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Change in pain and its relation to change in activity in osteoarthritis

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SUMMARY

Objective: Trials testing promising interventions in knee osteoarthritis (OA) often fail to show pain reductions. This may be due to change in activity whereby a person's pain decreases, leading them to increase their activity levels, in turn increasing pain back to baseline levels. Using data from a trial of a beneficial treatment for knee pain, we explored whether activity changes might mask a treatment's effect on pain, by looking at whether activity levels increased with effective treatment and whether change in activity level related to change in pain.

Design: During the InRespond trial (ISRCTN55059760) participants wore an accelerometer for 7 days before and during treatments. We assessed change in pain on treatment using scores for overall knee pain and pain in a nominated pain-aggravating activity both in the last week and evaluated change in different types of activity using accelerometer data. Principal components analysis tested whether change in activity and pain outcomes were correlated and created composites combining them. We then tested whether activity, pain or the composites showed a treatment effect, and examined their responsiveness.

Results: In the 61 participants (mean age 64.5 years, 38% women, mean overall knee pain score 5.08 (0–10)), activity levels mostly decreased during the trial. Principal component analyses suggested that pain and activity did not correlate highly, loading on different components. Treatment that showed significant effects on pain did not show similar effects on either activity (e.g. the active treatment had a slightly greater reduction in total steps taken than the control treatment (difference 1942.6 steps/week, $p = 0.42$) nor on composites combining activity and pain. Pain outcomes were the most responsive; static loading (standing) outcomes were the most responsive activity outcome.

Conclusion: We found no evidence to support the hypothesis that activity levels increase during effective OA treatment and might account for the negligible pain effects of OA treatments.

1. Introduction

In osteoarthritis (OA), interventions that have shown promise often fail to produce positive treatment effects in randomised trials [1]. There are numerous possible explanations for this occurrence, including the lack of treatment efficacy and targeting the wrong subtype of OA. One additional explanation is that the trial design may not be optimal to detect treatment efficacy. Pain, a core outcome for OA trials [2,3], and featured in 95% of OA trials [4], may be influenced by complex factors including activities of participants. Activity has been found to both exacerbate and reduce pain in OA; on the one hand increased injurious joint loading may lead exacerbation of pain [5], whereas therapeutic exercise may reduce pain [6].

In-keeping with the 'fear/avoidance' model of pain [7], patients with OA likely maintain their activity level at an acceptable/tolerable pain level so as to avoid exacerbating pain. There is evidence that pain is a primary reason for avoiding or limiting physical activity [8,9]. When an intervention *reduces* pain, patients may increase their activity levels, and

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this may increase their pain back to this tolerable level. A trial that assesses only pain and not activity may miss this change in activity and pain, showing only an absence of pain reduction. Recent work using observational data has shown that combining information on pain and walking together can produce increased sensitivity to change over time [10], and stronger associations with radiographic OA [11], making this a promising approach to detect treatment effects in interventional clinical trials.

We sought to investigate the possibility that increased physical activity which may increase pain, occurs in patients on effective treatment and that this may mask the treatment effect. We note that this inquiry is necessarily limited to treatments shown to be efficacious. We examined this question in the context of the InRespond trial, a trial demonstrating that, in selected patients, a lateral wedge insole reduced pain in those with knee OA [12].

We hypothesized that with an effective treatment that reduced pain, physical activity may increase and that this, in turn, may exacerbate knee pain, yielding a blunted pain response to effective treatments. To test this hypothesis, we used data from the InRespond trial to firstly test whether there was change in activity during a period when the participant was randomised to effective treatment. We suspected that pain reduction might not affect all types of activity equally, so we explored whether specific types of activity changed. Next, we characterised the relationship between pain and activity – testing our assumption that pain and activity were related. Assuming that this was the case, we then attempted to create a single multidimensional composite outcome that combined activity and pain which would be more sensitive to change than the pain outcome alone and could be an outcome in future treatment studies.

2. Methods

This is a secondary analysis using data from the InRespond trial (ISRCTN55059760), a randomised controlled cross-over trial of 5° lateral wedge insoles with medial arch support *versus* neutral insoles in persons with painful medial knee OA [12]. In the trial, persons with painful knee OA were screened by examination to exclude those with patellofemoral tenderness and in a gait laboratory to exclude persons who did not show reductions in their knee adduction moments when using the wedge insole were randomized to either wedge or neutral insole. The study design was a 24-week AB crossover trial, with 8 weeks' intervention and an 8-week washout between treatments. Each participant therefore had four visits: the baseline pre-randomisation visit, the 8-week visit at the end of the first treatment period, a 16-week visit at the end of the washout and a 24-week visit at the end of the second treatment period.

2.1. Participants

Inclusion and exclusion criteria for trial participants have been published [12], but were generally: age 40–85 years; knee pain in the past week of $\geq$4 out of 10 on an 11-point scale, and Kellgren/Lawrence (K/L) [13] grade of 2–4 in the painful knee (as scored by a musculoskeletal radiologist) on a posteroanterior or anteroposterior radiograph obtained within the last 2 years that showed definite medial (but no definite lateral) narrowing. Patellofemoral OA had to be less severe than medial OA and could not have a K/L grade of $\geq$3. Additionally subjects must have had medial joint line tenderness upon examination by an experienced physical therapist (MJC), a stable medication regimen for 3 months, and a willingness to wear insoles in shoes for $\geq$4 h daily. The knee with the more severe pain was selected as the study knee, although each participant was provided with bilateral insoles and instructed to wear them in both shoes. In the rare case where pain was rated equally in both knees, the dominant knee was selected for the study.

2.2. Activity monitoring

Activity data collection was performed using the ActivPAL accelerometer (PAL Technologies Ltd., Glasgow, UK); a small thigh-mounted 3-axis accelerometer (sampling rate: 20 Hz) to collect data on acceleration, orientation, and time worn, using proprietary algorithms to derive step count, and classify device orientation. Activity monitors were posted to participants approximately 10 days prior to the baseline, 8 week, and 24 week visits, meaning that activity data were contemporaneous with the timeframe of the pain questions asked at the clinic visit. Participants were asked to wear the activity monitors constantly throughout the 7-day monitoring period until the visit, when the device was returned, and data downloaded. The device attached to the thigh directly with water resistant tape (Tegaderm™, 3 M Medical, Bracknell, UK). No instructions on target activity levels were provided, and participants were expected to continue their typical daily activity levels throughout the trial. We did not obtain 16 week accelerometer data to limit respondent burden and because we assumed an absence of carryover effects to the baseline on the second treatment period, corroborated in our analysis of the pain outcomes [12].

For each of the three ActivPAL observations, the first 7 complete days' worth of activity data were used in the analysis, giving a fixed, comparable time period across all visits and patients. ActivPAL software (ActivPAL 3 software, version 7.2.32) calculated step count and the amount of time monitored. Additionally, the samples collected were categorised according to the devices' orientation into one of three categories: oriented upright and moving (during which we assumed the participant to be walking/active); upright, but not moving (in which we assumed the participant was standing/weight bearing on their knees); and oriented horizontally (during which we assumed the participant was sedentary - sitting/lying/not weight bearing on their knees).

The output from the ActivPAL software outlined above allowed the calculation of the following nine derived activity outcomes deemed *a priori* to be meaningful for patients with knee OA: total steps taken; total time spent sedentary; total time spent standing; total time spent walking; total upright time (the sum of the time spent standing and walking); and estimated total energy expenditure (calculated automatically by the software). Using the participants' baseline height to approximate stride length (where stride length = baseline height $\times$ 0.415 for males, and baseline height $\times$ 0.413 for females [14]), we calculated the average walking speed to be $\frac{\text{total steps taken} \times \text{estimate stride length}}{\text{total time walking}}$. We also calculated the total number of 'fast' steps taken. Fast steps were defined in two ways: 1) steps taken at a rate of $\geq$100/min (hereon: 'rapid steps'), and 2) Steps taken at a speed of $\geq$1.2 m/s (hereon: 'brisk steps'). This latter definition required the step speed, and was therefore deemed potentially more accurate, but with an additional assumption about stride length. Both definitions were based on data from a previous study, consistent with more intense, higher-loading walking patterns thought to indicate intense loading/weight bearing, and which we assumed would exacerbate more pain than slower walking [15,16].

2.3. Pain outcomes

InRespond featured three pain outcomes: the KOOS pain subscale, and two 0–10 numerical rating scales (NRS) for pain intensity; one assessing knee pain in the last week, and one for pain in a nominated pain-aggravating activity. For this latter outcome, participants were asked to rate average pain in the last week during the one action deemed to consistently cause the most knee pain (for example, walking downstairs). This activity was selected by the participant at the baseline visit, and fixed throughout the study. For both NRS's, a rating of 0 indicated no pain at all, and 10 indicated the worst pain imaginable. All three pain outcomes were assessed at the baseline, 8 week, 16 week, and 24 week visits. The 16-week observation was excluded from this analysis, as contemporaneous activity data was not available at this visit (see above).

2.4. Statistical analysis

The analysis for this study was carried out in three stages.

The initial stage examined the relationship between pain and activity outcomes in which we constructed composites using principal components analysis (PCA) using a method previously described [17]. The components created in the PCA would be the composite outcomes. We expected to see one of two possible solutions from the principal components analysis: a one-component model (assuming that pain and activity are highly correlated, and therefore collapsed into one factor), or a two-component model (assuming that pain and activity are moderately correlated, splitting into two factors). Additionally, we examined scree plots of the PCA model to test which definition was most appropriate. If it was apparent from the scree plot that neither the one- nor the two-component models were appropriate, and that a solution with more than two components was a better fit for the data, we extracted the appropriate number of components. All solutions would be compared in the subsequent analyses. We used orthogonal rotation before examining component loadings to enhance interpretability (except in the one-component solution, as it makes no difference to the loading coefficients).

In the second analysis stage, we took the selected outcomes and composites generated from the PCA, and assessed whether activity and/or pain changed after 8 weeks' intervention. To assess change in activity, we used random-effects panel linear regression. We analysed the data using a regression model featuring the change from baseline to post-treatment visit (at weeks 8 and 24) of the outcome of interest as the outcome, with treatment type (coded where 0 = neutral insole, and

Table 1
Baseline characteristics of study sample.

Outcome	Statistic	Neutral insole first (AB) group (N = up to 31)			Lateral wedge first (BA) group (N = up to 30)		
		# of observations	Observed data only	Observed & Imputed (N = 31 in all cases)	# of observations	Observed data only	Observed & Imputed (N = 30 in all cases)
Females	frequency (%)	31	10 (32.26)	–	30	13 (43.33)	–
Age at screening visit	mean (SD)	31	64.65 (9.35)	–	30	64.37 (8.33)	–
BMI at screening visit	mean (SD)	30	28.24 (3.47)	–	30	28.33 (3.42)	–
Total time ActivPAL monitor worn for (days)	median (IQR)	31	6.97 (6.89–7.00)	6.97 (6.89–7.00)	27	6.98 (6.87–7.00)	6.98 (6.82–7.00)
Total Steps taken	median (IQR)	31	52548.00 (34378.00–65728.00)	52548.00 (34378.00–65728.00)	27	48064.00 (32084.00–59730.00)	48684.80 (39800.60–59609.40)
Time spent sedentary (lying/sitting) (hrs)	median (IQR)	31	124.37 (119.55–132.69)	124.37 (119.55–132.69)	27	127.09 (112.99–134.88)	126.76 (114.79–133.91)
Time spent standing (hrs)	median (IQR)	31	29.20 (18.76–33.84)	29.20 (18.76–33.84)	27	28.19 (21.27–36.49)	28.89 (21.57–35.95)
Time spent walking (hrs)	median (IQR)	31	11.60 (7.64–13.77)	11.60 (7.64–13.77)	27	11.07 (7.27–12.88)	10.96 (7.80–12.88)
Upright time (hrs)	median (IQR)	31	39.38 (29.85–45.84)	39.38 (29.85–45.84)	27	37.75 (31.45–51.19)	39.30 (31.95–48.69)
Total energy expenditure (MetH)	median (IQR)	31	232.86 (225.15–239.35)	232.86 (225.15–239.35)	27	232.28 (225.83–235.33)	230.93 (225.63–235.55)
Walking speed (km/h)	median (IQR)	31	3.18 (3.00–3.51)	3.18 (3.00–3.51)	27	3.21 (3.03–3.33)	3.20 (3.03–3.35)
Total number of 'rapid' steps taken[a]	median (IQR)	31	13103.00 (7777.00–21821.00)	13103.00 (7777.00–21821.00)	27	12558.00 (8842.00–16321.00)	12786.60 (8934.20–17599.80)
Total number of 'brisk' steps taken**	median (IQR)	31	10049.00 (5795.00–16441.00)	10049.00 (5795.00–16441.00)	27	8763.00 (7536.00–11720.00)	8919.80 (7293.10–12051.20)
Pain in last week	mean (SD)	31	4.94 (1.95)	4.94 (1.95)	30	5.23 (1.33)	5.23 (1.33)
Pain in nominated activity	mean (SD)	31	6.03 (1.83)	6.03 (1.83)	30	6.00 (1.58)	6.00 (1.58)
KOOS pain subscale score†	mean (SD)	31	54.93 (16.91)	54.93 (16.91)	30	55.56 (12.51)	55.56 (12.51)
KOOS symptom subscale score†	mean (SD)	31	56.68 (19.47)	–	28	57.91 (16.10)	–
KOOS ADL subscale score†	mean (SD)	31	63.66 (18.10)	–	29	62.12 (13.40)	–
KOOS sports and recreation subscale score†	mean (SD)	28	47.14 (27.77)	–	24	43.96 (19.56)	–
KOOS QoL subscale score†	mean (SD)	31	40.12 (19.15)	–	30	40.21 (16.22)	–

Variables denoted with a dash (–) were not included in the imputation model.
'Observed & Imputed' column presents descriptive statistics estimated from the imputation datasets. Medians were estimated with simultaneous quantile regression.
[a] 'Rapid step' defined as a step taken at a rate ≥ 100 steps/min; **'brisk step' defined as a step taken at a speed ≥ 1.2 m/s; †KOOS subscales are reverse-scored from 100 to 0 - Increases represent improvement; decreases represent worsening; ADL = Activities of Daily Living; QoL = Quality of Life.

1 = lateral wedge insole) as the predictor variable, and baseline score of the outcome as a covariate. This model therefore assessed change after 8 weeks of intervention for the pain outcomes, the activity outcomes and the composites, using two post-treatment observations per participant (one for each of the two interventions, neutral and lateral wedge insole), and one baseline (pre-randomisation) observation. The panel model accounted for within-person correlation, as there were multiple observations per participant.

A total of 18 regression models were run, one for each of the 12 outcomes of interest (3 pain outcomes, and 9 activity outcomes), and a further 6 for the 6 composite components extracted from the PCA (corresponding to the 3-, 2-, and 1-component solutions extracted). We also included the total ActivPAL wear time at baseline and follow-up as covariates, to control for the different lengths of use (which was approximately, but not exactly 7 days for every patient [Table 1]). We did not control for ActivPAL wear time in the models that only considered pain, as wear time was irrelevant to these models.

In the third stage of analysis, to assess responsiveness of all outcomes, the pain, activity and composite outcomes were all converted to z-scores, allowing for direct comparisons of the magnitude of change between outcomes with different units and variances. All outcomes and composites were collapsed into one 'z-score' variable, with a categorical variable to indicate the outcome type (coded from 0 to 17, representing the 18 considered outcomes – 3 pain outcomes, 9 activity outcomes, and 6 composites). We formally tested for differences in magnitude of responsiveness in a random-effects panel linear regression model, with change in the 'z-score' variable at follow-up as the outcome, and treatment type (coded 0 = neutral insole, and 1 = lateral wedge insole), outcome type (the categorical variable coded 0–17), and a treatment type-by-outcome type interaction effect as predictor variables, and 'z-score' at baseline, total ActivPAL wear time at baseline, and follow-up as covariates.

In all analyses, we used multiple imputation by chained equations (MICE) assuming missing data were missing-at-random. The multiple imputation model used data from all three visits of interest (baseline, 8 weeks, and 24 weeks) and predictive mean matching (PMM) to best emulate the distributions of the observed variables. The PCA was performed individually on each of the 10 imputed datasets, and the extracted components re-combined to produce one estimate per component using Rubin's rules [19,20] after performing the change-over-time analysis.

Baseline characteristics were described using means and standard deviations for normally distributed continuous variables, medians and interquartile ranges for skewed continuous variables, and frequencies and percentages for categorical variables. 95% confidence intervals were constructed around all estimates to assess precision, and statistical significance. All analyses were conducted using Stata (version 14.0) [21].

3. Results

Baseline characteristics of InRespond participants are shown in Table 1. Activity levels varied widely, with total step counts ranging from 2940 steps per day to 21,567 steps per day. In total, 308 (15.30%) of the 2013 possible observations were imputed: 3.58% of baseline observations, 15.65% of post-treatment 1 observations, and 26.68% of post-treatment 2 observations. The imputed and observed datasets showed similar results, with slightly decreased activity levels in the imputed datasets (Table 1).

Stage 1. Association between Activity & Pain (Principal Components Analysis).

Scree plots from the principal components analysis of all pain and activity outcomes (see Supplementary Fig. 1) suggested a three-component solution, and therefore this was extracted alongside the planned one- and two-component solutions.

Variable loadings on the one component solution were essentially split, with all activity variables loading highly, and pain outcomes loading almost not at all (see Table 2). For example, total step taken was highly correlated (0.95) with this component but pain in the last week was weakly correlated with it (0.07). We called this component the 'activity' composite.

The two-component solution however, produced two components that featured limited overlap between pain and activity (see Table 2). The walking-related activity variables loaded strongly on the first component, and the three pain outcomes loaded moderately onto the second component, as well as sedentary time, standing time, and upright time (the sum of standing and walking time). We called these two components the 'walking' and 'loading/pain' composites, respectively.

Finally, the three-component solution produced, like the one-component solution, little overlap between pain and activity. The first component ('alt_walking') loaded almost exclusively with the walking-related activity outcomes. The variables that correlated best with this component were total number of rapid or brisk steps taken (correlation = 0.96) whereas pain on nominated activity was the variable with the weakest correlation (0.02). The second ('static loading') loaded with sedentary time, standing time, and upright time, suggesting that this type of non-walking activity time was discrete from walking, but also discrete from pain. The third component ('pain') loaded strongly with the 3 pain outcomes only, and had only negligible loading from the activity outcomes.

Stage 2. Differences in Pain and Activity between Footwear Conditions.

With respect to pain outcomes, change in pain during nominated activity differed between the two insole conditions, favouring the lateral wedge insole (b = −0.72 pts; 95% CI -1.30 to −0.15; p = 0.01). The lateral wedge insoles also produced a change in pain in the last week (−0.79 pts 95% CI -1.32 to −0.26; p < 0.01), although the between-conditions test was only of borderline significance (b = −0.51; 95% CI -1.20 to 0.18, p = 0.15; Table 3).

Activity levels decreased under both treatment conditions. Only walking speed remained unchanged (Table 3). Correspondingly, total sedentary time increased significantly. Both the number of rapid steps and total standing time were significantly reduced on lateral wedges and not on neutral insoles, but the difference between the two treatments did not reach significance (see Table 3). In general, there were no noteworthy differences between insoles in activity parameters, although confidence intervals around estimates were wide.

3.1. Differences in composite outcomes between Footwear Conditions

We then assessed whether the composite outcome scores differed between neutral and lateral wedge insoles (see Table 3). The 'activity', 'walking', and 'alt-walking' composites decreased in both the lateral and neutral insole conditions during treatment, and no difference was found between the interventions. The 'loading/pain' composite did not differ either within or between conditions. The 'static loading' composite (comprised mostly of sedentary/standing variables) was significantly lower after 8 weeks of lateral wedge use, but not after.

Differences between insole conditions in all composite outcomes did not meet the threshold for statistical significance.

Stage 3. Responsiveness of All Outcomes – Pain, Activity, and Composites.

With respect to responsiveness, only the pain in nominated activity produced a significant difference between insole treatments, suggesting that this outcome was the most sensitive to change following intervention (see Table 4). This outcome was both the most sensitive pain outcome and the most sensitive outcome overall. The next-most responsive pain outcome was the 'pain in the last week' outcome, with the KOOS pain subscale being the least responsive.

Of the activity outcomes, time spent standing was the most sensitive outcome to change on treatment. Upright time, which was the sum of

Table 2
Combining Pain and Activity Measures at baseline from 61 participants in the InRespond Trial: Results of Factor Analyses for 1, 2 and 3 component solutions[c].

Outcome	1-component solution	2-component solution		3-component solution		
	Component 1 - "Activity"	Component 1 - "Walking"	Component 2 - "Loading/Pain"	Component 1 - "walking"	Component 2 - "Static Loading"	Component 3 - "Pain"
Total steps taken	0.95 (0.93–0.94)	0.96 (0.93–0.95)	0.12 (0.15–0.21)	0.94 (0.90–0.93)	0.28 (0.27–0.32)	0.04 (0.03–0.10)
Time spent sedentary (lying/sitting) (hrs)	−0.62 (−0.65 to −0.62)	−0.43 (−0.39 to −0.32)	−0.74 (−0.81 to −0.76)	−0.23 (−0.22 to −0.18)	−0.88 (−0.89 to −0.87)	0.15 (0.12–0.15)
Time spent standing (hrs)	0.50 (0.49–0.53)	0.29 (0.16–0.26)	0.76 (0.76–0.83)	0.04 (−0.01 to 0.02)	0.96 (0.93–0.95)	−0.07 (−0.11 to −0.06)
Time spent walking (hrs)	0.94 (0.85–0.89)	0.92 (0.81–0.86)	0.22 (0.25–0.32)	0.86 (0.71–0.79)	0.39 (0.41–0.49)	0.03 (0.06–0.16)
Upright time (hrs)	0.72 (0.71–0.74)	0.54 (0.40–0.50)	0.71 (0.74–0.82)	0.31 (0.24–0.27)	0.94 (0.95–0.96)	−0.05 (−0.04 to −0.02)
Total energy expenditure (MetH)	0.80 (0.77–0.79)	0.81 (0.75–0.79)	0.10 (0.14–0.21)	0.73 (0.65–0.70)	0.34 (0.34–0.39)	0.16 (0.15–0.20)
Walking speed (km/h)	0.42 (0.35–0.39)	0.53 (0.47–0.54)	−0.29 (−0.30 to −0.20)	0.71 (0.65–0.70)	−0.39 (−0.41 to −0.32)	−0.06 (−0.20 to −0.08)
Total number of 'rapid' steps taken[a]	0.91 (0.81–0.88)	0.95 (0.87–0.93)	0.01 (0.03–0.07)	0.96 (0.92–0.96)	0.14 (0.08–0.14)	0.05 (0.00–0.05)
Total number of 'brisk' steps taken[b]	0.86 (0.80–0.84)	0.92 (0.87–0.90)	−0.05 (−0.01 to 0.01)	0.96 (0.92–0.95)	0.04 (0.01–0.08)	0.03 (−0.01 to 0.05)
Pain in last week	0.07 (0.04–0.11)	0.28 (0.27–0.36)	−0.68 (−0.62 to −0.55)	0.10 (0.05–0.11)	−0.09 (−0.09 to −0.04)	0.91 (0.89–0.91)
Pain in nominated activity	0.01 (0.00–0.07)	0.21 (0.23–0.31)	−0.66 (−0.61 to −0.52)	0.02 (0.02–0.05)	−0.07 (−0.09 to −0.03)	0.91 (0.87–0.90)
KOOS pain subscale score[c]	−0.01 (−0.01 to 0.04)	−0.20 (−0.26 to −0.20)	0.63 (0.52–0.60)	−0.03 (−0.05 to 0.01)	0.09 (0.07–0.13)	−0.84 (−0.83 to −0.77)

Components have been given summary names by the authors to help interpretation.
Coefficient displayed is the correlation in observed dataset (minimum/maximum in multiple imputation datasets), The higher this coefficient, the greater the correlation with the underlying component. For example, in the 3-component solution, pain outcomes 'load' on the 3rd factor with all pain variables showing high correlation with the component. The negative sign for loading for KOOS is because less pain translates into higher KOOS pain scores.
[a] 'Rapid step' defined as a step taken at a rate ≥100 steps/min.
[b] 'Brisk step' defined as a step taken at a speed ≥1.2 m/s.
[c] KOOS pain subscale is reverse-scored - Increases represent improvement; decreases represent worsening.

standing and walking time, had marginally less responsiveness (standing time standardised change = −0.23; 95% CI -0.53 to 0.07; p = 0.13 *versus* upright time standardised change = −0.22; 95% CI -0.52 to 0.07; p = 0.14), suggesting that walking time added little to improve responsiveness. The other activity outcomes had relatively poor responsiveness overall, with standardised changes ranging from −0.17 (total energy expenditure) to −0.01 (total number of brisk steps).

Improvements in responsiveness using the composite outcomes

Table 3
Change in Pain and Activity after 8 Weeks' use of Intervention.

Outcome	Neutral insole	Lateral wedge	Difference between interventions
	least squares mean (95% CI), p***	least squares mean (95% CI), p	least squares mean (95% CI), p
Individual outcomes			
Total steps taken	−8412.55 (−12731.49 to −4093.60), <0.01	−10355.14 (−14560.76 to −6149.52), <0.01	−1942.60 (−6716.94 to 2831.75), 0.42
Time spent sedentary (lying/sitting) (hrs)	3.87 (0.72–7.02), 0.02	6.84 (3.63–10.06), <0.01	2.97 (−1.12 to 7.07), 0.16
Time spent standing (hrs)	−0.85 (−3.60 to 1.90), 0.55	−3.49 (−6.23 to −0.74), 0.01	−2.64 (−6.40 to 1.12), 0.17
Time spent walking (hrs)	−1.82 (−2.71 to −0.94), <0.01	−2.16 (−3.09 to −1.23), <0.01	−0.33 (−1.37 to 0.70), 0.52
Upright time (hrs)	−2.67 (−5.78 to 0.44), 0.09	−5.65 (−8.77 to −2.52), <0.01	−2.97 (−7.07 to 1.12), 0.16
Total energy expenditure (MetH)	−1.96 (−3.78 to −0.14), 0.04	−3.09 (−5.00 to −1.18), <0.01	−1.13 (−3.05 to 0.79), 0.25
Walking speed (km/h)	−0.02 (−0.14 to 0.09), 0.71	0.00 (−0.11 to 0.11), 0.95	0.02 (−0.13 to 0.17), 0.81
Total number of 'rapid' steps taken[a]	−2092.76 (−4272.99 to 87.47), 0.06	−2394.42 (−4472.64 to −316.20), 0.02	−301.67 (−2679.79 to 2076.46), 0.80
Total number of 'brisk' steps taken[b]	−1463.11 (−3260.23 to 334.01), 0.11	−1622.24 (−3471.36 to 226.88), 0.09	−159.13 (−2566.60 to 2248.33), 0.90
Pain in last week[‡] *(0–10)*	−0.28 (−0.79 to 0.22), 0.27	−0.79 (−1.32 to −0.26), <0.01	−0.51 (−1.20 to 0.18), 0.15
Pain in nominated activity[‡] *(0–10)*	−0.24 (−0.77 to 0.29), 0.38	−0.96 (−1.49 to −0.43), <0.01	−0.72 (−1.30 to −0.15), 0.01
KOOS pain subscale score[c‡] *(100–0)*	4.75 (1.03–8.47), 0.01	4.00 (0.40–7.60), 0.03	−0.75 (−4.94 to 3.45), 0.73
Composite Outcomes			
1-component model: 'Activity' component	−0.33 (−0.54 to −0.12), <0.01	−0.48 (−0.69 to −0.27), <0.01	−0.15 (−0.38 to 0.09), 0.22
2-component model: 'Walking' component	−0.35 (−0.55 to −0.15), <0.01	−0.48 (−0.67 to −0.28), <0.01	−0.13 (−0.34 to 0.09), 0.24
2-component model: 'Loading/Pain' component	−0.02 (−0.27 to 0.23), 0.87	−0.10 (−0.35 to 0.15), 0.43	−0.08 (−0.42 to 0.26), 0.64
3-component model: 'Alt-walking' component	−0.26 (−0.47 to −0.04), 0.02	−0.26 (−0.46 to −0.06), 0.01	0.00 (−0.26 to 0.26), 0.98
3-component model: 'Static loading' component	−0.20 (−0.46 to 0.06), 0.13	−0.45 (−0.71 to −0.20), <0.01	−0.25 (−0.60 to 0.10), 0.15
3-component model: 'Pain' component[a]	−0.22 (−0.45 to 0.02), 0.07	−0.43 (−0.66 to −0.20), <0.01	−0.22 (−0.49 to 0.05), 0.11

In all components, except the 'pain' component (denoted '***'), increases in the score represent beneficial effects; decreases represent negative effects.
***P values relate to a test of whether the coefficients stated differ from zero.
All estimates come from models controlling for ActivPAL wear time, except those denoted with a [‡].
[a] 'Rapid step' defined as a step taken at a rate ≥ 100 steps/min.
[b] 'Brisk step' defined as a step taken at a speed ≥ 1.2 m/s.
[c] KOOS pain subscale is reverse-scred - Increases represent improvement; decreases represent worsening.

Table 4
Comparative Responsiveness of Pain and Activity Outcomes[c].

Outcome	Difference between interventions (expressed in standard deviations)
	least squares mean (95% CI), p
Individual outcomes	
Total steps taken	−0.07 (−0.37 to 0.23), 0.65
Time spent sedentary (lying/sitting) (hrs)	0.16 (−0.14 to 0.45), 0.29
Time spent standing (hrs)	−0.23 (−0.53 to 0.07), 0.13
Time spent walking (hrs)	−0.07 (−0.38 to 0.24), 0.65
Upright time (hrs)	−0.22 (−0.52 to 0.07), 0.14
Total energy expenditure (MetH)	−0.17 (−0.47 to 0.13), 0.26
Walking speed (km/h)	0.07 (−0.34 to 0.48), 0.72
Total number of 'rapid' steps taken[a]	−0.02 (−0.33 to 0.29), 0.91
Total number of 'brisk' steps taken[b]	−0.01 (−0.35 to 0.33), 0.95
Pain in last week[‡]	−0.25 (−0.58 to 0.08), 0.14
Pain in nominated activity[‡]	−0.33 (−0.62 to −0.04), 0.02
KOOS pain subscale score[c‡]	−0.04 (−0.34 to 0.26), 0.81
Composite Outcomes	
1-component model: 'Activity' component	−0.13 (−0.42 to 0.16), 0.38
2-component model: 'Walking' component	−0.13 (−0.43 to 0.16), 0.37
2-component model: 'Loading/Pain' component	−0.02 (−0.32 to 0.28), 0.88
3-component model: 'Alt-walking' component	0.00 (−0.32 to 0.31), 0.99
3-component model: 'Static loading' component	−0.24 (−0.55 to 0.08), 0.14
3-component model: 'Pain' component***[‡]	−0.24 (−0.53 to 0.06), 0.12

In all components, except the 'pain' component (denoted '***'), increases in the score represent beneficial effects; decreases represent negative effects.
All estimates come from models controlling for ActivPAL wear time, except those denoted with a [‡].
Numbers shown are z scores. The larger the z score, the greater the change with the treatment.
[a] 'Rapid step' defined as a step taken at a rate ≥100 steps/min.
[b] 'Brisk step' defined as a step taken at a speed ≥1.2 m/s.
[c] KOOS pain subscale is reverse-scored - Increases represent improvement; decreases represent worsening.

(Table 4) were mixed. The 'loading/pain' composite from the 2-component model, and the 'activity' composite from the 1-component model had greater responsiveness than any of their constituent walking and loading-related outcomes. Only the pain composite from the 3-component model produced a difference between insoles that approached statistical significance.

4. Discussion

The hypothesis for this study was that, with an effective pain-reducing treatment, physical activity may increase, in turn exacerbating knee pain, therefore making an efficacious treatment look less beneficial when the analysis focused on pain alone. However, we found little evidence that activity changed nor that this affected the measurement of pain. We examined a variety of different measures of activity assessed using an accelerometer before and during treatment and found little evidence that any of them changed during treatment.

We found only a weak association between pain and activity outcomes. There was some limited overlap between static knee loading variables (standing/sedentary time) and pain, but only in one of the three PCA models tested. In a person with knee pain, standing may be an avoidable behaviour, whereas walking may be more difficult for patients to avoid without disruption to daily activities.

The pain treatment effect size reported in this study is smaller than that in the main trial report [12], although, like in the main report, the outcome previously found to be most sensitive to change, pain on nominated activity [22], showed the largest treatment effect and met criteria for statistical significance. The diminished effect sizes are perhaps due to this analysis making use of the pre-randomisation design (which used 3 observations per participant – baseline, and 2 post-treatment observations), rather than the one used in the trial publication [18] which used 4 observations per participant – 2 pre- and two post-treatment observations, and correspondingly a different imputation model. This latter analysis was not possible, as activity level was not recorded at week 16 in the trial (the post-washout observation). We excluded the post-washout pain observations in order to use only the follow-ups where activity was collected, allowing a fair direct comparison between pain and activity.

Our study addressed a different question than previous studies. Using data from the OAI, Lo et al. [10] reported that the correlation of WOMAC pain score adjusted for physical activity level with Kellgren and Lawrence grade was better than its correlation with WOMAC pain score alone, suggesting an association of activity with severity of radiographic OA. Allen and colleagues [11] showed in knee OA patients that activity adjusted pain correlated better with functional limitation than did pain alone. Both these studies were cross sectional and did not address the effect of treatment on pain or the combination of pain and physical activity.

There are several limitations to our study. This was an exploratory study, and was not designed initially to address the pain/activity hypothesis examined in this paper: As already mentioned, the InRespond trial did not collect activity post-washout, and with the large variances in the activity outcome seen in this trial (Table 1) that may be important to the analysis. The absence of data at this time point may have led us to fail to show significant findings because of the enhanced variance induced by imputation. The treatment effect in InRespond was small and it is possible that activity levels would be more likely to fluctuate with a more effective treatment.

In this study, we have assumed a relatively simple relationship between pain and activity that ignores psychological factors, such as the influence of coping strategies or depressive symptoms, which might obfuscate the relationship between pain and activity.

Our definitions of brisk and rapid walking were informed by expert advice from researchers in the OA community familiar with activity patterns typical of patients with OA. However, the mean walking speed (approximately 3 km/h) was relatively close to the definition of a brisk step (1.2 m/s = 4.32 km/h) Further work examining the choice of cut-off value for brisk and rapid steps may be appropriate to establish how this impacts sensitivity to change in activity. We used two definitions of rapid walking – one that used data directly from the accelerometer only, and one that made an additional assumption about average stride length based on participant height. Both definitions had similar effect sizes, and correlation between the two definitions was high (Baseline Pearson's correlation = 0.92; 95% CI 0.81 to 1.03; $p < 0.001$; post-treatment Pearson's correlation = 0.92; 95% CI 0.76 to 1.07; $p < 0.001$), indicating very little difference between the two definitions.

We found no effect of treatment on our composite outcomes, but our analysis may not have been sufficiently powered to detect such effects. Due to the nature of the device used and outcomes chosen to describe activity, it was not possible to discern precise information about particular types of activity undertaken by study participants, and how these may have changed during the study. For example, we were not able to distinguish stair use or participation in exercise. Collecting more self-report data on change in activity levels (for example asking participants about participation in exercise), or making use of a more complex device that captures more of this type of information objectively (for example using a GPS-linked smartwatch/smartphone) would allow further insight into these possible manifestations of activity change.

5. Conclusion

This study found modest changes in pain but little change in activity following treatment with lateral wedge insoles in those with painful medial knee OA. Activity did not increase with pain reduction. The creation of composite outcomes combining data on pain and activity outcomes identified intriguing interrelations between static loading-type outcomes (standing time and sedentary time) and pain, and not walking-type variables, but these composites did not improve the ability to detect treatment effects.

Competing interest statement (financial support)

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Data sharing and integrity

Stata code and datasets used for this analysis are available from the corresponding author: matthew.parkes@manchester.ac.uk. The corresponding author (MJP) had full access to all the data in the study, and takes responsibility for the integrity of the data, and the accuracy of the data analysis.

Author's contributions

Matthew J Parkes, PhD: Conception and design, analysis, drafting of article, final approval, Richard K Jones, PhD: Conception and design, revising article, final approval, Suzanne C Carter, BSc (Hons): Acquisition of data, revising article, final approval, Anmin Liu, PhD: Acquisition of data, revising article, final approval, Michael J Callaghan, PhD: Acquisition of data, revising article, final approval, David T Felson, MD MPH: Conception and design, interpretation of data, revising article, final approval, Matthew Parkes (matthew.parkes@manchester.ac.uk) takes full responsibility for the integrity of this work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ocarto.2020.100063.

References

[1] F.E. Watt, M. Gulati, New drug treatments for osteoarthritis: what is on the horizon? Eur. Med. J. Rheumatol. 2 (1) (2017) 50–58. http://www.ncbi.nlm.nih.gov/pubmed/30364878%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC6198938.

[2] N.E. Foster, M.A. Holden, E.L. Healey, S. Tooth, E.M.N.E. Hay, Improving the Effectiveness of Exercise Therapy for Older Adults with Knee Pain: A Pragmatic Randomised Controlled Trial (The Beep Trial), vol. 101, Physiother, United Kingdom, 2015, p. eS404. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=cctr&NEWS=N&AN=CN-01126500.

[3] J.W.J. Bijlsma, Patient centred outcomes in osteoarthritis, Ann. Rheum. Dis. 64 (1) (2005) 1–2, https://doi.org/10.1136/ard.2004.025072.

[4] T.O. Smith, M. Mansfield, G.A. Hawker, et al., Uptake of the OMERACT-OARSI hip and knee osteoarthritis core outcome set: review of randomized controlled trials from 1997 to 2017, J. Rheumatol. (2019) 181066, https://doi.org/10.3899/jrheum.181066, jrheum.

[5] T.B. Birmingham, K.A. Marriott, K.M. Leitch, et al., Association between knee load and pain: within-patient, between-knees, case-control study in patients with knee osteoarthritis, Arthritis Care Res. (2018), https://doi.org/10.1002/acr.23704.

[6] G.H. Lo, S.M. Musa, J.B. Driban, et al., Running does not increase symptoms or structural progression in people with knee osteoarthritis: data from the osteoarthritis initiative, Clin. Rheumatol. 37 (9) (2018) 2497–2504, https://doi.org/10.1007/s10067-018-4121-3.

[7] M. Leeuw, M.E.J.B. Goossens, S.J. Linton, G. Crombez, K. Boersma, J.W.S. Vlaeyen, The fear-avoidance model of musculoskeletal pain: current state of scientific evidence, J. Behav. Med. (2007), https://doi.org/10.1007/s10865-006-9085-0.

[8] F.J. Keefe, G. Affleck, C.R. France, et al., Gender Differences in Pain, Coping, and Mood in Individuals Having Osteoarthritic Knee Pain: A Within-Day Analysis, Pain, 2004, https://doi.org/10.1016/j.pain.2004.03.028.

[9] A. Hutchings, M. Calloway, E. Choy, et al., The Longitudinal Examination of Arthritis Pain (LEAP) study: relationships between weekly fluctuations in patient-rated joint pain and other health outcomes, J. Rheumatol. 34 (11) (2007) 2291–2300. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=17937461.

[10] G.H. Lo, J. Song, T.E. McAlindon, et al., Validation of a new symptom outcome for knee osteoarthritis: the Ambulation Adjusted Score for Knee pain, Clin. Rheumatol. 38 (3) (2019) 851–858, https://doi.org/10.1007/s10067-018-4352-3.

[11] K.D. Allen, G. Lo, L.M. Abbate, et al., Composite measures of physical activity and pain associate better with functional assessments than pain alone in knee osteoarthritis, Clin. Rheumatol. (2019), https://doi.org/10.1007/s10067-019-04530-4.

[12] D.T. Felson, M. Parkes, S. Carter, et al., The efficacy of a lateral wedge insole for painful medial knee osteoarthritis after prescreening:A randomized clinical trial, Arthritis Rheumatol. (2019), https://doi.org/10.1002/art.40808. January.

[13] J.H. Kellgren, J.S. Lawrence, Radiological assessment of osteo-arthrosis, Ann. Rheum. Dis. 16 (4) (1957) 494–502, https://doi.org/10.1136/ard.16.4.494.

[14] D.W. Grieve, R.J. Gear, The relationships between length of stride, step frequency, time of swing and speed of walking for children and adults, Ergonomics (1966), https://doi.org/10.1080/00140136608964399.

[15] D.K. White, T. Neogi, Y. Zhang, J. Niu, P.P. Katz, Association of slow gait speed with trajectories of worsening depressive symptoms in knee osteoarthritis: an observational study, Arthritis Care Res. 69 (2) (2017) 209–215, https://doi.org/10.1002/acr.22928.

[16] S.A.M. Fenton, T. Neogi, D. Dunlop, et al., Does the intensity of daily walking matter for protecting against the development of a slow gait speed in people with or at high risk of knee osteoarthritis? An observational study, Osteoarthr. Cartil. (2018), https://doi.org/10.1016/j.joca.2018.04.015.

[17] M.J. Parkes, M.J. Callaghan, L. Tive, M. Lunt, D.T. Felson, Responsiveness of single versus composite measures of pain in knee osteoarthritis, J. Rheumatol. 45 (9) (2018) 1308–1315, https://doi.org/10.3899/jrheum.170928.

[18] M.G. Kenward, J.H. Roger, The use of baseline covariates in crossover studies, Biostatistics (2010), https://doi.org/10.1093/biostatistics/kxp046.

[19] I.R. White, Strategies for handling missing data in randomised trials, Trials 12 (S1) (2011) A59, https://doi.org/10.1186/1745-6215-12-S1-A59.

[20] D.B. Rubin, in: D.B. Rubin (Ed.), Multiple Imputation for Nonresponse in Surveys, John Wiley & Sons, Inc., Hoboken, NJ, USA, 1987, https://doi.org/10.1002/9780470316696.

[21] StataCorp. Stata Statistical Software: Release 14 (2015), https://doi.org/10.2307/2234838, 2015.

[22] M.J. Parkes, M.J. Callaghan, T.W. O'Neill, L.M. Forsythe, M. Lunt, D.T. Felson, Sensitivity to change of patient-preference measures for pain in patients with knee osteoarthritis: data from two trials, Arthritis Care Res. 68 (9) (2016) 1224–1231, https://doi.org/10.1002/acr.22823.