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What mediates treatment effects in a pre-surgery physiotherapy treatment in surgical candidates with degenerative lumbar spine disorders? A mediation and conditional process analysis of the PREPARE randomized controlled trial

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ACCEPTED

Abstract

Objectives: Treatment guidelines recommend targeting both physical and psychological factors in interventions for degenerative lumbar spine disorders. Studying treatment mechanisms gives information on key factors explaining outcome improvement which can refine treatments for future research. This study explores treatment mediators in a physiotherapy treatment on disability, pain intensity and health related quality of life (HRQoL) in surgical candidates with degenerative lumbar spine disorders compared to waiting-list controls. An additional aim was to evaluate patients' expectation as a moderator of treatment outcome.

Methods: Data collected from 197 patients in a single blinded randomized controlled trial comparing 9 weeks of multifaceted physiotherapy to waiting-list were used in this conditional process analysis. Analysis was carried out on group differences for change in Oswestry Disability Index (ODI), Pain Visual Analog Scale (VAS) back pain, EuroQol-5D (EQ-5D) and EQ-VAS. The putative moderation role of expectations and mediation role of change in physical variables and psychosocial variables were tested.

Results: Change in self-efficacy mediated improvement in all outcomes. Improvement in ODI was also mediated by change in depression, VAS was mediated by change in fear avoidance beliefs and EQ-VAS was mediated by change in activity level and fear avoidance beliefs. Improvements were moderated by patients' treatment expectations.

Discussion: Self-efficacy, fear avoidance beliefs, physical activity level and patients' treatment expectations were found to be important factors explaining treatment effects. Self-efficacy was the consistent mediator for effects of the pre-surgical physiotherapy on disability, back pain intensity and HRQoL.

Keyword: Degenerative lumbar spine disorder, Low Back Pain, Physiotherapy, Mediation analysis, Expectation.

INTRODUCTION

Low back pain (LBP) is a global health challenge.¹ Treatment guidelines state that evidence based non-surgical treatment should be exhausted before considering surgical treatment.²⁻⁴ Treatment guidelines for LBP with or without sciatica, including specific diagnosis/pathology, recommend a multimodal treatment including exercise, self-management and psychological approaches.³⁻⁶ Details regarding recommended treatment approaches, for example specifics about the content and how this is best delivered, are lacking and the mechanisms behind treatment effects for patients with LBP are not well understood. Conditional process analysis provides opportunity to investigate treatment mediators and moderators, giving knowledge of key factors explaining treatment outcome.⁷⁻⁹ Treatment mediators help explain how treatment may lead to an effect on an outcome, by looking at which factors change as a result of treatment, and which are then related to a change in the outcome. Treatment moderators are pre-existing factors that influence the relation between treatment and the outcome. Exploring treatment mediators and moderators has an important implication for clinical practice aiming to increase effectiveness in treatments through more focused interventions.⁷⁻⁹ Previous studies have mostly evaluated potential psychological mediators of psychological based interventions alone or in combination with a physical intervention for patients with chronic low back pain (CLBP).^{7,9-11} These studies commonly base their hypothesis on a potential association between treatment outcome, catastrophizing and fear avoidance.⁹⁻¹³ Available studies have small samples, lack analyses of multiple potential mediators and are based on heterogeneous interventions and measures. Therefore, any firm conclusions cannot be drawn.^{7,11} Future consideration of all potential mediating factors incorporated in a biopsychosocial framework has been requested.^{8,9,12,14} There is a need to broaden the view when investigating

potential mediators to further develop more focused interventions for CLBP by suggesting both psychosocial and physical change potentially being mediators of treatment effect. There is also a large body of evidence suggesting patients' expectations play a role in treatment outcomes for musculoskeletal pain including CLBP.¹⁵⁻¹⁷ This indicates that expectations may have a moderating effect on the treatment needed to be addressed.

The PREPARE study compared a structured multifaceted physiotherapeutic intervention to usual care for patients with degenerative lumbar spine disorders who were candidates for spinal surgery. The pre-surgery physiotherapy showed positive effects on treatment outcomes in the pre-surgical phase.^{18,19} The aim of this secondary analysis was to explore potential treatment mediators in the PREPARE intervention. An additional aim was to evaluate patients' expectations as a moderator of treatment outcome.

MATERIALS AND METODS

This paper presents mediation and conditional process analysis on a single blinded, 2-arm, randomized controlled trial. The PREPARE trial methods, intervention details and the patient outcome set have been published elsewhere.¹⁸⁻²⁰ The study was approved by the Regional Ethics Committee in Linköping (dnr 2012/167-31). The patients gave their written consent to participate in the study. The manuscript follows the CONSORT guidelines.²¹

Subjects and setting

Patients were consecutively recruited from the Spine Clinic at the University Hospital in Linköping, Sweden, between October 2012 and March 2015. Patients fulfilling the following inclusion criteria were approached by research staff: age of 25-80 years, MRI confirmed diagnosis of degenerative lumbar spine disorder (disc herniation, lumbar spinal stenosis, degenerative disc disease or spondylolisthesis grade 1-2), scheduled for surgery, fluent in Swedish. Patients were excluded if there were indications for acute surgery, presence of severe spinal pathology, or previous surgery on the same lumbar spinal level. A total of 242

patients met the inclusion criteria. After written and oral information, 197 patients gave consent to participate and random concealed block allocation was used to form the waiting-list (n=98) and physiotherapy (n=99) groups (Figure 1).

FIGURE 1.

Intervention

Patients in the waiting-list group received usual care which included information about the surgical procedure and postoperative rehabilitation. Patients in the physiotherapy group received the usual care intervention and pre-surgery physiotherapy twice a week for 9 weeks containing:

1. Active physiotherapy according to a treatment-based classification (TBC)²²;
a) Specific exercise and mobilization, or b) Motor control exercises, or c) Traction.
2. Tailor-made general supervised exercise program. The program included strength-, cardiovascular- and mobility exercises. Dose and intensity of the exercise were set and progressed over time. The program was also individualized to the patients' specific impairments.
3. Behavioral approach to increase activity level and decrease fear-avoidance behavior.
4. Daily physical activity for at least 30 min. The patient wrote a daily logbook over physical activity.

The interventions were performed at one of eleven public health care physiotherapy clinics in Östergötland County. Further details are described in the study protocol by Lindbäck et al.²⁰

Measures

Treatment Outcomes

Patient Reported Outcome Measures (PROMs) and physical measures were collected before randomization and after 9 weeks intervention in the pre-surgical phase.

The PREPARE study's primary outcome was the Oswestry Disability Index (ODI) which is a valid measure of pain related function and activity limitations.²³ Several secondary outcomes were also included in the PREPARE study.²⁰ Back pain intensity during the last week was rated on a validated Visual Analog Scale (VAS).²⁴ Health-Related Quality of Life (HRQoL) was evaluated with EuroQol 5D including two scales: the EQ-index (EQ-5D) and the EQ-VAS.^{25,26}

Potential mediators

Nine potential mediators representing content of the pre-surgical intervention were investigated:

Psychological wellbeing was evaluated with validated patient-reported subscales of the Hospital Anxiety and Depression Scale (HADS), HADS-depression and HADS-anxiety.^{27,28} Self-efficacy was measured with the validated Self-efficacy Scale (SES).²⁹ Fear avoidance beliefs was measured with the validated Fear Avoidance Beliefs Questionnaire subscale for physical activity (FABQ-PA).^{30,31} The Patient Enablement Instrument (PEI) was used to measure self-perceived ability to understand and cope with illness.³²

Gait speed was measured as the patients' fastest gait speed (meters/second) on a ten meters walk distance, which is a valid and reliable measure for gait capacity.³³ Lower extremity strength was measured through maximum voluntary isometric muscle force in the quadriceps femoris muscle with a hand-held dynamometer, which is a reliable and valid method.³⁴⁻³⁶ The same measurement procedure as in former studies measuring normative values was used.³⁴

The highest peak torque obtained was recorded for each leg in kilogram (Kg) and a mean value was calculated. Physical activity level was measured through two questions. One addressed weekly frequency of low intensity level physical activity (daily activity level) given four options with intervals of times/week the patient has been physical active. The other question addressed the dose and intensity level of physical exercise (activity level). Five

response levels were given: seldom active (Inactive), irregular performance of low intensity activity (Mildly active), regular performance of low intensity activity (Walking), regular performance of moderate intensity activity (Moderately active) or regular performance of moderate - high intensity activity (Very active).

Theoretical rational for potential mediators

Potential mediators were selected on the basis of one or more of the following criteria (Table 1):

- **On the theoretical basis of expected treatment effect**

The multifaceted intervention in the PREPARE study was aimed to target both physical and psychosocial aspects of patients' illness. All potential mediators were aimed to be targeted by the pre-surgical intervention and expected to have impact on treatment outcome measures. Based on these assumptions, there was a theoretical basis supporting the choice of each mediator. Appendix 1, Supplemental Digital Content 1, <http://links.lww.com/CJP/A720> describes the scoping theoretical overview of potential mediators.

- **On the basis of a significant improvement in outcome from the intervention**

Outcomes which were reported significantly improved in the physiotherapy group compared to the waiting-list group after intervention in the pre-surgical phase were investigated as potential mediators. All potential mediators were in previous studies^{18,19} reported to be significantly improved, except for HADS anxiety.¹⁹ Furthermore, PEI and daily activity level were added.

- **On the basis of construct validity within an outcome measure**

A potential mediator could be selected based on construct validity of domains within a specific outcome measure. This motivated the choice of complementing the HADS measure with the anxiety domain included in the analysis.³⁷

TABLE 1.

Potential moderator

Pincus et al. has suggested the following criteria for treatment effect moderator analysis in clinical trials: 1) The moderator must be measured prior to randomization; 2) the moderating effect should be based on theory/evidence; 3) measurement should be reliable and valid; 4) the interaction between potential moderators and treatment should be specifically tested.³⁸ In a recent systematic review of LBP treatment effect moderators for clinical trials, Gurung et al. applied these criteria and patient expectations was identified as a moderating variable.³⁹ Patient treatment expectations on treatment outcome was therefor used in the present study to evaluate potential moderating effect on treatment outcome. Patient treatment expectations was measured prior to randomization through the question “What expectations do you have on upcoming treatment/training this time?”, also used in previous studies.⁴⁰⁻⁴² Four response levels were given: “Fully recovered”, “Much improved”, “Some improvement” or “I do not expect to be recovered or improved”.

Statistical Analysis

Statistical analysis was completed using IBM SPSS Statistics for Windows, version 25.0. Baseline characteristics and outcome measures at baseline are presented in means with standard deviation (SD) and frequency/proportion (%). Student’s t-test was used for comparison of characteristics and outcome measures at baseline between physiotherapy and waiting-list groups. Chi 2 was used for comparison of treatment expectations, activity level and daily activity level across groups at baseline. Ordinary least-squares regression was used for comparison of PEI and daily activity level between physiotherapy and waiting-list groups from baseline to follow-up with adjustment for age, gender and diagnosis.

To examine whether changes (baseline to follow-up) in the proposed mediators were influenced by treatment condition (a path) and whether changes in the mediator were

associated with change in the outcome measures (b path), mediation analysis was conducted. The indirect effect (ab product) for each potential mediator on the outcome variable and the total indirect effect for all potential mediators on the outcome variable were estimated. The direct effect (c') of treatment condition on change in outcome measures was also estimated. Figure 2 shows the progression of the mediation analyses, starting with establishing path coefficients. The conditional process analyses were then conducted to estimate moderated mediated effect on treatment outcomes when taking patient treatment expectations into account. These analyses apply ordinary least-squares multivariate linear regression methodology as described by Hayes.⁴³ The analyses were conducted after ensuring assumptions of regression were adequately satisfied. The PROCESS macro available for SPSS was used to conduct mediation and conditional process analyses.⁴⁴ Categorical variables (activity level and daily activity level) were handled as continuous variables due to restriction in the PROCESS macro. Scales were redirected to make a positive estimate an improvement for change in the physiotherapy group compared to the control group for all outcome measures in the mediation and moderated mediation analyses. Statistical adjustments were made for age, gender and diagnosis in both mediation analyses and conditional process analyses.

FIGURE 2.

A bias-corrected bootstrap confidence interval was conducted for the indirect effects in both mediation analyses and in the conditional process analyses. The procedure was set to repeat 5000 times and a 95% confidence interval (Boot 95% CI) was constructed. If the confidence interval is entirely above or below zero this supports the claim of a significant indirect effect. Bootstrap yields higher power and lower type 1 errors compared to the Sobel test.^{45,46}

The principle of intention to treat (ITT) was followed in line with the PREPARE study protocol.²⁰ Missing data in longitudinal PROMs were handled through multiple imputation

methods described by Lindbäck et al.¹⁹ Imputation for missing data in objective physical outcome measures were conducted as separate entities using Expectation Maximization method.⁴⁷ Missing data fulfilled the assumption of missing at random. A sensitivity analysis of the imputed data was conducted showing no significant differences between the ITT compared to per protocol.

In line with Austin & Steyerberg 2015⁴⁸, our sample of 197 exceeds the required sample size for the number of independent variables in our multivariate linear regression analyses and a significance level α 0.05.

RESULTS

Descriptive data for baseline characteristics, outcome measurements and measurements for potential mediators are presented in table 2 and table 3.

TABLE 2.

TABLE 3.

The physiotherapy group significantly improved in all outcome measures compared with the waiting-list group from baseline to follow-up after 9 weeks pre-surgical intervention^{18,19}, except for HADS anxiety subscale score.¹⁹ The physiotherapy group significantly improved in PEI ($P=0.028$) and daily activity level ($P=0.006$) compared with the waiting-list group from baseline to follow-up.

Estimations and significance levels for a and b paths for each mediator and c' can be found in Appendix 2, Supplemental Digital Content 2, <http://links.lww.com/CJP/A721>. The main results from the mediation analyses with total and specific indirect effects on the outcome measures through proposed mediators are presented in table 4.

When controlling for proposed mediators, the specific indirect effect (ab product) in differences between groups in ODI change was significantly mediated by a between group change to the advantage of the physiotherapy group in SES (1.405, Boot 95%CI 0.261 -

2.976) and the HADS subscale for depression (0.883, Boot 95%CI 0.159 - 1.823). The total indirect effect for multiple mediators represents a 2.848 decreased ODI score for the physiotherapy group compared to the control group (Boot 95%CI 0.862 - 4.950).

When controlling for proposed mediators, the specific indirect effect (*ab* product) in differences between groups in VAS back pain intensity change was significantly mediated by a between group change to the advantage of the physiotherapy group in SES (2.107, Boot 95%CI 0.301 - 4.417) and in FABQ-PA (1.140, Boot 95%CI 0.023 - 2.860) in the physiotherapy group. The total indirect effect for multiple mediators represents a 4.308 decreased VAS back pain intensity score for the physiotherapy group compared to the control group (Boot 95%CI 0.677 - 8.184).

When controlling for proposed mediators, the specific indirect effect (*ab* product) in differences between groups in EQ5D change was significantly mediated by a between group change to the advantage of the physiotherapy group in SES (0.029, Boot 95%CI 0.004 - 0.062), although there was no significant total indirect effect.

When controlling for proposed mediators, the specific indirect effect (*ab* product) in differences between groups in EQ-VAS change was significantly mediated by a between group change to the advantage of the physiotherapy group in SES (1.153, Boot 95%CI 0.038 - 2.936), FABQ-PA (1.087, Boot 95%CI 0.099 - 2.322) and activity level (1.166, Boot 95%CI 0.161 - 2.598). The total indirect effect for multiple mediators represents a 3.454 increased EQ-VAS score for the physiotherapy group compared to control (Boot 95%CI 0.697 - 6.271).

TABLE 4.

When adding patients' treatment expectations to the model, it had a significant moderating effect on all treatment outcomes through self-efficacy as a mediator, on ODI through HADS depression as a mediator, and EQ-VAS through activity level and FABQ-PA as mediators (Table 5). The indirect effect on change in VAS back pain through change in FABQ-PA was

not moderated by patients' treatment expectations. Patients' treatment expectations had a significant moderating effect for patients who expected much improvement. This means, for the patients who experienced changes in potential mediators, expectations of much improvement were linked to better outcomes. When expecting full recovery there were no significant moderating effects. Although, improvement in EQ-VAS was mediated by increase in activity level which was moderated when having expectations for much improvement or full recovery.

TABLE 5.

DISCUSSION

Based on previously published effects of a multifaceted primary care physiotherapeutic intervention for patients with degenerative lumbar spinal disorders who were candidates for surgery,^{18,19} the aim of the current study was to explore treatment mediators and patients' expectations as a moderator. The result showed that change in SES mediated the physiotherapy intervention effects on disability, back pain intensity and HRQoL. Change in FABQ-PA was shown to mediate effects on VAS back pain and EQ-VAS. Self-efficacy and fear avoidance beliefs seem to be important to target in the intervention for positive treatment effects. The findings are supported by previous study results indicating that different psychological interventions alone or in combination with exercise for CLBP resulted in treatment effects through a common set of psychological factors where self-efficacy and fear avoidance beliefs frequently occurred as mediators.^{7,8,11,12}

Self-efficacy and fear avoidance beliefs have been identified as key components in the development and refinement of the cognitive-behavioral Fear-Avoidance Model⁴⁹ which is commonly used to explain the development of pain and disability in patients with musculoskeletal pain. The study was not designed to confirm a specific model and the Fear-Avoidance Model was not tested in full, although these exploratory results add to the

evidence for self-efficacy and fear avoidance beliefs being potential mediators of treatment outcome. The present study results highlight the importance of psychosocial aspects of biopsychosocial interventions to improve disability, pain and HRQoL outcomes in patients selected for surgery. In a qualitative study of a subsample of the PREPARE cohort, patients experienced effects on most domains of the biopsychosocial model.⁵⁰ This was also seen in the analysis of the biopsychosocial related outcomes of the RCT¹⁹, but the current analysis displays that self-efficacy and fear avoidance beliefs may be the important treatment facets of the intervention. The intervention in this study is multifaceted, making it hard to extract exactly what aspects in the intervention contributes the most to enhance these factors. One can theorize that providing positive reassurance and patient experience to maintain mastery of a task through practice is the most important source of self-efficacy, because it is based on the person's own experience.⁵¹ The emphasis in the intervention is supervised training tailored to the patient, making the patient experience reassurance of their ability to be active.

In the current study we used objective physical outcome measures as potential mediators. Only one study has previously targeted physical factors as possible mediators in a multifaceted intervention to prevent LBP.¹⁴ Stevens et al hypothesized that fear avoidance beliefs, perceived muscle strength and physical exertion at work and increase in use of assistive devices at work would mediate less days with LBP and LBP intensity in workers in elderly care. The muscle strength and physical exertion at work were only measured through two self-rated questions. The hypothesis was not confirmed since the results showed no indirect effect through any of the proposed mediators. Our study results showed that an increase in activity level mediated the effect in EQ-VAS, indicating that activity level is important and relates to outcome at a general level as a person's self-rated health.

Patients' treatment expectations were found to have a positive moderating effect on all indirect effect of mediators on treatment outcomes, except for change in FABQ-PA in relation

to change in back pain intensity. Expectations of much improvement of the treatment had a significant moderating effect. However, when expecting full recovery there were no moderating effects except for the indirect effect on EQ-VAS through change in physical activity. Literature suggests that patients with positive expectations seem to be more likely to benefit from treatments across medical conditions.¹⁵ Although, unrealistic expectations on treatment outcome has also shown unfavorable results.^{52,53} Preoperative unrealistic expectations may also contribute to poor outcome after lumbar surgery.⁵⁴ All patients answered the question regarding treatment outcome expectations before randomization. Despite the possible influence of expectations of not just pre-surgery physiotherapy but also surgery, patients could still experience improvement of non-surgical treatment. Getting a structured multifaceted physiotherapeutic treatment earlier in the course of the disease might be more beneficial, especially before surgery is considered as an option. This can strengthen the possibility to influence patients understanding of their back pain and the prognosis⁵⁰ and thereby their expectations. It might be relevant to address the appropriateness of a patient's treatment expectations and if needed guide towards realistic expectations.

A multi-mediator model was used to explore treatment mediators in the multifaceted intervention. This is recommended when analyzing mediators⁵⁵, since it is most likely that several mediators exist and could lead to treatment effect.^{8,55} A single-mediator model is often too simplistic and unlikely to be the case in reality, therefore its' usefulness is limited.⁸ The construction of a change variable from baseline to follow-up is theoretically representative of the change in these variables during the whole 9 week treatment exposure process. However, change in mediators and outcome variables are measured over the same period of time, not providing the strict temporal precedence of the mediating variables.⁵⁵⁻⁵⁷ Therefore, it is appropriate to tentatively temper conclusions that change in self-efficacy and fear avoidance beliefs mediate change in the outcome. The ambiguity regarding the strict temporal

precedence of when mediators influence outcomes would be possible to study if repeated measures were available for the pre-surgery physiotherapy exposure phase. Furthermore, the current analyses cannot determine if there are early or late phase changes in self-efficacy and fear avoidance beliefs during the 9 weeks pre-surgery physiotherapy that mediate change in pain intensity, disability and HRQoL. Despite this tentative tempered conclusion, these findings remain important as a step towards understanding treatment mechanisms.

In conclusion, when considering a broad series of potential treatment targets (ie mediators), self-efficacy and fear avoidance beliefs seem to be important for outcomes in a multifaceted treatment for patients with degenerative lumbar spine disorders who are candidates for surgery. Improvement in physical activity level seems to be important for treatment effect on self-rated health. Patients' treatment expectations moderate the treatment effects and should be taken into consideration in pre-surgical interventions. The results contribute to a better understanding for what factors the physiotherapist need to target and change to achieve positive treatment effects. This is a step towards a better understanding of effect mechanism in physiotherapy interventions and development of more tailored and focused interventions.

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FIGURE 1. Consolidated Standards of Reporting Trials (CONSORT) flowchart of the randomized controlled trial.

FIGURE 2. Mediator model examining the treatment effects on disability (ODI), back pain intensity (VAS back pain) and health related quality of life (EQ-5D and EQ-VAS) via potential mediators. *a* paths, *b* paths and *c*´ are presented. HADS, Hospital Anxiety and Depression Scale; SES, Self-efficacy scale; PEI, Patient Enablement Instrument; FABQ-PA, Fear Avoidance Beliefs Questionnaire-Physical Activity.

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Table 1. Potential mediators for treatment effects selected on the basis of different criteria

	Potential mediators selected on the theoretical basis of expected treatment effect	Potential mediators selected on the basis of a received significant improvement in outcome from the intervention	Potential mediators selected on the basis of construct validity within an outcome measure
HADS anxiety	x		x
HADS depression	x	x	x
SES	x	x	
FABQ-PA	x	x	
PEI	x	x	
Gait speed	x	x	
Quadriceps strength	x	x	
Activity level	x	x	
Daily activity level	x	x	

HADS, Hospital Anxiety and Depression Scale; SES, Self-Efficacy Scale; PEI, Patient Enablement Instrument; FABQ-PA, Fear Avoidance Beliefs Questionnaire-Physical Activity.

TABLE 2. Descriptive statistics of baseline characteristics for patients with degenerative lumbar spine disorders. Comparison between patients allocated to physiotherapy and waiting-list groups.

	Physiotherapy (n=99)	Waiting-list (n=98)	<i>P</i>
Age, mean (SD)	57 (13.3)	61 (11.5)	0.082
Gender, women, n (%)	54 (54)	51 (52)	0.726
Diagnosis, n (%)			0.286
Spinal stenosis	59 (60)	70 (71)	
Disk herniation	23 (23)	17 (17)	
Spondylolisthesis	8 (8)	7 (7)	
Degenerative disc disease	9 (9)	4 (4)	
Pain duration back or leg pain>1y, n (%)	57 (64)	62(67)	0.635

SD, standard deviation.

TABLE 3. Descriptive statistics of outcome measures at baseline for patients allocated to physiotherapy and waiting-list groups.

Measure	Score range	Physiotherapy (n=99)	Waiting-list (n=98)	
		Mean (SD)	Mean (SD)	<i>P</i>
ODI	0-100	37.9 (12.8)	40.5 (12.6)	0.155
VAS back pain	0-100	56.0 (24.4)	59.7 (21.6)	0.264
EQ-5D	-0.594-1	0.4 (0.3)	0.4 (0.3)	0.720
EQ-VAS	0-100	50.7 (18.3)	47.7 (20.5)	0.280
HADS anxiety	0-21	5.4 (4.0)	5.6 (3.8)	0.668
HADS depression	0-21	4.4 (3.5)	4.4 (3.0)	0.955
SES	0-200	134.4 (38.3)	127.1 (30.7)	0.142
FABQ-PA	0-24	16.0 (5.8)	16.0 (5.3)	0.993
Gait speed		1.5 (0.4)	1.5 (0.3)	0.863
Strength		22.1 (6.5)	21.9 (7.385)	0.803
Activity level last 12 mo, n (%)	1 Inactive 2 Mildly active 3 Walking 4 Moderately active 5 Very active	9 (9) 16 (16) 49 (50) 23 (23) 2 (2)	19 (19) 21 (22) 40 (41) 15 (15) 3 (3)	0.134
Daily activity level last 12 mo, n (%)	1 Inactive 2 Sometime/week 3 Several times/week 4 Daily	7 (7) 24 (24) 40 (41) 28 (28)	8 (8) 27 (27) 29 (30) 34 (35)	0.462
Treatment expectations, n (%)	1 Fully recovered 2 Much improvement 3 Some improvement 4 No improvement	32 (32) 55 (56) 12 (12) 0 (0)	38 (39) 56 (57) 4 (4) 0 (0)	0.104

SD, standard deviation; ODI, Oswestry Disability Index (higher score indicates higher disability); VAS, Visual Analog Scale (higher score indicates higher pain intensity); EQ-5D, EuroQol 5 dimensions (higher score indicates better health); EQ-VAS, EuroQol-Visual Analog Scale (higher score indicates better health); HADS, Hospital Anxiety and Depression Scale (higher score indicates more signs of symptoms); SES, Self-Efficacy Scale (higher score indicates better self-efficacy); FABQ-PA, Fear Avoidance Beliefs Questionnaire-Physical Activity (higher score indicates more signs of fear avoidance beliefs).

TABLE 4. Specific and total indirect effects of independent variables on depending variables trough proposed mediators (n = 197). A positive estimate indicates an improvement in the dependent variable.

Independent variable	Dependent variable	Covariates	Mediators	Estimate	Boot 95% CI		R^2
					Lower	Upper	
Randomization	ODI	Gender Age Diagnosis	HADS anx	0.004	-0.645	0.558	0.320**
			HADS dep	0.883*	0.159	1.823	
			SES	1.405*	0.261	2.976	
			FABQ-PA	0.170	-0.378	0.753	
			PEI	0.507	-0.013	1.378	
			Gait speed	0.272	-0.163	0.753	
			Strength	-0.337	-1.080	0.225	
			Activity level	0.032	-0.489	0.572	
			Daily activity	-0.087	-0.734	0.369	
			Total=2.848*		0.862	4.950	
Randomization	VAS back pain	Gender Age Diagnosis	HADS anx	-0.003	-0.837	0.821	0.240**
			HADS dep	-0.829	-2.830	0.272	
			SES	2.107*	0.301	4.417	
			FABQ-PA	1.140*	0.023	2.860	
			PEI	1.170	-0.122	2.952	
			Gait speed	1.432	-0.039	3.856	
			Strength	-1.243	-2.943	0.001	
			Activity level	0.213	-1.011	1.644	
			Daily activity	0.462	-0.787	2.110	
			Total=4.308*		0.677	8.184	
Randomization	EQ-5D	Gender Age Diagnosis	HADS anx	0.000	-0.009	0.010	0.170**
			HADS dep	0.008	-0.010	0.028	
			SES	0.029*	0.004	0.062	
			FABQ-PA	0.007	-0.007	0.025	
			PEI	-0.003	-0.020	0.016	
			Gait speed	0.015	-0.001	0.037	
			Strength	-0.011	-0.032	0.006	
			Activity level	-0.001	-0.017	0.017	
			Daily activity	-0.010	-0.029	0.005	
			Total=0.036		-0.008	0.084	
Randomization	EQ-VAS	Gender Age Diagnosis	HADS anx	-0.001	-0.556	0.537	0.230**
			HADS dep	-0.485	-1.800	0.717	
			SES	1.153*	0.038	2.936	
			FABQ-PA	1.087*	0.099	2.322	
			PEI	0.690	-0.082	2.038	
			Gait speed	0.579	-0.301	1.542	
			Strength	-0.066	-1.135	0.942	
			Activity level	1.166*	0.161	2.598	
			Daily activity	-0.668	-1.891	0.085	
			Total=3.454*		0.697	6.271	

Boot 95% CI, 95% bootstrap confidence interval; ODI, Oswestry Disability Index; VAS, Visual Analog Scale; EQ-5D, EuroQol 5 dimensions; EQ-VAS, EuroQol-Visual Analog Scale; HADS anx, Hospital Anxiety and Depression Scale subscale for anxiety; HADS dep, Hospital Anxiety and Depression Scale subscale for depression; SES, Self-Efficacy Scale; FABQ-PA, Fear Avoidance Beliefs Questionnaire-Physical Activity; PEI, Patient Enablement Instrument.

$p < 0.05$, R^2 , coefficient of determination.

* Boot 95% CI \neq 0

** $p < 0.001$

TABLE 5. Specific indirect effects of independent variables on dependent variables through mediators moderated by treatment expectations (n=197). A positive estimate indicates an improvement in the outcome measure/dependent variable.

Independent variable	Dependent variable	Covariates	Mediator	Estimate (SE)	Treatment expectations **	Boot 95% CI	
					-1 SD Mean +1 SD	Lower	Upper
Randomization	ODI	Gender Age Diagnosis	HADS depression	0.883 (0.6)	1.123	-0.034	2.215
				0.930 (0.5)*	1.726	0.152	1.943
				0.972 (0.6)	2.329	-0.002	2.314
			SES	0.648 (0.9)	1.123	-1.111	2.389
				1.414 (0.7)*	1.726	0.248	2.904
				2.180 (1.1)*	2.329	0.383	4.586
Randomization	VAS back pain	Gender Age Diagnosis	SES	0.992 (1.4)	1.123	-1.651	3.673
				2.164 (1.1)*	1.726	0.346	4.448
				3.336 (3.3)*	2.329	0.514	6.808
Randomization	EQ-5D	Gender Age Diagnosis	SES	0.014 (0.02)	1.123	-0.024	0.053
				0.030 (0.02)*	1.726	0.004	0.066
				0.050 (0.02)*	2.329	0.007	0.102
Randomization	EQ-VAS	Gender Age Diagnosis	SES	0.530 (0.8)	1.123	-1.016	2.364
				1.156 (0.8)*	1.726	0.046	2.970
				1.783 (1.2)*	2.329	0.105	4.793
			Activity	1.486 (0.9)*	1.123	0.060	3.657
				1.120 (0.6)*	1.726	0.109	2.535
				0.732 (0.6)	2.329	-0.429	2.092
			FABQ-PA	1.257 (0.8)	1.123	-0.160	3.101
				1.083 (0.6)*	1.726	0.074	2.347
				0.910 (0.7)	2.329	-0.440	2.422

SE, standard error; Boot 95% CI, 95% bootstrap confidence interval; ODI, Oswestry Disability Index; VAS, Visual Analog Scale; EQ-5D, EuroQol 5 dimensions; EQ-VAS, EuroQol-Visual Analog Scale; HADS depression, Hospital Anxiety and Depression Scale subscale for depression; SES, Self-Efficacy Scale; FABQ-PA, Fear Avoidance Beliefs Questionnaire-Physical Activity.

* Boot 95% CI \neq 0

** Patient treatment expectations score range from 1-4 where 1 is highest expectations "Fully recovered".

Appendix 1.

The scoping theoretical overview of expected treatment effect on potential mediators (*a* path) and relationship between potential mediators and disability, pain and/or health related quality

	<i>a</i> path Theoretical basis supporting how intervention mode in PREPARE targets the potential mediator	<i>b</i> path Theoretical basis supporting relationship between potential mediator and disability, pain and/or HRQoL
HADS anxiety	Exercise: Stonerock ¹	Pain: Melzack ²
HADS depression	Exercise: Kvarm ³ , Knapen ⁴ , Cooney ⁵	Pain: Melzack ² HRQoL: Schuch ⁶ , Rodríguez ⁷
SES	Exercise, information: Bandura ⁸ , Kernan ⁹ Goalsetting: Bandura ⁸ Graded physical activity/exercise: Tryon ¹⁰ , Petruzzello ¹¹	Disability: Woby ¹² Pain: Woby ¹²
FABQ-PA	Graded physical activity: Tryon ¹⁰ , Petruzzello ¹¹ Exercise: Klaber ¹³ Safty-cues/ Knowledge about pain in relation to condition: Smith ¹⁴	Disability: Vlaeyen ¹⁵ , Wertli ¹⁶ Pain: Vlaeyen ¹⁵ , Goodin ¹⁷ , Wertli ¹⁶
PEI	Goalsetting: Mansell ¹⁸ , Du ¹⁹ Knowledge about the condition and pain: Mansell ¹⁸ , Du ¹⁹	Disability: Enthoven ²⁰ HRQoL: Enthoven ²⁰ , Ožvačić Adžić ²¹
Gait speed	Exercise: Hortobagyi ²² , Liu ²³	Disability: den Ouden ²⁴ HRQoL: Middleton ²⁵ , Ekström ²⁶
Quadriceps strength	Exercise: Garber ²⁷	Disability: den Ouden ²⁴ , Martien ²⁸ , Beaudart ²⁹
Activity level	Graded physical activity: Marley ³⁰ Goalsetting: McEwan ³¹ , Marely ³⁰ Self-monitoring of the behavior: Marely ³⁰	Disability: Den Ouden ²⁴ , Geneen ³² Pain: Hoge ³³ , Geneen ³² , Smith ¹⁴ , Koltyn ³⁴ HRQoL: Geneen ³²
Daily activity level	Graded physical activity: Marley ³⁰ Goalsetting: McEwan ³¹ , Marley ³⁰ Self-monitoring of the behavior: Marely ³⁰	Disability: Geneen ³² , Lin ³⁵ Pain: Geneen ³² HRQoL: Geneen ³²

of life (HRQoL) (*b* path). HADS, Hospital Anxiety and Depression Scale; SES, Self-Efficacy Scale; PEI, Patient Enablement Instrument; FABQ-PA, Fear Avoidance Beliefs Questionnaire-Physical Activity.

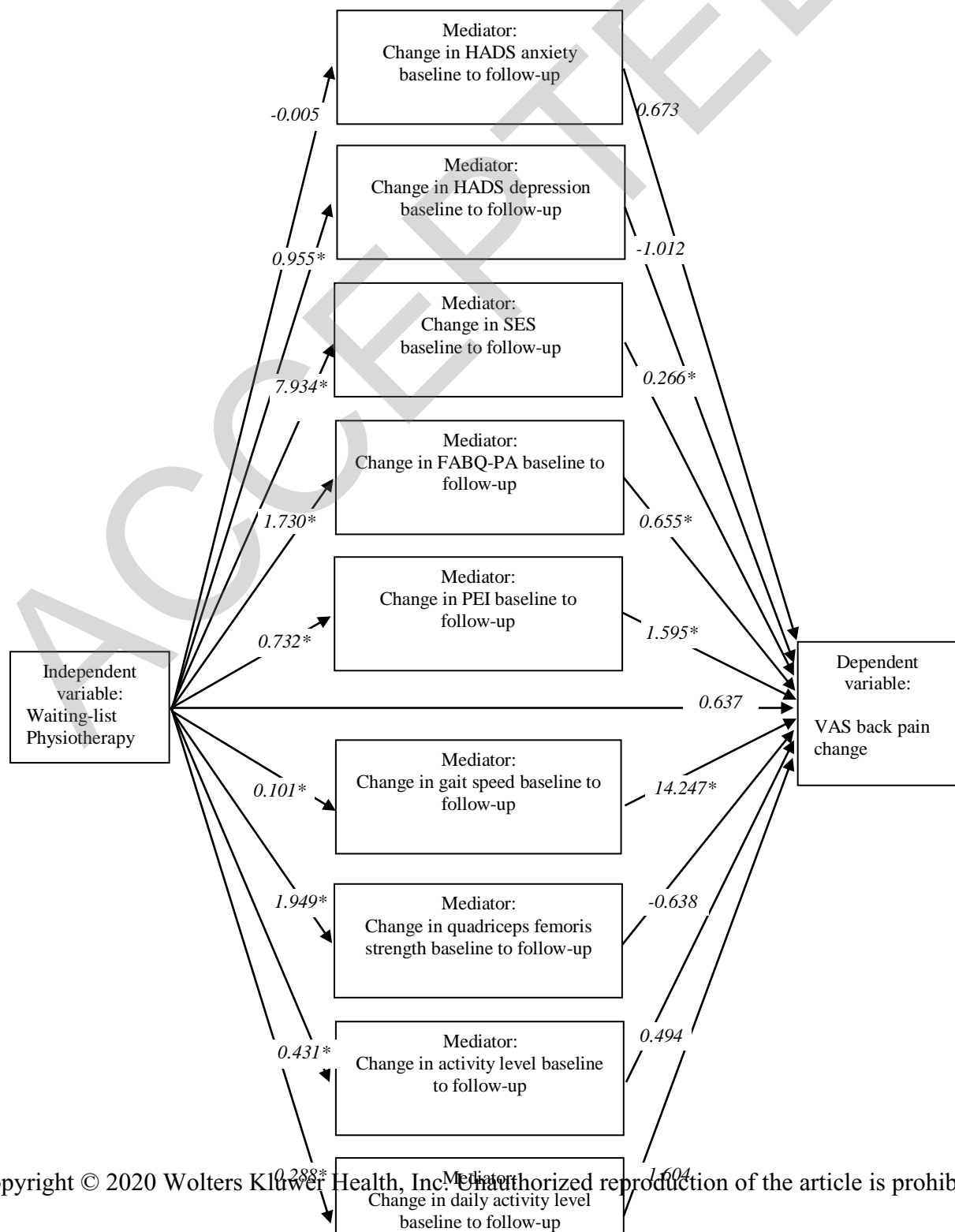
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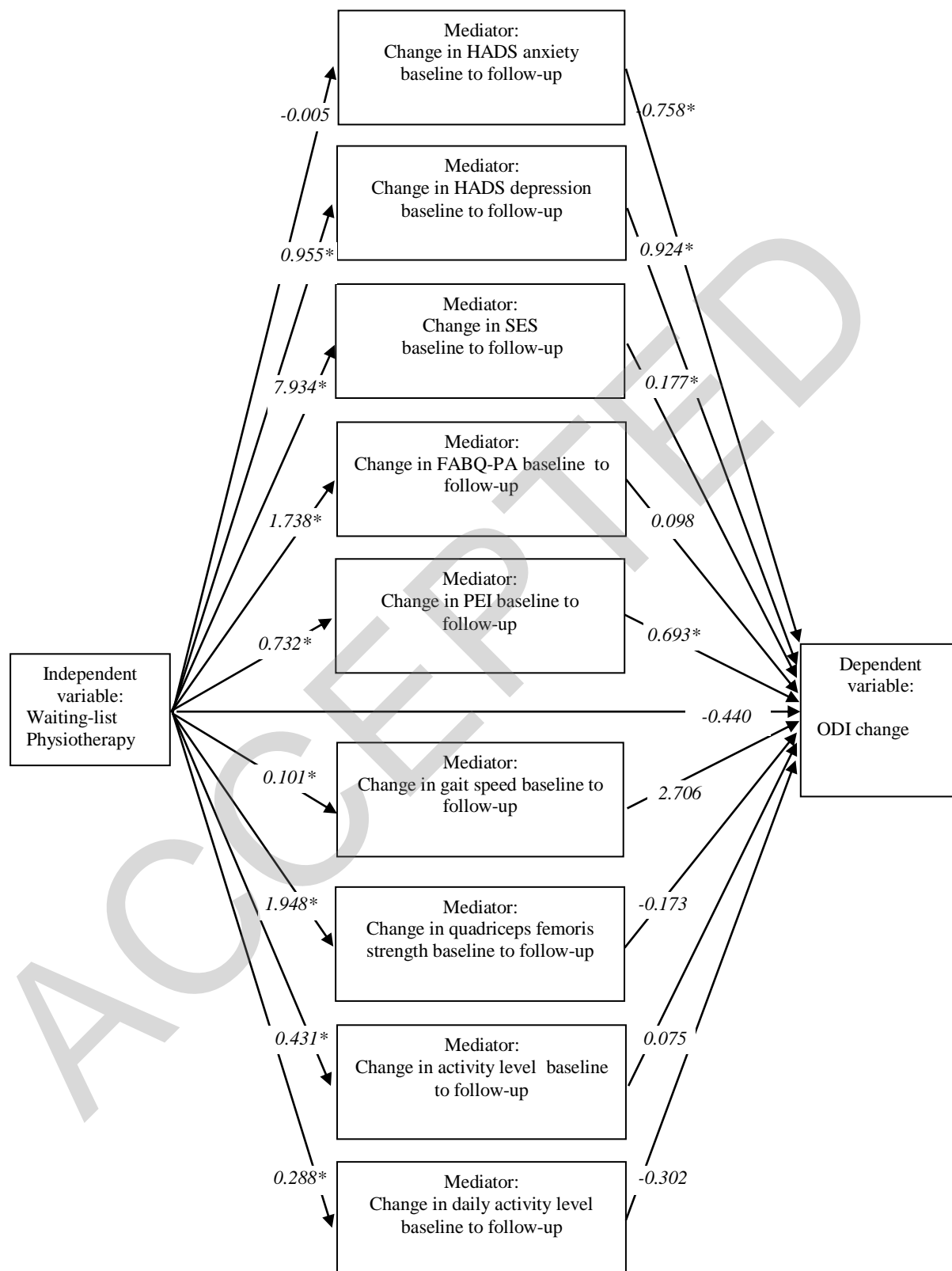
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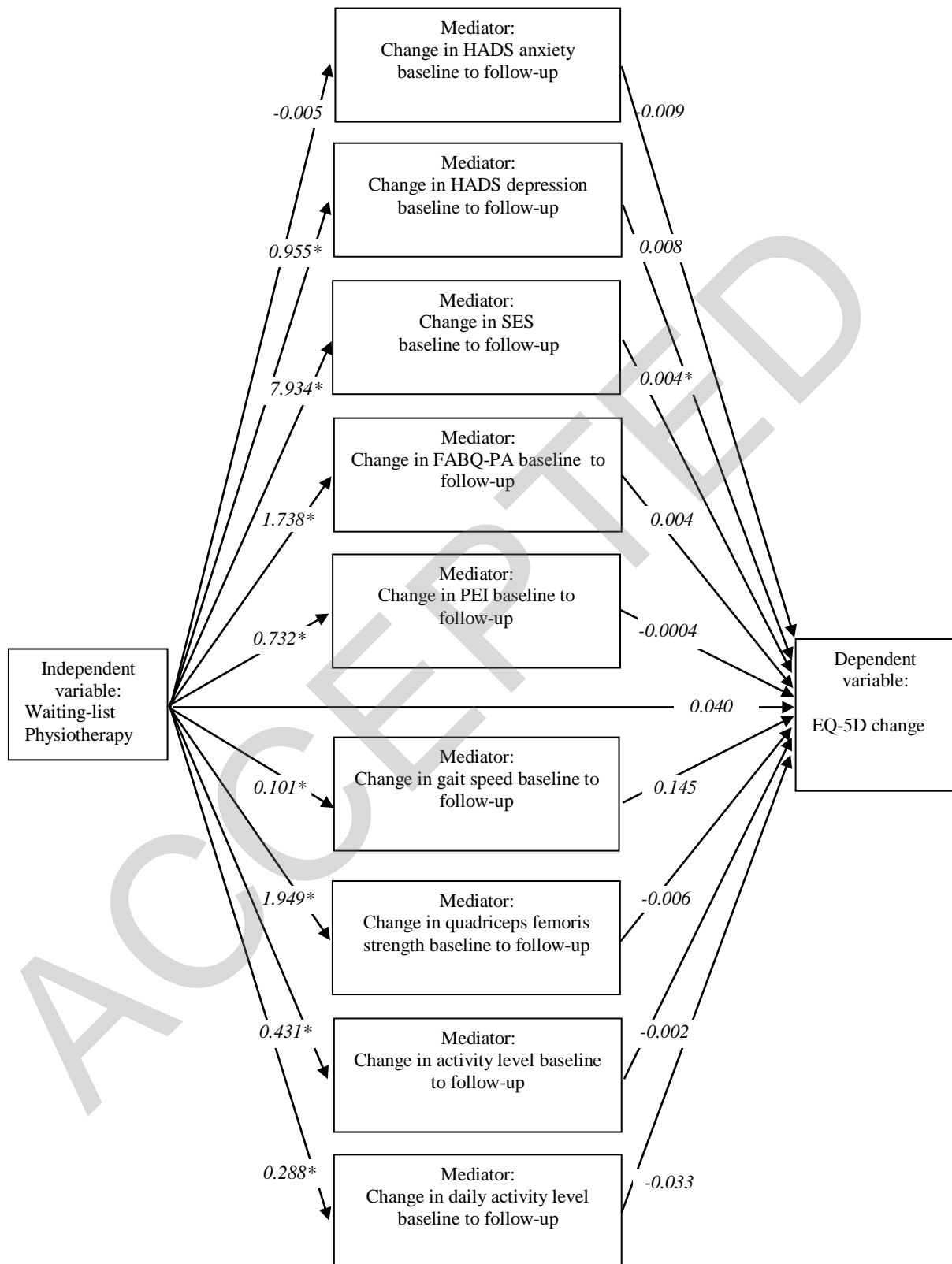
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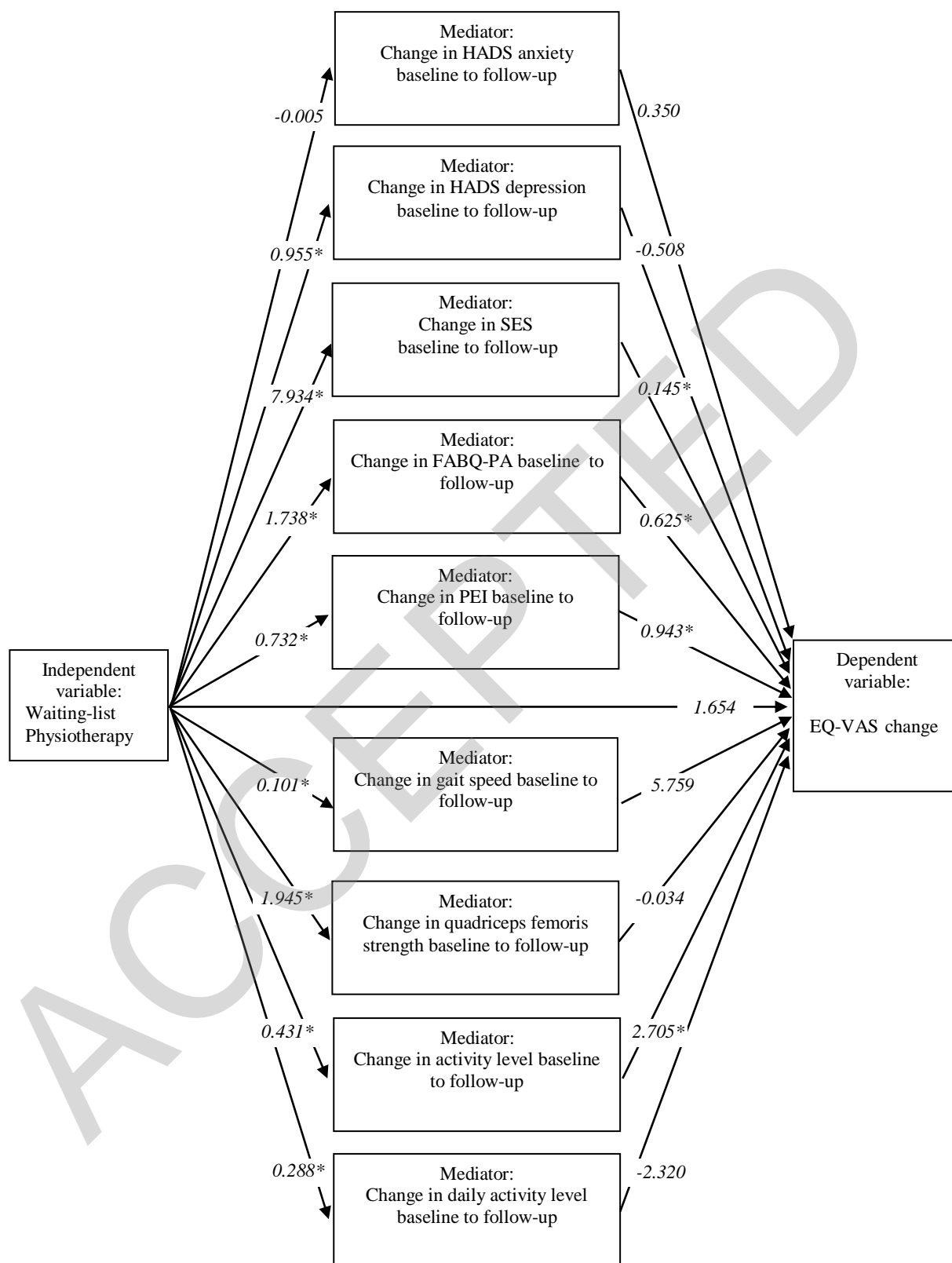
Appendix 2.

Mediator models examining the treatment effects on disability (ODI), back pain intensity (VAS back pain) and health related quality of life (EQ-5D and EQ-VAS) via potential mediators. Estimates for *a* paths, *b* paths and *c'* are presented. HADS, Hospital Anxiety and Depression Scale; SES, Self-Efficacy Scale; PEI, Patient Enablement Instrument; FABQ-PA, Fear Avoidance Questionnaire- Physical Activity; * $p < 0.05$.









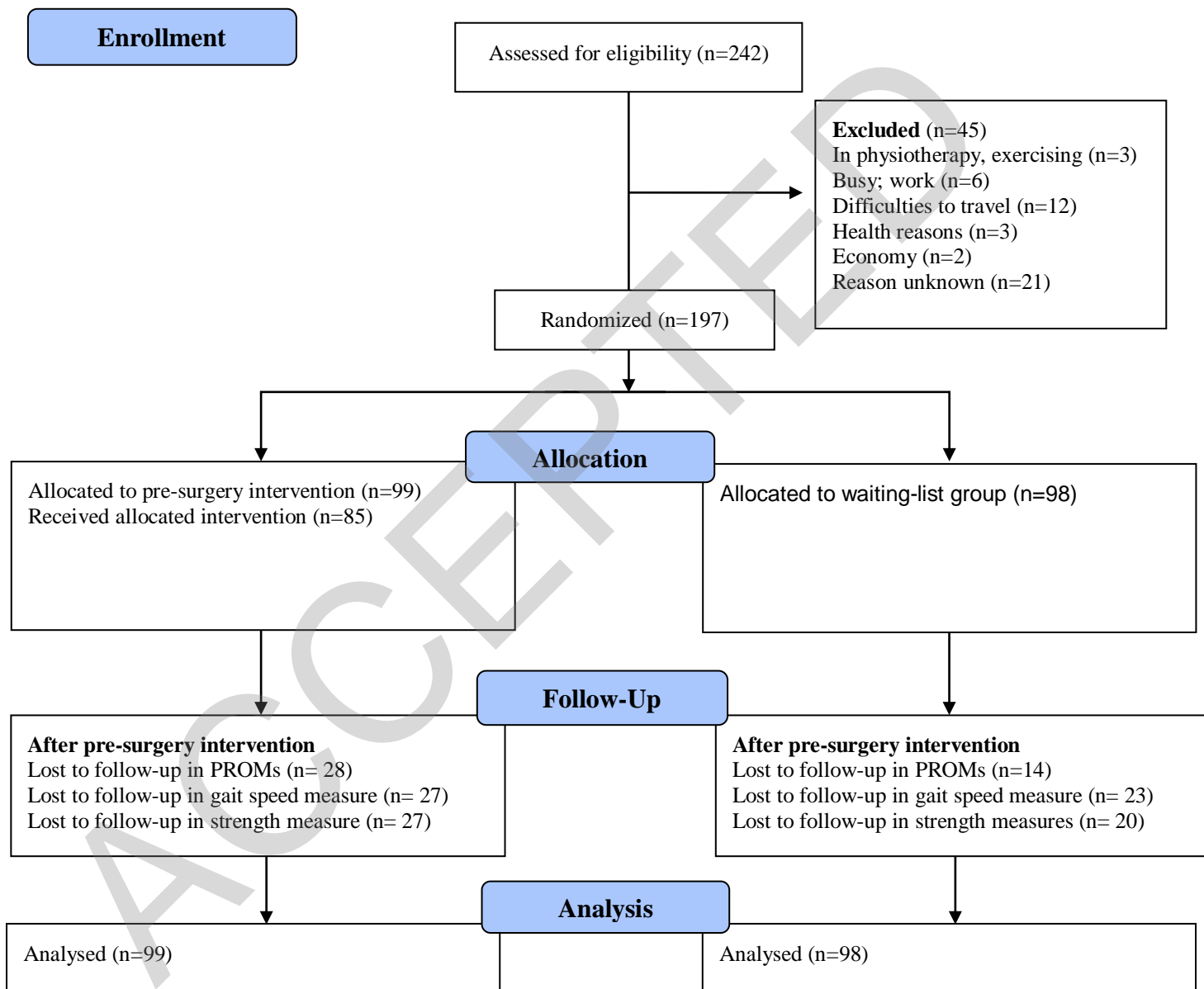


FIGURE 1. Consolidated Standards of Reporting Trials (CONSORT) flowchart of the randomized controlled trial.

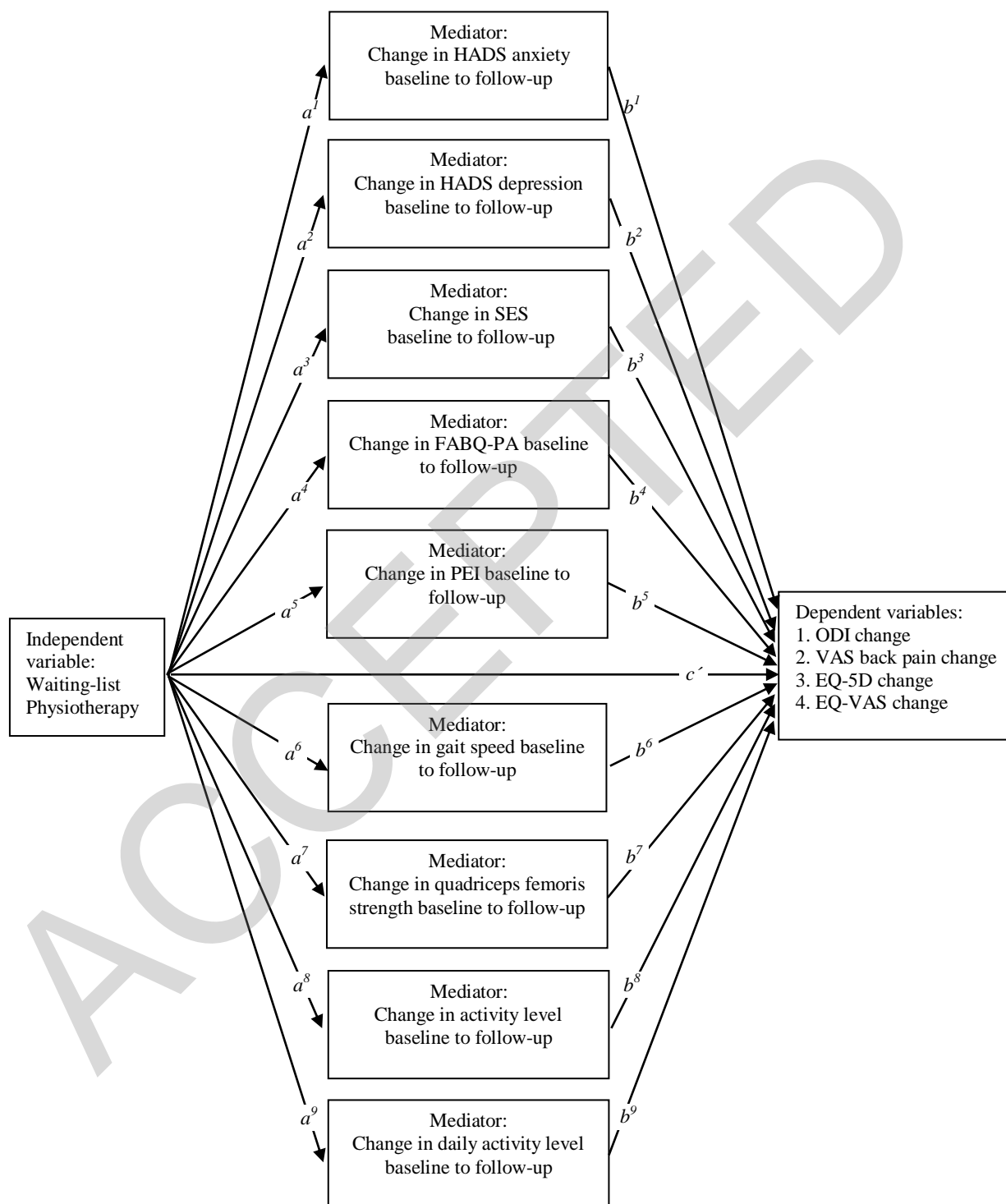


FIGURE 2. Mediator model examining the treatment effects on disability (ODI), back pain intensity (VAS back pain) and health related quality of life (EQ-5D and EQ-VAS) via potential mediators. a paths, b paths and c' are

presented. HADS, Hospital Anxiety and Depression Scale; SES, Self-efficacy scale; PEI, Patient Enablement Instrument; FABQ-PA, Fear Avoidance Beliefs Questionnaire-Physical Activity.

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