each using slightly different methods have reported some consistency in subgroups of PFP patients.

Therapist fidelity to the assessment process was high with only 3 patients with incomplete clinical assessments. This suggests that the assessments were feasible in practice within both primary and tertiary care physiotherapy clinics. Exploratory analyses also suggested that clinical assessment test scores of hamstring length are not informative in terms of subgrouping. From a clinical perspective these results are very interesting as hamstring stretching is often a component of physiotherapy treatment regimens for PFP. While hamstring tightness does not appear to be an important factor for subgrouping in PFP, our results compared to normative data found tight hamstrings in 24.4% (n=31) participants indicating that some patients may benefit from treatment. The research therapists conducting the tests found the assessment of quadriceps strength easier than the hip abductor measurement and we test scores were moderately highly correlated (r=0.72), so further investigation of the 'added value' of performing both tests is merited. Further work to identify the optimal thresholds for individual and combined clinical assessment tests which best classify PFP participants into the three novel subgroups is currently being undertaken. This work could potentially reduce the burden of assessment by reducing the number of tests required.

Other measures were included to assess patient characteristics such as the Hopkins Symptom Checklist and the Movement Specific Reinvestment Scale. However, these tests did not seem to contribute significantly to our understanding of subgroups or were difficult to administer e.g. the Short-form McGill Pain Questionnaire, so we propose to exclude these tests in future studies of subgrouping PFP patients. WHODAS II scores were moderately highly correlated (Spearman's r = -0.68) with the EQ-5D-5L, which has become firmly established as the 'gold standard' quality-of-life outcome measure for musculoskeletal physiotherapy practice in the UK [29], so on this basis we would also exclude the WHODAS II from further studies.

The baseline characteristics of the participants suggest that the study population was representative of PFP patients attending physiotherapy clinics [23, 30, 31]. The ratio of females to males was 2 to 1, a high proportion had bilateral pain (53%), and only a small percentage (13.8%) of patients reported a traumatic onset of pain. While the BMI profile of this cohort might be higher than expected for athletes with PFP, it was still lower than that of the UK general population and reflects that this was a general clinical population [32]. Mean clinical assessment test scores were also consistent with published findings for PFP patients [33-35]. Across the whole sample, pain scores were relatively

low, and function scores, levels of physical activity and quality-of-life scores were relatively good, as might be expected for what is considered a relatively low grade bothersome musculoskeletal condition. There were marked differences in the relative frequency of men and women across the subgroups. Although overall there were about twice as many women as men in the study population, there were relatively more men in the 'strong' group. While this observation might be considered inevitable because females tend to have lower muscle strength than males, about half or 4 in 10 were women in this subgroup, dependent on the method used (table 6). Analysis suggested that subgroups were stable for female participants but the number of males were too small for further analysis (data not shown). Further research should focus on potential differences in characteristics between subgroups and on investigating whether there are differences in subgroups between genders.

There were also differences between the subgroups with respect to some of the other participant characteristics. While it is not possible from this cross-sectional study to identify the direction of the relationship between the test scores and these other characteristics, they may provide further insights into aetiology or sequelae, which could guide further research on preventative strategies or therapeutic management. The 'weak and tighter' subgroup, generated by latent class analysis, had significantly higher mean BMI, with the majority being overweight and lowest physical activity, when subgroups were generated by the hierarchical approach. Being overweight has been associated with patellar cartilage loss [36, 37]. The speculated relationship between patellofemoral pain and patellofemoral osteoarthritis and the known relationship between obesity and knee osteoarthritis suggests that this observation is worthy of further investigation [6]. Whether the development of patellofemoral OA is potentially greater in this group compared to other two groups is at this stage highly speculative. In the short term it might however, point towards the need for adjunct strategies to promote activity and encourage weight loss in this subgroup, in addition to strengthening and flexibility exercises. While lower limb muscle weakness in PFP patients is well known, it was more surprising that a 'strong' subgroup existed with a trend towards less pain, higher function and better quality of life. This might suggest that the other well-known observation in PFP patients, that of poor neuromuscular control, is important and interventions focussing on movement control are required [38, 39]. The significantly younger age of the 'weak and pronated foot' group is interesting but initial suggestions of a developmental issue, are tempered by us specifically recruiting over 18 year olds to minimise the chance of 'growth spurt' problems. Other studies have demonstrated higher levels of passive ankle dorsiflexion in adolescents with knee pain [40] and this might suggest strategies including foot orthoses are warranted specifically for this subgroup.

Limitations

This was not an efficacy trial and there are no outcome data following treatment. Therefore it is unclear whether using the 3 subgroups suggested by this study will have any impact on modifying clinical practice or more importantly on improving patient outcomes. We considered that we needed at least 150 participants but recruited 130 of which 127 had sufficient data to be included in the exploratory analyses. Recruitment had to close because of time constraints. Although the target sample size was not reached, confidence intervals for subgroups based on a priori thresholds are relatively precise and similar subgroups across hierarchical cluster and latent profile analysis have been generated. However given the small number of men in the sample, we could not confirm that subgroupings are similar in different genders. Additionally the study focussed specifically on the young adult population aged 18-40, so it is unknown if these subgroups are relevant to adolescents or older patients.

There are a myriad of different approaches for subgrouping data and these will tend to give different results for the same dataset [25]. We chose to explore the data using two different approaches to provide some internal validation. We were to some extent reassured that generated subgroups could be given the same nomenclature. However, there were important differences in participant characteristics and the mean test scores between the groups. This makes clinical interpretation difficult. The two approaches differ in how they generate subgroups with latent profile analysis splitting the sample into smaller groups whereas hierarchical agglomerative clustering has a bottom-up approach. Also, latent profile analysis differs from cluster analysis methods in that individuals are not assigned definitively to classes based on a chosen distance measure but are typically assigned to classes based on probabilities of membership of each class, usually estimated via maximum-likelihood estimation of the parameters of a specified model. Unlike cluster analysis, there is no requirement to explicitly scale each variable as the classification is based directly on the distributional properties of the variables and classifications are therefore unaffected by the choice of a variable's scale. Because of these features, latent profile analysis is increasingly considered a better analytical approach to hierarchical clustering methods [40]. It also provides information on the most likely number of clusters (by using the AIC and BIC), whereas this is more difficult to assess in hierarchical clustering methods. However, hierarchical clustering may more closely reflect clinical decision-making where test scores are assessed sequentially to build up a picture of the main problem of the patient. Further validation of the subgroups using other datasets is required which would also provide further information on the relevance of patellar mobility and other patient

characteristics. Furthermore, it will be important to determine if the optimising treatments based on subgroups will improve patient outcomes.

SUMMARY & CONCLUSIONS

Three subgroups of patients with PFP have emerged based on six clinical assessment tests. A 'strong' subgroup had the greatest rectus femoris length, lowest pain scores, significantly more males, better function and better quality-of-life and were the oldest. A 'weak and tighter' subgroup had significantly higher BMI, MFIQ and SLANSS with a trend towards lower physical activity levels and the longest duration of PFP. A 'weak and pronated foot' subgroup had the greatest patellar mobility, was significantly younger at time of first assessment and had the shortest duration of PFP. The study suggests that the six assessment procedures are feasible for therapists in primary care and hospital settings to perform in routine practice. We propose to undertake further work to validate these subgroups using external datasets, to examine optimal thresholds to assign participants to groups and, to assess whether more targeted intervention, based on these subgroups, would improve patient compliance and outcome, and as a result be more cost-effective.

What are the new findings

- Three subgroups of patellofemoral patients have been identified
- The subgroups are: 'strong'; 'weak and tighter'; 'weak and pronated'
- 6 simple low cost clinical tests can be used to identify the subgroups

How might it impact on clinical practice in the near future

- Targeted intervention based on these subgroups may improve patient outcomes

Competing interests

The authors declare that they have no competing interests

Author's contributions

JS Contributed to study conception, design and attained project funding. Contributed to project management and manuscript preparation.

JJ Contributed to project management and interpretation of data, manuscript preparation.

MC, JR Contributed to study conception, design and attained project funding. Contributed to project management and manuscript preparation.

EW Contributed to study conception and design. Contributed to manuscript revising.

CS Contributed to study conception, design and analysis and interpretation of data. Contributed to project management and manuscript preparation.

MS Contributed to study design and attained project funding. Contributed to project management interpretation of data and manuscript preparation.

DM Contributed to study conception, design and analysis and interpretation of data. Contributed to project management and manuscript preparation

JD Contributed to study conception design and attained project funding. Contributed to drafting the manuscript.

RH Contributed to service user patient involvement throughout the project.

VB Contributed to the study design, data collection, protocol and quality assurance of strength measurements and interpretation and drafting of the manuscript.

ER Contributed to the study design, facilitated the acquisition of data.

NA Contributed to study conception, design and manuscript preparation.

PD Contributed to study conception, design, project management, data analysis and interpretation and manuscript preparation.

All authors read and approved the final manuscript.

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Figure 1: Participant flow chart

Figure 2: Subgrouping of participants based on cut-offs 1 SD from population-based mean*