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Mediators of treatment effect in the Back In Action trial: Using latent growth modelling to take change over time into account

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Abstract (232/250 words)

Objectives

To test whether change in fear-avoidance beliefs was a mediator of the effect of treatment on disability outcome;

To test an analytical approach, latent growth modelling, not often applied to mediation analysis.

Methods

Secondary analysis was carried out on a randomised controlled trial designed to compare an intervention addressing fear-avoidance beliefs (*n*=119) with treatment as usual (*n*=121) for patients with low back pain, which found the intervention to be effective. Latent growth modelling was used to perform a mediation analysis on the trial data to assess the role of change in fear-avoidance beliefs on disability outcomes. The product of coefficients with bias-corrected bootstrapped confidence intervals was used to calculate the mediating effect.

Results

A statistically significant mediating effect of fear-avoidance beliefs on the effect of treatment on disability outcome was found (standardised indirect effect -0.35 (bias-corrected 95% CI -0.47 to -0.24)). Poor fit of the latent growth model to the data suggested that other factors not accounted for in this model are likely to be part of the same mediating pathway.

Discussion

Fear-avoidance beliefs were found to mediate the effect of treatment on disability outcome. Measurement of all potential mediator variables in future studies would help to more strongly identify which factors explain observed treatment effects. Latent growth modelling was found to be a useful technique to apply to studies of treatment mediation, suggesting that future studies could employ this approach.

Introduction

Worldwide, the prevalence of low back pain (LBP) has been estimated to be 9.4% (95% CI 9.0 to 9.8) [1], with lifetime prevalence estimates of between 51% and 84% [2]. In the UK, LBP has been found to affect between 49%-80% of the population at some point in their lifetime, leading to high costs in terms of healthcare, workplace absence [3] and impact on individual quality of life [4]. In the UK, musculoskeletal (MSK) conditions are predominantly managed in primary care, with back pain being the most common reason for patient health care visits [5]. While the prognosis of patients with an acute episode of LBP is often good [6,7], prognosis varies substantially for individual patients [8] and persisting symptoms are reported by many patients up to a year after their initial consultation [6,8].

Psychological factors (for example, fear-avoidance behaviours and beliefs [9,10,11,12,13,14,15,16,17], catastrophising thoughts [9,18], self-efficacy [9,19] and depression [9,11,14,20] have been found to be strong predictors of LBP outcomes and evidence suggests they are potentially important in influencing the effect of treatment. Guidelines on the management of LBP also recommend screening for and management of psychological factors [21,22]. However, it remains unclear how interventions addressing psychological factors improve patient outcomes [23], with mixed results being found in primary care populations in particular [24].

In order to improve the effectiveness of future interventions, key factors explaining improved patient outcomes must be identified to guide interventions [25,26]. These factors, known as treatment mediators, help explain how a treatment led to an effect on the outcome of interest [27] by looking at which factors change as a result of treatment, which are then related to a change in the outcome [28,29].

It has been acknowledged that just because a factor is prognostic (has been found to be related to outcome) does not mean it is necessarily *causally* related to outcome [24]. Temporality (change over time) has been identified a fundamental characteristic used to determine whether a hypothesised treatment mediator is on a causal pathway [29,30,31]. For example, we may hypothesise that a

treatment designed to effect fear-avoidance caused a reduction in fear-avoidance beliefs, which in turn led to an improvement in patient function. However, the improvement in function could have occurred first, which led to the reduction in fear-avoidance beliefs. Without serial measurement of both the proposed mediator and outcome it is not possible to know the order in which the change occurred. In order to establish how changes in factors are related over time, at least three measurements should be taken over different time points (e.g. [29]). Typically in intervention studies, measures are only taken pre- and post-intervention which only gives information on whether a change takes place or not, providing limited information about how a factor changes over time as a result of the intervention.

The Back In Action study [32] compared a psychological intervention with treatment as usual in 240 patients with LBP. The intervention centred on addressing patient's fear-avoidance beliefs and helping to improve their functioning. Measures of psychological factors and function were taken at baseline and at four follow-up points (two-, six-, 12- and 24-month follow-up). The intervention was successful in reducing disability across all time points compared with the control group, with statistically significant differences observed between the two groups [32]. The authors of the original study hypothesised that the proposed intervention led to a reduction in fear-avoidance beliefs and disability compared to usual care, but acknowledged that the results were not able to identify which part(s) of the intervention were most effective.

A mediation analysis therefore provides an ideal opportunity to test this potential treatment mechanism and determine whether reductions in fear had a significant influence within the pathway leading to improved disability outcomes in this trial. Latent growth modelling is a technique which allows the inclusion of multiple time points, thereby providing a more accurate estimate of change [33]. The aim of the analyses reported in this paper was to test whether change in patients' fear-avoidance beliefs mediated the relationship between their allocation to the active intervention and the change seen in disability in comparison to controls.

Materials and Methods

Back In Action Intervention: Conceptual model

The intervention used in the study was based on approaches described by Balderson et al [34] that include assessing and addressing patients' fear-avoidance beliefs, anxiety and activity limitations, performing a clinical assessment to rule out red flags indicating the need for prompt medical intervention, and providing treatment recommendations in line with goals set by the patient. The intervention included four visits with a physiotherapist or psychologist to identify and address fears about pain, discuss activity and exercise goals and develop an action plan to try and resume normal activities. Exercises provided were relevant to the patient's action plan and progress was reviewed at the end of treatment. In addition to these visits, patients also received a book on back pain self-management (Moore et al 1999, cited in [32]) and a 40 minute video on back pain (Patient Education Media Inc. 1996, cited in [32]). The control group received treatment as usual, which was heterogeneous including medications, physiotherapy and a wide variety of other interventions. Full details of the original trial are provided elsewhere [32].

Outcome measure

Low back pain-specific disability was measured via the 23-item Roland-Morris Disability Questionnaire (RMDQ) [35]. A higher score on the tool is suggestive of increased disability. This tool has been found to have good test-retest reliability and internal consistency in a primary care LBP population [36,37]. In the present study, Cronbach's alpha showed that the 23-item RMDQ had a good internal consistency (0.88).

Potential mediator

Fear-avoidance beliefs were measured using a modified version of the Tampa Scale for Kinesiophobia (TSK) which contained 10 of the original 17 items [38]. The trial authors multiplied the mean item score by 17 (the number of items in the original tool) so that the scores from the shortened version could be compared to the original version. A higher score suggests increased fear-avoidance beliefs. This version of the TSK has not been widely tested in terms of its psychometric properties, and in the

present study was found to have a Cronbach's alpha value of 0.66, suggesting questionable internal consistency and also potentially weakened associations between this measure and measures of other variables in the analysis.

Statistical analysis

Latent Growth Modelling

Latent Growth Modelling allows the examination of variables across time, both within and between participants [39,40,41]. Latent Growth Models (LGMs) consist of an intercept latent factor and a slope latent factor [42]. The intercept factor represents the starting point for the trajectory of a factor (its baseline status) while the slope represents the change in the trajectory of that factor over time. The use of the term "trajectory" in this context refers to the path each individual's fear-avoidance beliefs and disability scores take over the measured time points. To correctly specify a LGM, factor loadings must be given to represent the intercept (usually all a value of 1, as this is the point at which each individual starts), and the slope factors (see below). LGMs can incorporate models where change is not linear and where assessment intervals are not equally spaced, provided that all participants have been assessed at the same time points [39,43]. It is also possible to allow the model to estimate certain factor loadings when the trajectory of a measure is not clear [39]. It should be noted that the factor loadings chosen are arbitrary and not reflective of actual score change on the measures included in the model.

Although in the present analysis it is the slope that is the factor of interest, the intercept is also important as where a person starts in an intervention will have an impact on their scores at subsequent points. Therefore, in this LGM, co-variance between the intercept and slope factors was also included, as this gives an indication of whether people who start at a lower or higher score for the mediator or outcome change at lower or higher rates. To perform the LGM analysis, three steps were carried out, which are outlined below.

Step 1: Investigate the shape of the observed growth trajectory (change) for the mediator and outcome variables

Change over time in both the mediator and outcome variables were estimated from the observed data, to ensure that the factor scores for the slope factor represented the observed trajectory and provided adequate fit to the data. This also allowed examination of differences in trajectories between the treatment and control groups, which was expected as the intervention had been shown to be effective.

Step 2: Combine the trajectories of the mediator and outcome variables

The LGMs of the mediator and outcome were combined into a single model so that the relationships with intervention allocation could be investigated [39]. This is described as a parallel process model, where the observed trajectories of the two measured variables are viewed as two separate processes that occur over the same period of time [39]. Including treatment group allocation as a co-variate (Control =0; Intervention =1) enabled examination of the differences between scores in the intervention and control groups.

Step 3: Full mediation model and estimates of mediated effect (with bootstrapped CIs)

The parallel process model was then used to estimate the mediating effect of fear-avoidance beliefs on the association between treatment allocation and disability outcome using the product of coefficients approach, which is the analytical approach recommended for carrying out mediation analysis [39,44,45]. The statistical interpretation of mediation analysis is made via separate effects (see Figure 3). The *c* path is the direct effect of treatment on outcome, before taking into account the effects of any specific mediating variables. Paths *a* and *b* make up the mediating pathway, with the mediating effect usually being described in the literature as the product of coefficients (*a* x *b*, or *ab*)[46]. The *ć* path denotes the total effect of the whole model (*ab*+*c*). Bias-corrected bootstrapped confidence intervals (CIs) were estimated to account for the often non-normal distribution of the mediated effect and to provide an estimate of the precision of the mediated effect rather than just the statistical significance [46]. In the present analysis, 1,000 bias-corrected bootstrapped samples were used to estimate 95% CIs.

Model Fit

Model fit indices show how well the hypothesised model fits the observed data [47]. In the present analysis, Chi square (X^2), Chi-square divided by degrees of freedom (X^2/df), Comparative Fit Index (CFI), Root Mean Square Error of Approximation (RMSEA) and Standardised Root Mean-square Residual (SRMR) were examined. Good or adequate fit is indicated by a non-significant X^2 value, a X^2/df of between 2 and 5, CFI of 0.96 or above, and a RMSEA and SRMR of 0.08 or below [43,48]. No one fit index is seen as superior, and the exact cut-off values are subject to debate [44]. It has therefore been recommended that overall judgement is made on the basis of several fit indices [33]. If the goodness-of-fit indices did not indicate good fit, modification indices were examined to check whether the hypothesised model could be improved by adding or removing factor loadings on specified paths [43]. Changes to the original model were only made if the modification made theoretical sense and substantially improved the model [43].

Missing data

Overall, follow-up rates in the original study were good with less than 30 participants lost to follow-up by 24 months in each group. Missing data was imputed using Expectation Maximisation (EM), a single imputation method suitable for use with small amounts of missing data [49]. This method assumes data are missing at random, which was checked using Little's MCAR (Missing Completely At Random) test [50] which will be non-significant if the data is MCAR. In addition to this test, baseline characteristics of responders and non-responders (split to show treatment and control groups separately) were examined for baseline differences between participants who responded or did not respond at each time point (*data not shown*).

All analyses were carried out using Microsoft Excel, SPSS PASW Version 18 and AMOS Version 19.

Results

Study sample descriptive data:

The Back In Action trial recruited 240 adult participants (119 in the treatment group and 121 in the control group) aged between 25 and 64 years, suffering with chronic LBP, from primary care settings in Seattle, Washington State, US. Non-response bias analysis indicated that there were differences in baseline levels of pain intensity, fear-avoidance beliefs, disability and pain duration between responders and non-responders in the two treatment groups. Fear-avoidance beliefs and disability scores of those in the treatment group were higher at baseline for responders to earlier follow-up points and lower at baseline for those responding to later follow-up points. Pain duration in the treatment group was shorter at baseline for responders to follow-up compared to non-responders.

The baseline characteristics of the study sample are provided in Table 1, and indicate that a slightly higher percentage of those in the treatment arm were female (64% compared with 60%) and also had a slightly longer duration of pain (110 days compared to 97). However, these differences were negligible and no other differences were seen between treatment and control for the other variables investigated. The mean (SD) scores for the potential mediator (TSK) and outcome variable (RMDQ) in the two intervention groups are given in Table 2. The observed trajectories of mean fear-avoidance beliefs and disability scores for the treatment and control groups based on all measured time points are presented in Figures 1 and 2. As expected, the biggest mean change in the intervention group was between baseline and the first follow-up point of two months for both the potential mediator (fear-avoidance beliefs) and the outcome variable (disability).

The reduction in fear-avoidance beliefs and disability over the two-month intervention period was smaller for the control group receiving usual care compared to the intervention group. The intervention group showed a linear decrease in disability scores compared to the control group, which showed no change in disability over the first two months and also no change between 12-month and 24-month follow-up. The mean RMDQ scores at baseline showed a small difference (0.7 point) despite randomisation.

Step 1: The non-linear trajectories needed to be accounted for in the full LGM. The factor scores were therefore estimated based on the observed trajectories, taking into account the unequal measurement points. The factor scores were based on the observed trajectory for both the treatment and control groups combined, as the groups were compared using the co-variate of treatment group allocation in the full mediation model. The factor scores for both the mediator and outcome trajectories provided adequate fit overall to the data, as indicated by the goodness-of-fit statistics (Fear-avoidance: $X^2=62.53_{(14)}$, $p<0.05$, $X^2/df=4.47$, CFI=0.95, RMSEA=0.12 (95% CI 0.09 to 0.15), SRMR=0.05; Disability: $X^2=49.95_{(14)}$, $p<0.05$, $X^2/df=3.57$, CFI=0.96, RMSEA=0.10 (95% CI 0.07 to 0.14), SRMR=0.04) and were therefore used in the subsequent analyses (see Figure 3). While not every index suggested good fit, the judgement is based on the results of all the different indices taken together, so as the majority of indices suggested good or adequate fit, the trajectories were judged to be acceptable.

Step 2: The two separate models were then combined to test for co-variances between each of the Intercept and Slope factors and explore how the potential mediator and outcome variables related to each other, before adding the intervention variable to complete the model. We assessed whether change in the potential mediator was related to change in the outcome variable. The model fit statistics indicated that the model provided fair fit to the data overall. Modification indices showed that allowing co-variation between the error terms for the TSK and RMDQ 12-month follow-up scores and between the error terms for the TSK and RMDQ two-month follow-up scores slightly improved model fit ($X^2=154.88_{(49)}$, $p<0.05$, $X^2/df=3.16$, CFI=0.94, RMSEA=0.10 (95% CI 0.08 to 0.11), SRMR=0.05). As it is likely that each of the measurement points are related to each other, and that this may be reflected in related error variance [51], we decided that allowing these co-variances made theoretical sense. Further modifications did not appear to be theoretically plausible and therefore no further changes to the model were made.

Table 3 gives the results of the means, co-variances and variances between the intercept and slope of each variable. The mean change in both TSK and RMDQ indicated a small, statistically significant decrease over time in both variables. The within-domain co-variance, relating to the intercept and slope of the same construct [43], showed a positive estimate between TSK intercept and slope and a negative estimate between RMDQ intercept and slope. This suggested that people who scored highly on the TSK at baseline had a higher rate of decrease in scores than those who scored lower, while for the RMDQ, people who scored higher at baseline had a lower rate of decrease in scores. However, both of these estimates were very small and did not reach statistical significance. The between-domain co-variances gave much higher, statistically significant values. The high value between the TSK and RMDQ slope factors suggested that as TSK scores change the RMDQ scores also change (an important pre-requisite for mediation). The high value between the two intercepts suggested that people who scored highly on the TSK are likely to also score highly on the RMDQ. Finally, the variances for each latent factor indicated strong individual variation amongst participants, especially in the initial scores.

Treatment allocation was then added to the model as a covariate. The model provided a very similar fit to the data as the model without the treatment group allocation variable. Modification indices indicated that allowing co-variation between the error terms for TSK and RMDQ scores at 12-month follow-up, TSK score at 12-month follow-up and RMDQ score at two-month follow-up, and TSK and RMDQ scores at two-month follow-up would result in a better fitting model (X^2=172.17$_{(54)}$, p<0.05, X^2/df=3.19, CFI=0.94, RMSEA=0.10 (95% CI 0.08 to 0.11), SRMR=0.04). The co-variation between TSK score at 12-month follow-up and RMDQ score at two-month follow-up is less intuitive than co-variances between the variables at the same time points, but could reflect a relationship between early change in disability and later change in fear-avoidance beliefs.

In the present analysis the values of interest are the regression coefficients between treatment allocation and the slopes for the mediator and outcome [43]. Allocation to the intervention group significantly predicted the rate of change for both the TSK and RMDQ measures (see Table 4). The

slope values for TSK and RMDQ suggest that change in the TSK and RMDQ measures was substantially higher in the intervention group, particularly for the change in TSK (-0.26 and -0.65 for TSK and RMDQ scores respectively).

Step 3: Finally, the full mediation model was tested by adding a path between the mediator and outcome variables. The bold lines on Figure 3 below highlight the mediating pathway. Each of the beta coefficients shown on this Figure represent the direct effect of each variable on the other, as indicated by the direction of the arrow. The standardised coefficients show that the intervention is associated with a decrease in the TSK slope (-0.44) and that this decrease is associated with a decrease in the RMDQ slope (-0.79). Table 5 shows that the mediated effect (product of coefficients; in this case, -0.44 * -0.79 = -0.35 (95% CI -0.47 to -0.24)) was statistically significant, indicating that differences between intervention and control in change in the observed trajectory of the fear-avoidance beliefs variable mediated some of the change in the observed trajectory of the outcome measure. However, none of the model fit statistics for this final model suggest that it provided a good fit to the data (X^2=1095.17$_{(63)}$, p<0.05, X^2/df=17.38, CFI=0.46, RMSEA=0.26 (95% CI 0.25 to 0.28, SRMR=0.36) and modifying the model did not help to improve fit.

Discussion

The aim of this study was to use a more novel analytical approach to assessing mediation in an RCT dataset. We sought to test the study's hypothesis that change in fear-avoidance beliefs explained the reduction in disability scores seen in the intervention arm of the trial (i.e. that change in fear-avoidance beliefs was a mediator of the relationship between treatment allocation and disability improvement). The results of the analyses showed that there were associations between the intervention and change in fear-avoidance beliefs, and between change in fear-avoidance beliefs and change in disability. There was a significant mediating effect of change in fear-avoidance beliefs on the relationship between allocation to the active treatment and change in disability. This suggested that targeting fear-avoidance beliefs in an intervention for chronic LBP patients would be beneficial.

However, the final mediation model provided a poor fit to the data. This means that the model as currently hypothesised does not fully explain how the treatment worked for this particular patient population, as there is key information missing. The study hypothesis, that allocation to the activation intervention arm was associated with a reduction in fear-avoidance beliefs and that this reduction was associated with a reduction in disability outcome, was therefore partially supported, but suggests that other mediating factors must be considered.

The Back In Action trial was a complex intervention, involving several sessions with a multidisciplinary team and several different components. While several of these sessions did focus on reducing fear-avoidance beliefs, much of the intervention actually focused on goal-setting and on plans to achieve those goals. These are likely to be highly variable depending on the individual patient, and could depend on factors such as self-efficacy or internal control, or the patient's relationship with their therapist. A systematic review also found pain catastrophising to be a potential mediator of treatment effect in interventions with a psychological component in non-inflammatory musculoskeletal pain [52], although there has been some recent debate around this with robust mediation analysis finding contradictory results [53]. Clearly further investigation of this factor is warranted. Both pain catastrophising and fear-avoidance beliefs are key components of the Fear-Avoidance Model (Vlaeyen et al 1995)[54], which has been used extensively to explain the development of pain and disability in patients with MSK pain. However, while strong evidence exists for the predictive value of each of these model components (e.g. Leeuw et al 2007[55]; den Hollander et al 2010[56]), studies investigating the causal nature of these relationships have suggested that the model does not work in the hypothesised order (Gheldof et al 2010[57]; Wideman et al 2013[58]). This model was not tested in full as part of the present study, but the results add to the evidence base for fear-avoidance beliefs being potential mediators of treatment outcome, even though the exact pathways through which this factor contributes has not been fully clarified as yet.

It could also be that the population included in the intervention did not score particularly highly on the fear-avoidance beliefs measure used, which would have limited the intervention's ability to impact on

patient scores. However, little information is available on an acceptable cut-off for a 'high' TSK score. Previous studies using the Swedish and Dutch versions of the 17-item TSK have recommended a cut-off of 37 for 'high' fear [54,59,60]. In this study, the trial authors scored the 10-item TSK in a way that made it comparable with the 17-item version. If these cut-offs are applied to the present study, it would appear that both the treatment and control groups have high fear at baseline (mean score over 37) and while in the treatment group this score decreases (below 37 at each follow-up point), in the control group the scores at each follow-up point remain above this cut-off.

Comparison with previous literature

This analysis adds to a currently small evidence base for treatment mediators of LBP interventions, and is the first study, to the authors' knowledge, that has used LGM for analysing mediators in a LBP intervention study. Guidelines from previous LGM studies in other areas of health psychology were followed [39,61]. A recent study also claimed to use Cheong et al's technique to carry out their mediation analysis on a RCT data from an intervention to prevent child behavioural problems [62], but while this study utilised LGMs they obtained their mediating effect using the Baron & Kenny approach [63] rather than using the product of coefficients approach used in the present study. The latter approach is recommended in the wider mediation literature (e.g. [46]) suggesting that it might represent stronger evidence of a mediated effect.

Potential limitations

The technique of latent growth modelling used to carry out this analysis proved a useful, if complex, technique for mediation analysis. It offers the potential to address a key problem within current mediation studies, temporal sequencing, which is not currently adequately addressed (see [30,31,32]. However, it must be acknowledged that latent growth modelling is a correlational technique and therefore it cannot be established whether the effect is in the hypothesised direction. The use of LGMs alone, as this study shows, cannot address temporal sequencing without including an adequate number of time points that will capture change when it occurs. In the present study, even though the Back In Action study collected data across five time points, it did not collect any data while the

intervention was taking place. This limits the assessment of treatment-mediated effects as it is likely that the follow-up scores show a more diluted effect of the intervention than at the time of participants receiving it. The analyses presented here showed that change in both fear-avoidance beliefs and disability happens early on, but it is still not possible to see when these variables changed and crucially, *which* changed first. One way of potentially addressing this issue would have been to look at the intercept of the mediating variable and the slope of the outcome, rather than the slopes of both variables (to see whether baseline levels of fear-avoidance beliefs predict change in disability) [64], but that would have been illogical in this analysis as the hypothesis was around change in the mediator as well as the outcome. Looking at change in the mediator at an earlier stage than change in the outcome is another option, but again not possible in this analysis as the first follow-up point was two months post-treatment, at which any change that was expected to happen in both the mediator and outcome variables would have already occurred. However, such analysis is possible using LGMs provided that there are enough time points to allow examination of early and later change. This again stresses the need for assessment points during treatment. This would of course need to be balanced with the consideration of response burden for participants and the potential for increased drop-out this additional burden may cause.

The final LGM mediation model was also found to be a poor fit to the data, suggesting other factors might be responsible for the treatment effect. We acknowledge that only testing a single potential mediator is limiting, and that other factors measured in the original study such as depression and anxiety could also be important potential mediators. However, these factors (and others, such as those mentioned above) were not considered as mediating factors in the original study, so they were not tested. It could be that the addition of other factors would have improved the fit of the model.

Implications for clinical practice and research

Clinically, the findings from this study suggest that fear-avoidance beliefs play a role in the explanation of treatment outcome when a treatment specifically targets this factor. Future treatments should perhaps include only patients who are found to be highly fear-avoidant, or tailor treatment to

focus fear-avoidance belief reduction on patients who are most severe. However, this analysis represents only one study and more research is needed to support these findings, preferably research that accounts for the limitations discussed above. Few additional variables that could have played a key role in the success of this intervention (such as self-efficacy) were measured, and the role of other factors in this intervention are therefore unclear. Another concern is that the measure of fear-avoidance beliefs available in this dataset has not been validated previously, and its internal consistency in this dataset was questionable. A stronger measure of fear-avoidance beliefs, to ensure more confidence that this construct is indeed a mediator of outcome, is required in future studies.

In order to improve the delivery of future interventions, it would also be helpful to see which aspect of the intervention led to a change in fear-avoidance beliefs. For example, if this was after the first session, when fear of pain was explicitly discussed, it could be that this session was the one that was important in changing fear-avoidance beliefs. Measurements taken during the treatment period would give much more information on key variables that the intervention aimed to change, so that future interventions can be tailored to only include sessions found to impact on factors of importance.

Conclusion

The reduction of fear-avoidance beliefs through a multidisciplinary intervention was found to be a significant mediating factor for the reduction of disability in chronic LBP patients in the Back In Action Trial. This study therefore supports the role of training clinicians in being able to target fear-avoidance beliefs as part of their overall skillset. One key issue still not resolved by this study is that of temporality. Future studies of treatment mediation need to address temporal relationships by including measures of key mediators and outcomes during the treatment period, in order to more confidently ascertain when reductions in fear tend to occur and thereby inform clinicians about when fear avoidance beliefs should be targeted within a course of treatment.

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Figure 1 Course of 10-item TSK scores (mediator variable) for intervention and control groups over two years follow-up

Figure 2 Course of 23-item RMDQ scores (outcome variable) for intervention and control groups over two years follow-up

Table 1 Baseline characteristics of study population (*n*=240)

Variable		**Treatment (*n*=119)**	**Control (*n*=121)**
Age in years, mean (SD)		49.67 (9.02)	49.82 (9.77)
Sex, % female		64.7%	60.3%
Education in years*, median (range)		6.00 (3-8)	6.00 (3-8)
Pain Intensity (1-10), mean (SD)	Average last three months	5.71 (1.84)	5.83 (1.82)
	Today	3.45 (2.49)	3.45 (2.57)
Pain duration (days), mean (SD)		110.50 (60.72)	97.39 (62.34)
Fear-avoidance beliefs (TSK – 10 item version), mean (SD)		41.47 (8.79)	41.25 (8.22)
Disability (RMDQ-23 item version), mean (SD)		12.10 (5.49)	11.36 (5.67)

**Education was graded in eight levels by asking participants what the highest grade of year of school they completed. This ranged from 1 (less than eight years) to 8 (postgraduate)*

Table 2. Changes over time (means and SDs) for potential mediator and outcome variables in the Back In Action trial

Variable	**Treatment (*n*=119)**	**Baseline**	**Two-month follow-up**	**Six-month follow-up**	**12-month follow-up**	**24-month follow-up**
RMDQ (23-item version)		12.10 (5.49)	10.02 (6.27)	8.91 (6.60)	8.46 (6.90)	7.76 (6.41)
TSK (10-item version)		41.47 (8.79)	36.41 (9.51)	34.99 (9.65)	35.27 (10.32)	34.11 (9.41)
RMDQ (23-item version)	**Control (*n*=121)**	11.36 (5.67)	11.44 (5.81)	10.01 (6.25)	8.99 (5.96)	9.02 (6.87)
TSK (10-item version)		41.25 (8.22)	39.96 (9.62)	39.17 (9.47)	37.55 (8.91)	38.58 (9.19)

Table 3 Means, co-variances, correlations and variances between mediator and outcome variables

	Variables	**Estimate**	**Standard Error**	***p*-value**
Means	TSK Intercept (*baseline value*)	41.14	0.56	0.00
	TSK Slope (*change over all time points*)	-3.06	0.32	0.00
	RMDQ Intercept	11.81	0.36	0.00
	RMDQ Slope	-1.38	0.15	0.00
Co-variances	TSK Intercept <-> TSK Slope	b= 1.06 β = 0.05	2.71	0.49
	TSK Intercept <-> RMDQ Intercept	b= 20.79 β = 0.60	3.10	0.00
	TSK Slope <-> RMDQ Slope	b= 3.64 β = 0.86	0.68	0.00
	RMDQ Intercept <-> RMDQ Slope	b= -0.31 β = -0.04	0.79	0.69
Variances	TSK Intercept	52.05	6.69	0.00
	TSK Slope	7.93	2.30	0.00
	RMDQ Intercept	23.06	2.81	0.00
	RMDQ Slope	2.24	0.50	0.00

b = *Unstandardised estimate*
β = *Standardised estimate*

Table 4 Mean values for mediator and outcome, related to treatment group allocation

	Variables	**Estimate**	**Standard Error**	**p-value**
Regression Coefficients	TSK Intercept	b = 0.10 β = 0.01	1.12	0.93
	TSK Slope	b= -0.26 β = -0.45	0.61	0.00
	RMDQ Intercept	b=0 .21 β = 0.02	0.72	0.77
	RMDQ Slope	b= -0.65 β = -0.22	0.29	0.02

b = *Unstandardised estimate*
β = *Standardised estimate*

Table 5 Mediating effect of change in fear-avoidance beliefs (10-item TSK) on the relationship between treatment allocation and change in disability (23-item RMDQ)

	Effect	**Model**	
		Standardised Estimates (95% CI)	**Unstandardised Estimates (95% CI)**
RMDQ (23-item)$^{\Delta}$	Total (*ć*)	-0.22 (-0.40 to -0.02)	-0.66 (-1.20 to -0.08)
	Direct (*c*)	-0.11 (-0.11 to 0.33)	-0.31 (-0.31 to 1.01)
	Indirect (*ab*)	-0.35 (-0.48 to -0.23)	-1.03 (-1.49 to -0.67)

$^{\Delta}$=*residualised change*

Figure 1 Course of 10-item TSK scores (mediator variable) for intervention and control groups over two years follow-up

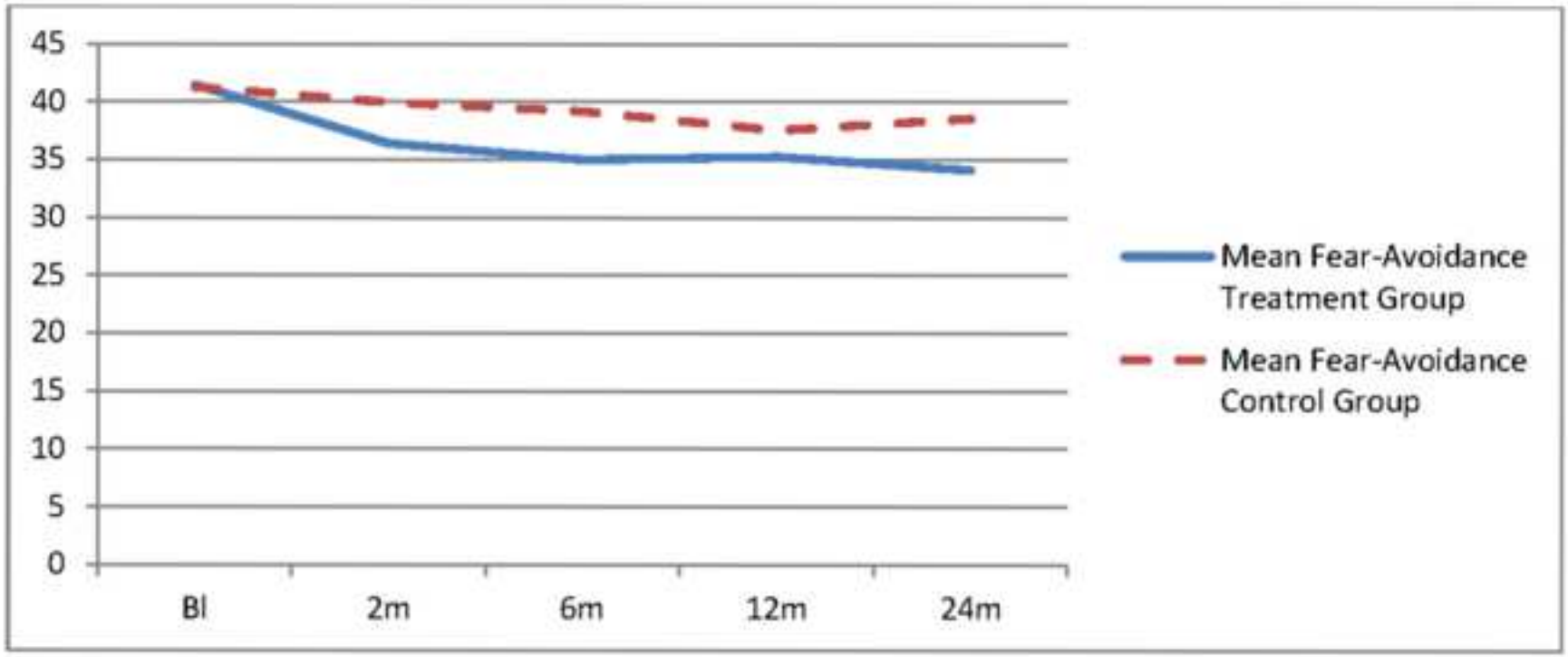


Figure 2 Course of 23-item RMDQ scores (outcome variable) for intervention and control groups over two years follow-up

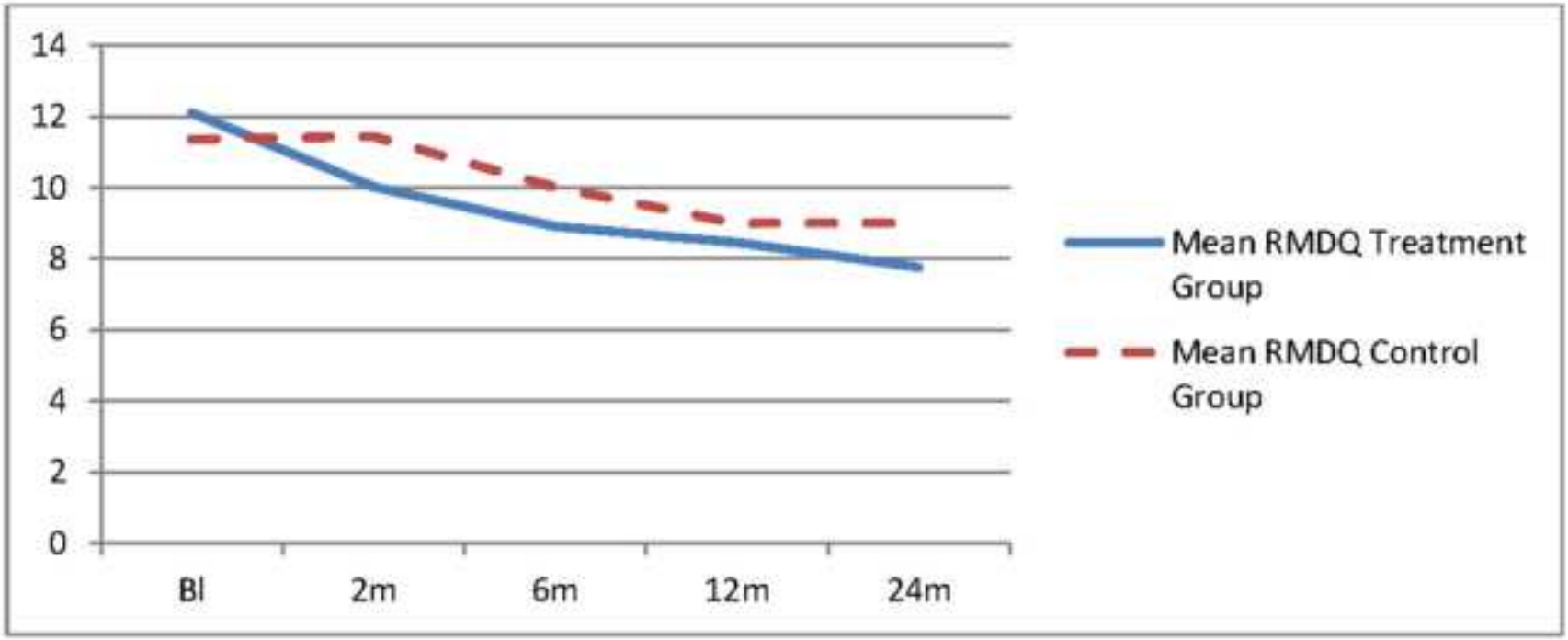
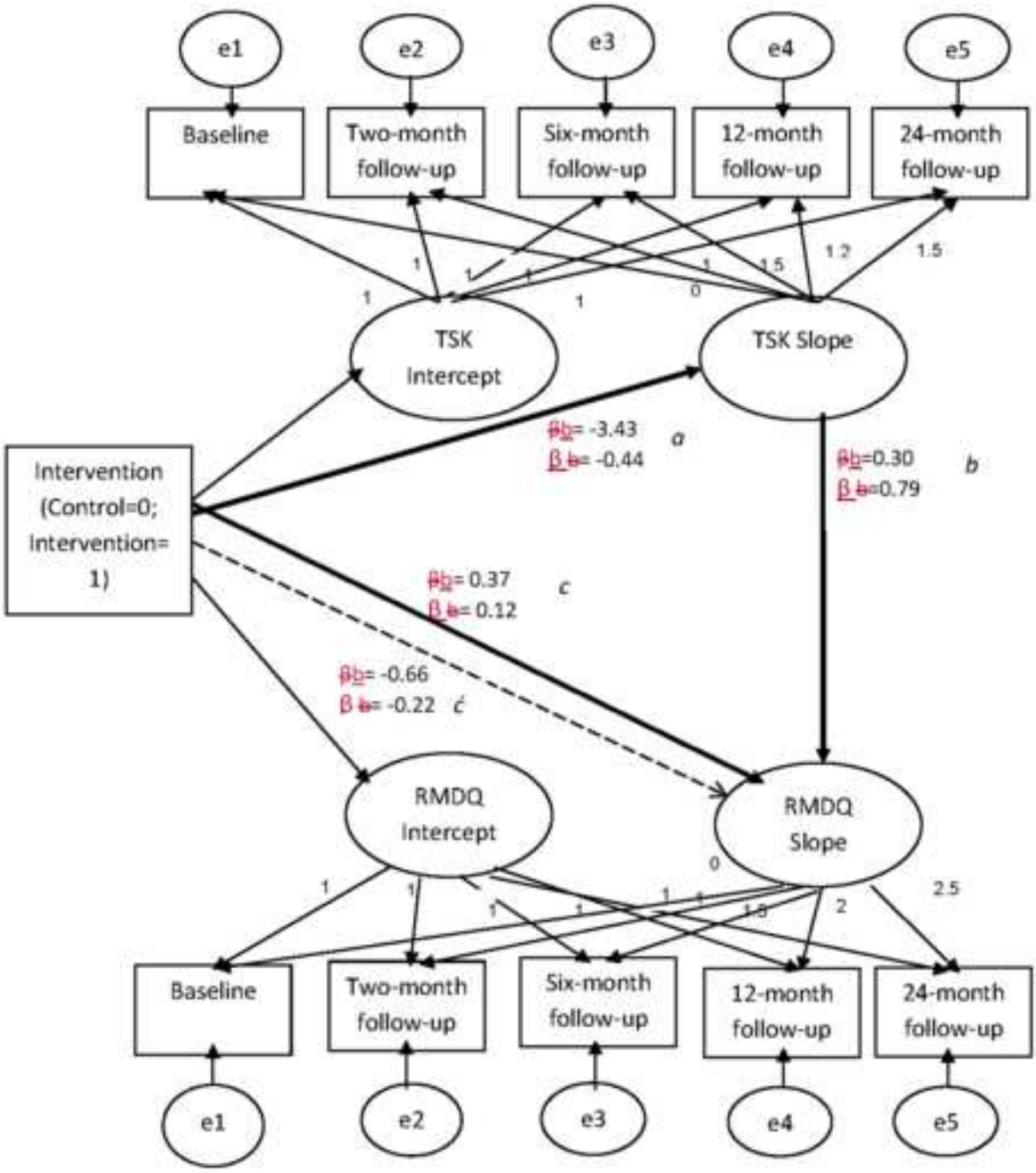


Figure 3 Full mediation model: Change in fear-avoidance beliefs (10-item TSK) as a mediator between treatment allocation and change in disability outcome (23-item RMDQ)



~~β = Unstandardised estimate~~

b = ~~Uns~~standardised estimate

β = Standardised estimate

NB: Total effects are taken from Table 5