**Title:** Do comorbidities predict pain and function in knee osteoarthritis following an exercise intervention, and do they moderate the effect of exercise? Analyses of data from three randomised controlled trials


**Abstract:**

**Background:** Although exercise is a core treatment for people knee osteoarthritis (OA), it is currently unknown whether those with additional comorbidities respond differently to exercise than those without. We explored whether comorbidities predict pain and function following an exercise intervention in people with knee OA, and whether they moderate response to: exercise versus no-exercise; and enhanced exercise versus usual exercise-based care.

**Methods:** Analysis of existing data from three randomized controlled trials (RCT): TOPIK (n=217), APEX (n=352), and BEEP (n=514). All three RCTs included: adults with knee pain attributable to OA; physiotherapy-led exercise; data on six comorbidities (overweight/obesity, pain elsewhere, anxiety/depression, cardiac problems, diabetes mellitus, and respiratory conditions); the outcomes of interest (six-month WOMAC knee pain and function). Adjusted mixed models were fitted where data was available; otherwise linear regression models were used.

**Ethical approval:** Obtained for original RCTs.

**Results:** Obesity compared to underweight/normal Body Mass Index was statistically significantly associated with knee pain following exercise, as was presence compared to absence of anxiety/depression. Presence of cardiac problems was statistically significantly associated with effect of enhanced versus usual exercise-based care for knee function, indicating enhanced exercise may be less effective in people with cardiac problems for

improving knee function. Associations for all other potential prognostic factors and moderators were weak and not statistically significant.

**Discussion/ conclusions:** Obesity and anxiety/depression predicted pain and function outcomes in people offered an exercise intervention, but only presence of cardiac problems might moderate the effect of exercise for knee osteoarthritis. Further confirmatory investigations are required.

**Keywords:**

Exercise

Comorbidity

Osteoarthritis

## Background

Osteoarthritis (OA) is a clinical syndrome of joint pain accompanied by varying degrees of functional limitation and reduced quality of life (NICE 2014). OA, particularly of the knee, is one of the leading causes of disability worldwide, and its burden is set to rise given the ageing, increasingly obese population (Cross et al 2014). In addition to their knee problem, individuals with knee OA are also likely to have other long-term conditions, commonly cardiovascular and pulmonary conditions, hypertension, and diabetes (Shafer et al 2014, Kadam et al 2004, de Rooij et al 2017). Comorbidity is defined as the presence of one or more additional diseases or disorders co-occurring with a primary disease or disorder (Feinstein 1970). In those with OA, the presence, number, and severity of comorbidities is associated with greater levels of pain, greater limitations to activities of daily living, and worse prognosis (van Dijk et al 2010).

Individuals with knee OA are typically managed in primary care. Clinical guidelines recommend exercise, including both general (aerobic) exercise and local (strengthening) exercise, as a core treatment for individuals with knee OA, irrespective of the presence of comorbidity (Larmer et al 2014). However, outcomes of exercise specifically in those with knee OA and comorbidity need further investigation. As exercise is a recommended treatment for both OA and other common long-term conditions (Pedersen & Saltin 2015), it is particularly important to determine how best to deliver a targeted approach to exercise programmes for this patient group. This could potentially reduce treatment burden and optimise outcomes for both OA and other long-term conditions (de Rooij et al 2017, NICE 2016).

Although exercise has been demonstrated to reduce pain and increase physical function in

individuals with knee OA, on average effect sizes compared to other treatments are small to moderate, and only approximately 50% of participants achieve a clinically important treatment response (Christensen et al 2015, Hay et al 2018, Foster et al 2007). Currently, it is not known whether individuals with comorbidity respond to exercise programmes in a similar way to those without comorbidity, or to different types of exercise (for example, standardised exercise, individually tailored exercise, lower limb-focused 'local' exercise, or local and general exercise). If outcomes from exercise are sub-optimal in those with comorbidities and knee OA, a targeted treatment approach, specifically tailoring exercise to meet the needs of this patient group may be warranted. This targeted approach has recently been shown to be effective compared to current medical care (and waiting for exercise) in individuals with knee OA and comorbidities in the Netherlands (de Rooij et al 2017). If the effectiveness of such targeted exercise programmes is confirmed in other countries and healthcare settings, this could potentially lead to improved treatment effects and patient outcomes, as well as more efficient use of healthcare services.

To inform future research, this study aimed to explore whether comorbidity influences the outcomes of exercise and outcomes of different types of exercise for individuals with knee OA. We used data from three large randomized controlled trials (RCT) of exercise interventions for patients with knee OA conducted in the United Kingdom (UK), that collected data on participants' other health problems (Hay et al 2018, Foster et al 2007, Hay et al 2006).

**Aim**

To investigate whether comorbidity (considered separately as: a) presence of a defined comorbidity, and b) number of comorbidities present) is associated with knee pain and

physical function outcomes following exercise intervention in patients with knee OA.

We assessed comorbidities as: (i) prognostic factors (Riley et al 2013), i.e. whether comorbidities were associated with outcome irrespective of the exercise intervention received, and (ii) treatment effect moderators (Hingorani et al 2013), i.e. whether the comorbidities were associated with the effects of (a specific type of) exercise intervention.

**Specific Objectives**

1. Determine whether comorbidity is associated with knee pain and physical function outcomes at six-months, following exercise intervention in individuals with knee OA (comorbidity as a prognostic factor).

2. Determine whether comorbidity is associated with the effects of exercise in terms of knee pain and function outcomes at six-months in comparison to a non-exercise control in individuals with knee OA (comorbidity as a potential moderator of treatment effect).

3. Determine whether comorbidity is associated with the effects of different types of enhanced exercise intervention in terms of knee pain and function outcomes at six-months in comparison to usual exercise-based care in individuals with knee OA (comorbidity as a potential moderator of treatment effect).

## Methods

### Study Design

This study used existing data from three RCTs investigating the effect of exercise for patients with knee OA (TOPIK [ISRCTN55376150] (Hay et al 2006), APEX [ISRCTN88597683]

(Foster et al 2007), and BEEP [ISRCTN93634563] (Hay et al 2018) ). Full details of these three clinical trials have been published elsewhere (Foster et al 2007, Hay et al 2006, Hay et al 2018) and are described in brief below.

**Study Participants**

All three RCTs included patients with knee pain attributable to OA in the primary care setting in the UK (family practice and community physiotherapy services), and data were collected on comorbidities. The trials had similar eligibility criteria.

**Interventions**

At least one exercise intervention arm was included in all three RCTs. The TOPIK trial compared "community physiotherapy" (3-6 physiotherapist-led sessions of advice about activity and pacing and an individualised exercise programme of strengthening, stretching and aerobic exercises) to a non-exercise control (an advice leaflet reinforced by a telephone call from a rheumatology nurse), and also featured an "enhanced pharmacy review" intervention (pharmacological management in accordance with an algorithm) that was not used in these analyses (Hay et al 2006). The APEX trial compared "advice and exercise" (up to 6 sessions of physiotherapist-led stretching, strengthening and balance exercises), "advice and exercise plus true acupuncture" (up to 6 sessions of physiotherapist-led exercise as previous plus acupuncture), and "advice and exercise plus non-penetrating sham acupuncture" (up to 6 sessions of physiotherapist-led exercise as previous plus sham acupuncture) (Foster et al 2007). The BEEP trial compared "usual physiotherapist-led exercise" (up to 4 sessions of lower-limb strengthening and flexibility exercises) to two types of physiotherapist-led enhanced exercise: "individually tailored exercise" (6-8 sessions of lower-limb strengthening, stretching and balance exercises that were individualised,

supervised and progressed) and "targeted exercise adherence" (8 to 10 sessions supporting patients to adhere to exercise and to engage in general physical activity over the longer-term) (Hay et al 2018).

**Outcomes**

All three RCTs measured knee pain and function at six-months post-randomisation using the Western Ontario and McMaster Universities Arthritis Index (WOMAC) (Bellamy et al 1988). These are the primary outcomes of interest for this study. The WOMAC pain subscale includes five items measuring self-reported pain during activities and gives a total score ranging from 0 (no pain) to 20 (maximum pain). The WOMAC function subscale includes 17 items and measures self-reported difficulty with a broad range of functional activities. The function sub-scale gives a total score ranging from 0 (no disability) to 68 (maximum disability). Both subscales are widely used in studies of knee OA, and their clinimetric properties have been established (McConnell et al 2001).

**Comorbidities**

The following six comorbidities previously shown to be associated with the impact or outcome of knee OA (Schafer et al 2014, Kadam et al 2004, de Rooij et al 2017, van Dijk et al 2010) were also collected as part of the three trial datasets: overweight/obesity derived from Body Mass Index (BMI) categorised into: underweight/normal (<25.0), overweight (25.0-29.9), and obese (>29.9); pain elsewhere other than the knee (a yes/no variable derived from a pain body manikin containing 50 body sites); anxiety and depression (one question within the EQ-5D instrument (EuroQol 1990) with response options of: ""I am not anxious or depressed", I am "moderately anxious or depressed" or "I am extremely anxious or depressed"); and presence (yes/no) of the following conditions: diabetes mellitus, cardiac

problems, and respiratory conditions. The last three comorbidities were derived from a combination of yes/no variables asking for presence of specific comorbidities, and through screening free-text participant responses for 'other comorbidities'.

"Number of comorbidities" was *a priori* categorised into: 0 (reference group), 1-2, and 3+ comorbidities.

**Statistical Analyses**

Descriptive statistics were used to ascertain similarity of baseline participant characteristics across the three RCTs. Stata v.15.1 (Stata Corporation, TX, USA) (StataCorp 2017) was used to conduct all analyses, under a frequentist approach, and with restricted maximum likelihood used for model estimation. A mixed model was used to pool data from the RCTs where data were available (only Objective 1), with clustering of participants within trials accounted for by assuming a random effect on the intercept term, and a Kenward-Roger (Kenward & Roger 1997) correction applied to the 95% confidence intervals (CI) to account for uncertainty in variance estimates (Riley et al 2010, Burke et al 2016, Legha et al 2018). Otherwise, linear regression models were fitted (Objectives 2 and 3); and for Objective 3 the two types of enhanced exercise in the BEEP RCT were pooled together. Model estimates (presented as mean differences (MD)), 95% CIs, and p-values are reported for each parameter. A two-sided p value of $<0.05$ was used to determine statistical significance. Missing covariate data were negligible within trials (<3.3% for each covariate) as shown in Supplemental table S1 (http://www.archives-pmr.org/), hence multiple imputation procedures were not necessary. Mixed model assumptions were tested and satisfied prior to analyses (no outliers were detected, outcome values were approximately normally distributed, and a linear functional form for continuous model covariates was appropriate).

Within the model building process, all models had a six-month follow-up outcome of either: i) a knee pain score (WOMAC pain scale (0-20)), or ii) a knee function score (WOMAC function scale (0-68)); with higher scores indicative of greater pain and greater dysfunction. Then, for each outcome, comorbidity (tested separately as: presence of a defined comorbidity, and number of comorbidities present) was entered into the model as either: a single model covariate (to test for a prognostic factor, Objective 1), or with an additional term for the interaction with treatment effect (to test for a moderator of exercise treatment effect; Objectives 2 and 3). Furthermore, the following effects were adjusted for throughout: baseline WOMAC pain (for knee pain outcome analysis only) or function (for knee function outcome analysis only), age, gender, and intervention allocation. Full details of each of the models are provided in the online supplement 1.

## Results

### Baseline Summary

Baseline characteristics of participants across all three RCTs were broadly similar and are summarised in Table 1. The mean (SD) age (in years) of participants in the TOPIK trial (n=217) was: 68.1 (8.3), in APEX (n=352): 63.2 (8.8), and in BEEP (n=514): 62.9 (9.8), respectively, and the overall mean (SD) baseline WOMAC pain/function scores across all three RCTs were 8.8 (3.6)/29.3 (12.8). Prevalence of each comorbidity was broadly similar across all trials, with approximately: 80% of participants being overweight/obese and with pain in at least one body site other than the knee; 50% with cardiac problems; <20% with respiratory conditions; and <13% with diabetes mellitus. Moderate and extreme

anxiety/depression were grouped together into one category for analysis due to the particularly low prevalence of extreme anxiety/depression (<3%), as were the 0 and 1-2 number of comorbidity groupings, due to low prevalence of 0 comorbidities (<3% also).

* Insert Table 1 approx. here

Multi-component comorbidities are summarised in Supplemental table S2; cardiac problems contained the most components (the most common of which was high blood pressure).

**Objective 1: association of comorbidity with outcome, following exercise (prognostic factor analysis)**

Obesity and anxiety/depression were statistically significantly associated with knee pain and function outcomes following a course of physiotherapist-led exercise.

* Insert Table 2 approx. here

Being obese was associated with less improvement in (WOMAC) pain score (MD 0.89, 95% CI: 0.23,1.54) and (WOMAC) function (MD: 2.34; 95% CI:0.12,4.56) at six-months, compared to having underweight/normal BMI (see Table 2). The association of overweight compared to underweight/normal BMI was weak and not statistically significant. Additionally, the presence compared to absence of anxiety/depression was statistically significantly associated with less improvement in pain and function at six-months ((MD: 0.76; 95% CI:0.25,1.28), and (MD: 1.93; 95% CI:0.18,3.68), respectively), as shown in Table 2.

None of the four remaining comorbidities were significantly associated with knee pain or function outcomes, following exercise intervention (see Table 2). Similarly, having 3+ comorbidities compared to 0-2 comorbidities was not shown to be a significant prognostic factor.

Note: full statistical parameter outputs for all models fitted are shown separately in Supplemental tables S3-S23 and S25.

**Objective 2: association of comorbidity with effect of exercise (moderator analysis)**

Using data from the TOPIK trial only, when assessed separately, none of the six comorbidities, nor number of comorbidities, were statistically significantly associated with a differential response to the effect of exercise compared to a non-exercise control (i.e. moderators of exercise treatment effect), in terms of pain or function outcomes at six-months (see Table 3).

* Insert Table 3 approx. here

**Objective 3: association of comorbidity with effect of specific type of exercise (moderator analysis)**

Using data from the BEEP trial only, the presence of cardiac problems was statistically significantly associated with the effect of enhanced exercise compared to usual exercise-based care in terms of WOMAC function outcome (p=0.041), indicating enhanced exercise may be less effective than usual physiotherapist-led exercise-based care for improving function in people with cardiac problems (Table 4). To visually aid understanding of this finding, the average unadjusted WOMAC function scores at baseline and six-months, for the

subgroups with or without cardiac problem and receiving either enhanced exercise or usual exercise interventions are shown in Figure 1. All groups improved in mean WOMAC function score at six-months compared to baseline. However, the percentage improvement from baseline was +7.7% in terms of the effect of enhanced exercise compared to usual exercise for the non-cardiac problems group, whilst participants with cardiac problems and offered enhanced exercise improved 6.1% less from baseline than those offered usual exercise. Further analysis conducted to assess moderation of the effect of each type of enhanced exercise showed that cardiac complaints statistically significantly moderated the enhanced effect of Individually Tailored Exercise, but not of Targeted Exercise Adherence (Supplemental table S24).

* Insert Table 4 and Figure 1 approx. here

Other comorbidities and the number of comorbidities were not significantly associated with the effect of a specific type of exercise (Table 4).

**Discussion**

This study aimed to investigate whether key comorbidities (overweight/obesity, anxiety/depression, pain in at least one body site other than the knee, cardiac problems, diabetes mellitus, and respiratory conditions), and number of comorbidities, are prognostic factors for knee pain and function, following physiotherapist-led exercise, and whether they might moderate participants' response to: exercise compared to no-exercise; and enhanced exercise compared to usual exercise interventions. This was the first study, to our knowledge, to use data from (up to three) similar RCTs to explore comorbidity as a potential prognostic factor and potential treatment effect moderator for participants with knee OA.

Firstly, we found that being obese, but not overweight, compared to being categorised as having an underweight/normal BMI, was a prognostic factor predicting less improvement in pain and function at six-months, following exercise intervention. Obesity has previously been associated with increased pain and poorer function in those with OA (Neogi 2013), and it is plausible that patients who are obese may have reduced exercise tolerance as a result of higher baseline pain levels or higher levels of joint inflammation (Vincent et al 2012).

Secondly, our analyses showed that being moderately or extremely anxious/depressed, compared to not anxious/depressed, was a prognostic factor for less improvement in pain and function at six-months, following exercise intervention. Anxiety and depression have been reported to be associated with reduced engagement and adherence to exercise (Marks 2012, Dobson et al 2016), which, in turn, may negatively influence treatment outcome (Pisters et al 2010, van Gool et al 2005). Depression has also been shown to be associated with lower exercise self-efficacy, which predicts physical activity levels in knee OA (Quicke et al 2017) and exercise behaviour initiation in inactive adults (Kangas et al 2015).

Finally, none of the six comorbidities were found to be an exercise treatment moderator in comparison to a non-exercise control. However, presence of cardiac problems was found to be a treatment effect moderator resulting in less improvement in functional ability, in terms of the effect of enhanced exercise compared to usual exercise-based care. These results are difficult to explain clinically, and therefore require further investigation to rule out chance findings

Our findings suggest that clinicians should be aware of the potential impact that comorbidity

can have on the clinical outcomes of knee OA patients who are offered exercise interventions. Screening for clinically relevant subgroups and providing additional comorbidity specific management support could be beneficial.For instance, for patients with anxiety/depression that are beginning an exercise programme, sign-posting for additional mental health assessment, talking therapies and tailored medication may improve clinical outcomes. For those who are obese, sign-posting to additional lifestyle programmes and actively addressing weight loss as part of the exercise programme may also be of benefit, although how effectively this is addressed currently can be variable (Holden et al 2019, Quicke et al 2019).

**Study Limitations**

This study aimed to incorporate the benefits of combining data from three RCTs Hay et al 2018, Foster et al 2007, Hay et al 2006), but for Objectives 2 and 3 only data from a single RCT were available, which particularly limited our analyses for detecting moderators of treatment effect. Detecting moderator effects requires a substantially greater sample size than for estimating overall treatment effect for which the RCTs were powered (for example, a simulation study has shown that if the magnitude of the moderator effect is equal to the overall effect, then a sample size inflation factor of 4 is required, which rises to more than 100 for more even subtle moderator effect sizes) (Brookes et al 2001), hence it is not surprising that we only detected one potential moderator. In our available data for example, there were only seven participants with diabetes mellitus who received community physiotherapy (Objective 2), resulting in a wide confidence interval (imprecise estimate) for pain outcome (MD: 2.04; 95% CI:-2.16,6.24). Therefore, due to the high uncertainty of many of our estimates, some potential moderators may remain unidentified at this stage due to Type II error and imprecision.

Furthermore, we could only test comorbidities that were present in all three RCTs, and to ensure consistency often had to collapse categories which may have led to loss of information (for example, angina, heart failure, and heart attack (all yes/no self-reported variables) were collected only in the BEEP RCT and were grouped into a generic 'cardiac problems' comorbidity). Another limitation concerns the validity of using self-reported data to assess comorbidity; there remains debate about the accuracy of such an approach.

This remains an exploratory study and caution must be taken when interpreting the results of such analysis. It is possible that some of the associations we detected (in particular for the single moderator) reflect spurious findings, perhaps caused by multiple testing. Further research to confirm the results of this study and further investigate the effect of comorbidity on the outcome of exercise interventions in people with knee OA is warranted, and currently underway (Holden et al 2017).

## Conclusions

Obesity and anxiety/depression were found to predict pain and function outcomes in people offered an exercise intervention, but only presence of cardiac problems might moderate the effect of physiotherapist-led exercise for knee OA. Confirmatory investigations are required to affirm the importance of comorbidities as prognostic factors, and more specifically, investigate their potential to predict the effects of exercise.

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