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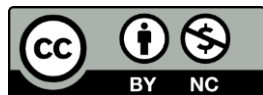
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Moderators of the Effect of Spinal Manipulative Therapy on Pain Relief and Function in Patients with Chronic Low Back Pain: An Individual Participant Data Meta-Analysis

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Mini- Abstract

This individual participant data meta-analysis assessed the effect of spinal manipulative therapy for chronic low back pain. Based on this review, there is no evidence to suggest that specific patients characteristics are associated with a clinically better response to SMT as compared with other recommended treatments for chronic LBP.

Abstract

Study design: Individual participant data (IPD) meta-analysis

Objective. To identify which participant characteristics moderate the effect of spinal manipulative therapy (SMT) on pain and functioning in chronic LBP.

Summary of Background. The effects of SMT are comparable to other interventions recommended in guidelines for chronic low back pain (LBP); however, it is unclear which patients are more likely to benefit from SMT compared to other therapies.

Methods. IPD were requested from randomized controlled trials (RCTs) examining the effect of SMT in adults with chronic LBP for pain and function compared to various other therapies (stratified by comparison). Potential patient moderators (n=23) were a-priori based on their clinical-relevance. We investigated each moderator using a one-stage approach with IPD and investigated this interaction with the intervention for each time point (1, 3, 6 and 12 months).

Results. We received IPD from 21/46 RCTs (n= 4223)). The majority (12 RCTs, n=2249) compared SMT to recommended interventions. The duration of LBP, baseline pain (confirmatory), smoking and previous exposure to SMT (exploratory) had a small moderating effect across outcomes and follow-up points; these estimates did not represent minimally relevant differences in effects; for example, patients with less than one year of LBP demonstrated more positive point estimates for SMT vs recommended therapy for the outcome pain, (mean differences ranged from 4.97 (95% CI: -3.20 to 13.13) at three months, 10.76 (1.06 to 20.47) at six months to 5.26 (-2.92 to 13.44) at twelve months in patients with over a year LBP. No other moderators demonstrated a consistent pattern across time and outcomes. Few moderator analyses were conducted for the other comparisons because of too few data.

Conclusion. We did not identify any moderators that enable clinicians to identify which patients are likely to benefit more from SMT compared to other treatments.

Key words: Individual participant data, meta-analysis, spinal manipulative therapy, manipulation, low back pain, chronic pain, moderators, randomized clinical trial, subgroup analysis, mobilization

Level of Evidence: 2

INTRODUCTION

Low back pain (LBP) is the world's leading cause of disability.¹ Non-pharmacological approaches are the first choice of treatment.² The treatment options include spinal manipulation and mobilization which are used by a variety of health care providers such as osteopaths, chiropractors and physiotherapists. These approaches can be used together or alone to treat patients with chronic LBP, and collectively defined as spinal manipulative therapy (SMT).

Many systematic reviews and meta-analyses have found that SMT is an effective treatment for patients with chronic LBP with a modest mean effect compared to other interventions.³⁻⁸ Whilst SMT can relieve LBP in some patients, it is not effective for everyone; the number needed to treat is in the range of five to ten.⁹ One potential explanation is that patients with 'non-specific' chronic LBP have different characteristics that influence the intervention effect, while another explanation can be the variation in duration, number and type of SMT. Relevant subgroups of patients with chronic LBP may exist that might benefit more or less from SMT.¹⁰ The first step in identifying these subgroups is to examine which participant or treatment characteristics moderate the treatment effect (e.g. age, duration of LBP).¹⁰⁻¹² These moderators are typically not presented in the traditional meta-analyses¹³ because aggregate data on relevant patient characteristics are often not available, are poorly reported, or derived and presented differently across studies. More importantly, if the results of subgroup analyses are reported, group averages or proportions are presented, which can result in ecological bias. The result is patient level intervention-covariate interactions are usually not examined or reported, even though they have the potential to better target the intervention.¹⁴ Whilst some authors have presented appropriate analyses of treatment moderation, few trials are large enough to exclude important moderator effects.¹⁰

One way to test interactions of these characteristics with the intervention is to use Individual Participant Data (IPD). IPD provides much increased statistical power and allows for standardized analyses across studies, using direct derivation of information desired on an individual level, independent of whether and how it was reported in original publications. Therefore, IPD potentially allows identification of clinical characteristics of patients with chronic LBP that may moderate treatment effects.

The specific objective of this IPD meta-analysis is to:

- Identify individual participant characteristics measured at baseline that moderate the effect of SMT for pain and function at one, three, six and twelve months in adults with chronic LBP versus 1) recommended interventions; 2) non-recommended interventions; 3) sham SMT; 4) SMT + other intervention versus SMT only and 5) mobilization versus manipulation.

METHODS

This study was conducted and reported according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses for IPD (PRISMA-IPD) guidelines¹⁵ (appendix eTable1, <http://links.lww.com/BRS/B675>). The protocol was registered with PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=25714) and approved by the Scientific Review Board of the Vrije Universiteit Amsterdam and by the Ethical Committee of the VU University Medical Centre Amsterdam. (Projectnr. 2015.544).

A detailed protocol has been published previously.¹⁶ The methodology presented in the current paper gives an overview of the moderator selection and analysis, while the eligibility criteria, search methods for identification of new trials (appendix eTable 11, <http://links.lww.com/BRS/B675>), risk of bias assessment, funnelplots (appendix eFig 1 and 2, <http://links.lww.com/BRS/B675>) collection and extraction of IPD are fully described in the published protocol.¹⁶

Types of outcome measures

Primary outcomes were pain (reported on a 0-10 or 0-100 NRS or VAS scale) and back-specific function on any scale e.g. Roland Morris Disability Questionnaire, Oswestry disability Index. All outcomes were self-reported and converted following decision rules (appendix eTable 4, <http://links.lww.com/BRS/B675>).

Moderators of treatment effect

Candidate moderators of treatment response were identified by the research team *a-priori* based on consensus (appendix eTable 5, <http://links.lww.com/BRS/B675>). In short, the selection of patient moderators was based on a specific rationale (e.g. understanding behavioral and sociocultural mechanisms by which response is modified or from prognostic research (treatment effect modification studies or prognostic factor research))¹⁰⁻¹² (see protocol¹⁶). Of 23 potential moderators identified; six were not analyzed, because data were insufficient, unavailable or only available at study level (patient preference/expectancy, comorbidities, alcohol use, income, non-specific LBP and for all treatment characteristics). The number and frequency of SMT treatments were measured at study level and not at patient level in the vast majority of the trials. The same accounts for type of SMT technique used. Therefore, contrary to the description in our protocol, we could not analyze moderating effects by these types of variables.

For psychological factors, analyses were only performed for combined depression scales. For other psychological scales, there were insufficient data.

Moderator analyses were classified into confirmatory or exploratory. Moderators in confirmatory analyses are those related to specific theory or evidence, while moderators in exploratory analyses relate to moderators for which no empirical evidence exists or for which a specific theory or mechanism is lacking. Our potential confirmatory moderators were age, gender, duration of LBP, psychological factors, treatment preference/expectation and baseline pain, function and quality of life. Other moderator analyses were exploratory (appendix eTable 5, <http://links.lww.com/BRS/B675>).¹⁷ In both cases, the analytical technique was the

same, but for the interpretation of those confirmatory moderators the evidence was considered to be stronger.

Preparing data for moderator analyses

If data on a variable of interest were not available, we attempted to extract this information based on other data in the trial (e.g. information about employment was missing, but there was a variable on sick leave). Whenever possible, we used continuous data as presented, unless dichotomizing facilitated the translation of findings to clinical practice or was needed to meaningfully combine data across trials. The cut-off points were determined by consensus of the steering committee (ADZ, MRdB, SMR, MWT and RO)(Appendix eTable 5, <http://links.lww.com/BRS/B675>). For age, we used 65 years as a cut-off point. Additionally, duration of LBP was dichotomized into less than one year versus greater than one year. Similarly, physical activity was categorized into low (1 or less exercise sessions per week), medium (2-3 exercise sessions per week) and high (>3 exercise sessions per week) and subsequently dichotomized into low-medium or high. The choice of cut-off for physical activity was further evaluated in a sensitivity analysis (low vs medium-high).

For the outcome pain, all pain scores were converted to a 0-100 points scale following a decision rule (appendix eTable 4, <http://links.lww.com/BRS/B675>). To allow pooling of different functional status measures, we recoded the individual scores into Z-scores. for each separate time point using pooled standard deviations as nominator. ($Z\ score = \frac{x_i - \bar{x}}{SD}$).

Analyzing these Z-scores resulted in standardized mean differences (SMD's). To ease interpretation of SMD's, we converted these to a mean difference (MD) for the 24 point Roland Morris Disability Questionnaire, by multiplying the SMD with the population standard deviation (SD) of the studies measuring Roland Morris Disability Questionnaire

($SD_{pooled} = \sqrt{\sum_{i=0}^n \frac{(n_i-1)*S^2}{(n_i-1)}}$ n_i = sample size for each trial; S = standard deviation for each trial).

Data analysis

We studied moderators of intervention effects when three or more trials within a comparison had data on the moderator and the outcome at a specific time point. We used the following comparisons: 1) SMT versus recommended interventions including non-pharmacological treatment (e.g. exercise) and pharmacological treatment (e.g. NSAIDs, analgesics); 2) SMT versus non-recommended interventions (e.g. light massage, diathermy, ultrasound; 3) sham 'placebo' SMT; 4) SMT + intervention versus intervention alone; 5) high-velocity low-amplitude SMT versus low-velocity low-amplitude SMT (i.e. manipulation vs. mobilization).¹⁶

Potential moderators were analyzed using a one-stage random effect IPD meta-analyses. The baseline outcome, treatment, potential moderator and interaction between treatment and moderator were included as fixed effects. Study specific intercepts were also included as fixed effects. Random treatment and interaction effects were added to the model. (see protocol¹⁶ and equation 2 in appendix eTable 6, <http://links.lww.com/BRS/B675>).¹⁸ We performed these analyses for each time point and each moderator separately to facilitate

convergence of models. Centering the patient-level covariates about their study-specific means enabled us to separate the within- and across-study interactions.¹⁹ The within-study interaction explained the patient-level variation in treatment response, while the across-study interaction represented the moderator effect on study level. We present the within-study interactions. A negative interaction coefficient indicates a more positive or less negative estimate of the intervention effect of SMT vs comparison for the index group compared to a / the reference group (e.g. females compared to males).

We refrained from presenting stratified results for subgroups of moderator variables, because these include a combination of within- and across-study information because of differences in proportions of persons within the separate subgroups between studies.

Synthesis of evidence

Assessment of clinical relevance for the main effects analyses was defined as a small, medium or large difference and based upon the recommendations of the Cochrane Back and Neck group.²⁰

In a consensus meeting with the project group, we discussed our results to determine whether a moderating effect was present. We considered a moderator effect to be present if the magnitude of the effect was at least half of our pre-specified clinically relevant main effects; i.e., more than 5-points (on a 100-point pain scale) or more than 0.25 for SMD on function and there was consistency in the direction of the moderators across three consecutive follow-up intervals for both pain and function. The arbitrary cut-offs of 5-points or 0.25 SMD were used to detect small differences within a moderator as SMT is a low intensity, low cost intervention.

As a crude method to guide interpretation and further synthesize evidence, we combined interaction effects with the main treatment effects, in case a moderator fulfilled the criteria for described above. Based on this, we assessed whether we could identify a clinically relevant treatment effect for potentially relevant moderators (e.g. interaction-effects around main effects near zero usually do not imply clinically meaningful effects within subgroups, while interaction effect reaching ten points on a 100 point scale does). We assumed that subgroup effects based on these interaction effects lie symmetrically around the main effects. For example, consider a moderator effect of 'gender' of -6 points on a 0-100scale, and a main effect of SMT of -8 points.

This would result in an approximated estimate of main treatment effect for men of -5 points (-8+3) and for women of 11 points (-8-3). These subgroup effects might indicate minimally relevant treatment effect for women, but not for men.

RESULTS

Characteristics of trials are presented in (Table 1), Risk of bias criteria and assessment are presented in the appendix eTable 2 and 3, <http://links.lww.com/BRS/B675>. For more details, see appendices and protocol.¹⁶

Identification of trials

In total, forty-three RCTs met the inclusion criteria, of which 21 (50%) provided data²¹⁻⁴¹ (fig.1) from 4223 participants. Baseline characteristics were compared to the published results of the individual trials. In two trials, the results differed from the published results: one trial provided only data from participants who gave consent to share their data³⁷ while for the second trial, all relevant baseline moderator data of the participants were lost.³⁵

Characteristics of study participants

Participant characteristics were fairly similar across all comparisons (Table 2 and appendix eTable 7, <http://links.lww.com/BRS/B675>). All trials except one³⁵ provided data on sex and age. The average age of the participants was 46.1 (SD 13.78) years, 54.4% were women.

For employment and BMI, moderator data were missing in 9.6% and 5.9 % of the participants respectively, while for all other moderators, data were missing in less than 2% of the participants.

Moderators of SMT for primary outcomes: pain and function

SMT vs recommended interventions

For most moderators, no moderating effects were identified except for the moderators described below. (Table 3, 4).

Confirmatory moderator analysis

For pain and/or function, we found a consistent moderator effect for duration of LBP. Patients with less than one year LBP showed more positive/less negative point estimates for SMT vs recommended therapy on pain, with MD of 4.97 (95% CI: -3.20 to 13.13) at three months, 10.76 (CI: 1.06 to 20.47) at six months and 5.26 (CI -2.92 to 13.44) at twelve months; for function: SMD were 0.07 (-0.29; 0.43) at one month, 0.02 (-0.30; 0.34) at three months; 0.19 (-0.02; 0.15) at six months to 0.13 (-0.25; 0.52) at twelve months) (Table 3, 4). These effects were small, except for pain at 6 months, which showed a moderate effect. Converted to a MD for the 24-point Roland Morris Disability Questionnaire, these moderating effects amount to 0.35 at one month, 0.10 at three months, 1.06 at six months and 0.78 at twelve months (Table 3, 4).

The direction of the main treatment effect of SMT versus recommended interventions for the outcome pain was in favor of SMT (e.g. six months: MD -5.56, 95% CI -9.63 to -1.50) (see appendix eTable 10, <http://links.lww.com/BRS/B675>). When adding the moderator effect of duration of LBP to the main treatment effect, the results may indicate minimally relevant effects, meaning that patients with shorter duration of LBP may benefit from SMT. For those with longer duration, SMT has similar benefit compared to recommended interventions.

For function, patients with pain score over 50 showed more positive/less negative point estimates for SMT vs recommended therapy on pain, with SMD of -0.20 (-0.36; -0.04) at one month, -0.20 (-0.37; -0.03) at three months, -0.22 (-0.39; -0.06) at six months and -0.14 (-0.33; 0.04) at twelve months. These effects were small.

Exploratory moderator analysis

For pain and/or function, we found a consistent moderator effect for smoking. Non-smokers showed more positive/less negative point estimates for SMT vs recommended therapy on pain, with MD of 3.19 (-3.20; 9.58) at one month, 2.45 (-3.68; 8.58) at three months, 6.02 (0.12; 11.92) at six months to 4.85 (-1.33; 11.03) at twelve months; for function: SMD were 0.24 (0.00; 0.48) at one month, 0.22 (-0.02; 0.47) at three months; 0.14 (-0.11; 0.38) at six months to 0.29 (0.02; 0.56) at twelve months) (see for conversion to the 24-point Roland Morris Disability Questionnaire Table 3, 4). These effects were small.

For pain and/or function, we found a consistent moderator effect for previous SMT for LBP. Patients that had no previous SMT showed more positive/less negative point estimates for SMT vs recommended therapy on pain, with MD of -3.97 (-13.12; 5.19) at one month, 5.34 (-3.25; 13.95) at three months, 6.86 (-1.63; 15.35) at six months to 15.59 (6.18; 24.99) at twelve months; for function SMD were -0.11 (-0.49; 0.26) at one month, -0.07 (-0.46; 0.32) at three months; 0.14 (-0.20; 0.49) at six months to 0.52 (0.09; 0.84) at twelve months) (Table 3, 4). This effect (i.e. patients that had no previous SMT improved more than patients that had previous SMT for the outcomes pain and function with SMT compared to other recommended treatments) was small, except for pain and functional status at twelve months, which showed a moderate effect. (Table 3, 4).

SMT vs non-recommended interventions, SMT as adjuvant therapy and Manipulation vs Mobilization

Ninety percent of the moderator analyses for these comparisons were not performed due to too few data. In the analyses performed (mainly age, sex and BMI), we found no consistent effect for any moderator. (Appendix eTables 8-9, <http://links.lww.com/BRS/B675>)

DISCUSSION

This study is the first large-scale IPD meta-analysis which attempted to identify potential moderators for those undergoing SMT for chronic LBP. In short, the results suggest no substantive moderation in the effect of SMT compared to other interventions. We did, however identify (possible) small moderation effects for the following confirmatory moderators: duration of LBP and greater pain at baseline, and for the exploratory moderators smoking and previous exposure to SMT. However these effects were too small to be clinically-relevant. This suggests that targeting SMT, based upon individual characteristics examined in this study is not warranted at this time.

Analyses of moderator effects of SMT have rarely been performed and have largely been restricted to aggregate meta-analytic approaches, These different approaches make it difficult to compare those results to ours. Results from an earlier systematic review¹⁰ indicated moderating effects of psychosocial and belief factors, expectations and baseline pain and disability.

Two earlier IPD studies evaluated moderators for other types of treatment for LBP and identified small effects for the following moderators: age, gender, BMI, no heavy physical demands, psychosocial factors, back pain disability, pain severity and medication use.^{42 43} However, our analyses suggest only a weak moderating effect of baseline pain for functional

status in our confirmatory analysis. There are a number of reasons why the results of our moderator analyses might differ from the other studies.^{10 43-45} Most importantly, these earlier studies examined various types of conservative treatments for LBP (e.g. cognitive behavioral therapy) and the comparisons were chosen differently than in our study.

An important difference of our IPD analysis compared to traditional aggregate meta-analyses is that we could adjust for covariates and were not dependent upon how these data were reported in the study publications. IPD allowed investigation for moderators in a more sophisticated and valid way. In the IPD analysis one can separate the between-study and the within-study interaction. The between-study interaction describes the moderation effects at study level. This is what is analyzed in a meta-regression or subgroup analyses in traditional aggregate meta-analysis. Results of these analyses can be severely affected by ecological biases.¹⁹ The real interest lies in the within-study interaction, which describes the effects of covariates on the treatment effectiveness at the patient level.

Strengths and limitations: The most important strength is our large data set (i.e. 21 RCTs) from various countries resulting in a dataset which included many different moderators and thousands of patients of which over 2000 were in the SMT vs recommended intervention comparison. Most moderator analyses in this comparison included more than 500 patients provided from at least three trials. It has been suggested that this might be robust.¹⁰ Far fewer patients were included in the moderator analyses for the other comparisons. Therefore, our (exploratory) moderator results should serve as a guide for future research only.

We collected a wide variety of moderators, but many moderators were measured differently across trials or were not measured at all. For example: duration of LBP was measured as a continuous variable in some trials and as a categorical variable. Only age, sex and BMI were measured similarly. This meant that in many instances we had to compromise our best detailed measures by categorizing the data, which led to loss of information. Importantly, there was a large diversity in frequency (1 to 6 times a week), duration (2 to 12 weeks) and number of treatments (2 to 36 (average of 8)) in included trials and these characteristics were measured at study-level in most trials. Therefore, the moderator analyses with treatment characteristics were not possible in contrast to what we planned in our protocol. A better understanding of the etiology of chronic LBP and key mechanisms involved in the effects of SMT would help to identify moderators.

We did not assess the effects of imputing missing data on outcomes and moderators. Methodology for imputing missing values in IPD meta-analysis is still in the developmental phase.^{46 47} To our knowledge standard imputation methods for IPD meta-analysis of moderator effects have not been described in the literature. These models are especially challenging as they should result in valid estimates for the one-stage models we used that distinguish within-study and between-study interaction effects.

Additionally, we did not investigate multiple moderators in the same analysis as no evident clinically important moderators were found, although others⁴³ looked at multiple moderator at a lower level of statistical significance. At this moment our study clearly presents exploratory results to inform future studies.

Another challenge we encountered is the definition of clinical-relevance of the treatment moderator effects. For main effects, three-levels of clinical relevance (small, medium and large) are broadly used across systematic reviews, and are recommended by the Cochrane Back and Neck Review Group.^{20 48} However, for moderator analysis, we think clinical relevance should not be defined by the same criteria as for the main treatment effects. Importantly, we interpreted the moderator effects considering hypothesized mechanisms and consistency of results across time and outcome measures. In summary, we used a consensus approach for the arbitrary cut-off points for drawing our conclusions to detect small difference within a moderator for low intensity, low cost intervention comparisons. This is subjective, but in our view the best method currently available.

Another potential limitation is selection bias. We included only 50% of the eligible trials, which is comparable to other IPD studies.^{49 50} However, the effect sizes, methodological quality and range of publication dates of studies where IPD was collected was comparable with the studies where no IPD was present. We also missed the data of the most recent trials as we only included trials until 2016, because collection of data for an IPD is time consuming as also seen in other IPD studies.⁴² It took four years to collect and analyze the data, which is comparable to IPD meta-analyses in other fields.^{43 51} When we updated our search May 4th, 2018, we found that the most recent trials were small in size, had few data on patient characteristics and were considered to have a high risk of bias.⁵²⁻⁵⁶ Therefore, it is not likely that these most recent trials or the studies where IPD was not provided, would materially change our results.

The clinical implication of this IPD study is that based on the evidence to date there is no justification for using specific patient characteristics to target SMT for chronic LBP patients.

In addition to more detailed study of the etiology of chronic LBP and mechanism(s) of SMT, future initiatives should focus on standardizing the manner in which inclusion and exclusion criteria, outcomes and moderators are measured and reported.^{54 57-59} This will facilitate an effective comparison of interventions across trials. Additionally, our wish is to form an international IPD repository of RCTs which have examined the effect of conservative treatment for LBP. This will provide an excellent resource for researchers with advantages such as the potential for future network meta-analysis and to standardize, safeguard and store data centrally. To facilitate this, we encourage researchers in future grant applications to obtain permission to share their data and to include costs of uploading their final data into a repository as well as permission from Research Ethical Committees and participants for sharing these data. However three large IPD meta-analyses of non-pharmacological treatments for low back pain have failed to find any consistent and clinically important moderation effects indicates that this line of research is very unlikely to generate important finding to improve patient care.

CONCLUSION

Based on the current IPD analyses, there is no evidence for moderating effects of specific patient characteristics that enable clinicians to identify which patients are likely to benefit more from SMT compared to other treatments. Future research dealing with the effectiveness of SMT would benefit from shared procedures for including important treatment effect modifiers.

ABBREVIATIONS

IPD: individual participant data

LBP: low back pain

MD: mean difference

PRISMA-P: Preferred Reporting Items of Systematic Reviews and Meta-Analyses Protocol

RCT: randomized clinical trial

RR: relative risk

SD: standard Deviation

SMD: standard mean difference

SMT: spinal manipulative therapy

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Key points

- The effects of SMT are comparable to other interventions recommended in guidelines for chronic low back pain (LBP); however, it is unclear which patients are more likely to benefit from SMT compared to other therapies.
- Based on this review, there is no evidence to suggest that specific patients or treatment characteristics are associated with clinically better response to SMT as compared to other (recommended) treatments for chronic low back pain.
- This may well be a result of the great variation in reporting of potential treatment modifiers.
- Future initiatives should also focus on standardizing the manner in which inclusion and exclusion criteria, outcomes and moderators are defined, measured and reported.
- This will facilitate an effective comparison of interventions across trials.
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Figure 1 Flow diagram of study inclusion

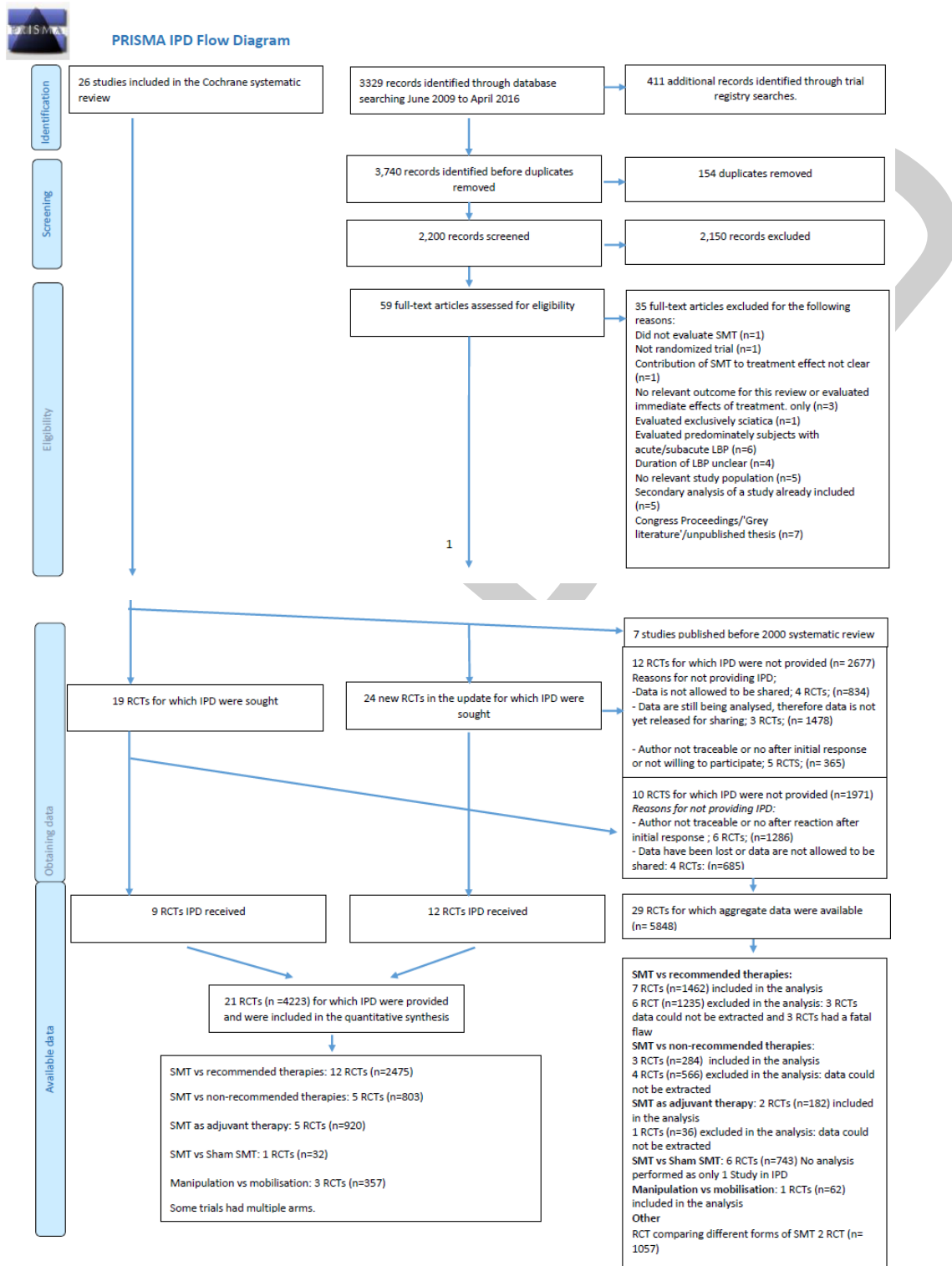


Table 1 Descriptives of studies evaluating the effects of SMT on outcomes included in the database (n=21) in alphabetical order of first author.

| Author (year) <i>Acronym</i> | Country | N | Interventions | Duration of LBP According to inclusion criteria | Type of manipulator | Type of manipulation | Max no. treatments allowed and duration of treatment |
|---------------------------------|-------------|-----|---|--|----------------------------|---|--|
| Balthazard (2012) | Switzerland | 42 | 1. Spinal manipulation Therapy plus active exercise (n = 22) 2. Detuned ultrasound plus active exercise (n = 20) | > 12 and < 26 weeks | Physiotherapist (n=1) | Manipulation and mobilization | 8 over 4-8 weeks |
| Bronfort (2011) | USA | 301 | 1. Supervised exercise (n= 101) 2. Spinal manipulative therapy (n=100) 3. Home exercise and advice (n=100); | > 6 weeks | Chiropractor (n=9) | Manipulation | Participants were discharged from care if the treating clinician felt that maximum clinical benefit was obtained. 12 wks of care |
| Bronfort (2014) | USA | 192 | 1. Spinal manipulative therapy plus home exercise and advice (n=96) 2. Home exercise and advice (n=96) | > 4 weeks | Chiropractor (n=11) | Manipulation and mobilization | as many as 20 over 12 wks |
| Cecchi (2010) | Italy | 210 | 1. Back school (n=70); 2. Individualized physiotherapy (n=70); 3. Spinal manipulative therapy (n=70) | > 6 mo | Physician (n=2) | Manipulation and mobilization | 4-6 sessions per week for 4-6 wks |
| Cook (2013) | USA | 154 | 1. Thrust manipulation(n=77) 2. Non-thrust manipulation (n=77) | No restriction | Physiotherapist (n=17) | Manipulation or mobilization (depending upon grp. assignment) | 1st 2 visit only afterwards clinician was allowed to choose technique they felt most beneficial for the patient |
| Ferreira (2007) | Australia | 240 | 1. General exercise (n=80) 2. Motor control exercise 3. Spinal manipulative therapy | > 3 mo | Physical therapist (n = ?) | Mobilization or manipulation; Maitland | 12 over 8 wks |
| Gudavelli (2006) | USA | 235 | 1. Flexion distraction mobilization (n=123) 2. Exercise therapy (n=112) | > 3 mo | Chiropractor (n = ?) | Mobilization (flexion-distraction) | 16 over 4 wks |
| Haas | USA | 400 | 1. 0 SMT (spinal manipulative therapy) + 18 LM (light | > 3 mo | Chiropractor | Manipulation or | 18 over 6 wks |

| | | | | | | | | |
|----------------------|---------|------|---|-----------------------|---|--|---|--------------------|
| (2014) | | | massage) (n=100) 2. 6 SMT + 12 LM (n=100) 3. 12 SMT + 6 LM (n=100) 4. 18 SMT + 0 LM (n=100) | | (n=12) | | mobilization | |
| Hidalgo (2015) | Belgium | 32 | 1. Spinal manipulative therapy (n=16) 2. Sham spinal manipulative therapy (n=16) | No restriction | Physiotherapist (n=1) | | Mobilization | 1 over 2 wks |
| Hondras (2009) | USA | 240 | 1. High-velocity low-amplitude Spinal manipulative therapy (n = 96) 2. Low-velocity variable amplitude spinal mobilization (n = 95) 3. Medical care (n=49) | > 4 wks | Chiropractor (n = 4) | | Manipulation or mobilization (flexion-distractio n) (depending upon grp. assignme nt) | 12 over 6 wks |
| Hsieh (2002) | USA | 206 | 1. Back school (n = 48) 2. Myofascial therapy (n = 51) 3. Joint manipulation (n = 49) 4. Combination of treatments 2 & 3 (n = 52) | > 3 wks to < 6 mo | Chiropractor (n = ?) | | Manipulation | 9 over 3 wks |
| Petersen (2011) | Denmark | 350 | 1. McKenzie therapy (n=175) 2. Spinal manipulative therapy (n=175) | > 6 wks | Chiropractor (n=3) | | Manipulation or mobilization | max 15 over 12 wks |
| Rasmussen-Bar (2003) | Sweden | 47 | 1. Stabilizing training group (n = 24) 2. Manual therapy group (n = 23) | > 6 wks | Manual therapist (n = ?) | | MOB | 6 over 6 wks |
| Skillgate (2007) | Sweden | 409 | 1. Naprapathy (n = 206) 2. Standard care or "evidence-based" care (provided by physician) (n = 203) | > 2 wks | Naprapath (n = 8) | | Manipulation or mobilization | 6 over 6 wks |
| UK Beam (2004) | UK | 1334 | 1. Best care in general practice (n = 338) 2. Best care plus exercise alone (n = 310) 3. Best care plus private manipulation alone (n = 180) 4. Best care plus NHS manipulation alone (n = 173) 5. Best care plus private manipulation plus exercise (n = | (Essentially) > 3 wks | Chiropractor, osteopath or physiotherapist (n = 84) | | Manipulation or mobilization | 8 over 12 wks |

172)

6. Best care plus NHS
manipulation plus exercise (n =
161)

| | | | | | | | |
|-----------------------|-----------|-----|---|---------|------------------------------|---|-----------------|
| Verma (2013) | India | 30 | 1. Exercise (n=15) 2. Lumbar mobilisation and exercise (n=15) | > 3 mo | Physioth erapist (n=?) | Mobiliza tion | 8 over 4 wks |
| Vismara (2012) | Italy | 21 | 1. Osteopathic manipulation and Specific exercise (n=10) 2. Specific exercise (n=11) | > 6 mo | Osteopat h (n=1) | Manipul ation or mobilizat ion | 10 over 10 wks? |
| Walker (2013) | Australia | 183 | 1. Sham group (n=91); 2. Usual chiropractic care group (n=92) | > 1wk | Chirop ractor (n=8) | Manipul ation or mobilizat ion | 2 over 2 wks |
| Wilkey (2008) | UK | 63 | 1) Hospital pain clinic (n = 33) 2) Chiropractic treatment (n = 30)* | >3 mo | Chirop ractor (n = ?) | Manipul ation | 16 over 8 wks |
| Xia (2015) | USA | 192 | 1. Thrust spinal manipulation (n=72) 2. Non thrust spinal manipulation (n=72) 3. Control (n=48) | > 4 wks | Chirop ractor (n=4) | Manipul ation or mobilizat ion | 4 over 2 weeks |
| Zaproudi na (2009) | Finland | 73 | 1. Traditional bone setting (n = 36) 2. Physical therapy (n = 37)** | > 3 mo | Bone- setter (n = 8) | Mobiliza tion | 5 over 10 wks |

wks = weeks; mo = months; ? = unclear/unknown

*More patients data provided than published

** Only patient data used if patient consented to be included in our database, therefore less patients than published

Table 2: Patient characteristics at baseline for groups receiving SMT vs groups receiving recommended interventions

| | <i>SMT vs recommended interventions</i> (m= 12; n=2475) | |
|--|--|---------------------------|
| <i>Demographic data</i> | SMT | Recommended interventions |
| <i>Age, mean (SD) years</i> (m=11, n=2409) | 47.13 (13.63) | 47.18 (13.99) |
| <i>Sex, n (%) female</i> (m=11, n=2412) | 667 (56.9) | 684 (55.2) |
| <i>BMI, mean (SD)</i> (m=8, n=1434) | 26.85 (5.12) | 26.79 (5.10) |
| <i>Ethnicity, n (%) white</i> (m= 5, n=861) | 409 (90.9) | 388 (88.1) |
| <i>Lifestyle factors</i> | | |
| <i>Physical activity, n (%)</i> (m= 6, n=824) | | |
| Low (1 or less than once a week) | 115 (31.9) | 166 (35.9) |
| Medium (2-3x a week) | 146 (40.4) | 166 (35.9) |
| High (more than 3x a week) | 100 (27.7) | 131 (28.3) |
| <i>Smoker, n (%) non-smokers</i> (m=6, n=1173) | 451 (79.5) | 453 (74.8) |
| <i>Alcohol use (%)</i> | * | * |
| <i>Socio-demographics</i> | | |
| <i>Marital Status, n (%) married; living with a partner</i> (m= 6, n=1173) | 397 (69.0) | 404 (67.6) |
| <i>Level of Education, n (%) low/ middle</i> (m= 7, n= 1672) | 600 (68.0) | 534 (67.6) |
| <i>Income, n (%)</i> | * | * |
| <i>Employment status, n (%) at work</i> (m= 9, n= 2126) | 818 (77.9) | 770 (71.6) |
| <i>Nature and severity of LBP</i> | | |
| <i>Duration of LBP, n (%) less than 12 months</i> (m=7, n=1252) | 121 (20.3) | 149 (22.9) |
| <i>Leg pain, n (%)</i> (m= 5, n=1038) | 320 (59.0) | 281 (56.7) |
| <i>Previous LBP treatment received, n (%)</i> (m=5, n=930) | 258 (27.7) | 218 (23.4) |
| <i>Previous physiotherapy for low back pain received, n (%)</i> (m=5, n=771) | 64 (8.3) | 72 (9.3) |
| <i>Previous SMT for low back pain received, n (%)</i> (m=6, n=988) | 209 (21.2) | 111 (11.2) |
| <i>Used medication for low back, n (%)</i> (m=6, n=1018) | 200 (19.6) | 269 (26.4) |
| <i>Non-specific, n (%)</i> | * | * |
| <i>Comorbidities</i> | * | * |
| <i>Type of treatment</i> | * | * |
| <i>Psychological factors</i> | SMT | Control |
| <i>Depression, n (%)</i> (m= 5, n=1297) | 43 (6.2) | 75 (12.5) |
| <i>Treatment preference/expectations</i> | * | * |
| <i>Primary outcomes</i> | | |

| Pain | SMT | Recommended interventions |
|--|---------------|---------------------------|
| <i>Combined pain score at baseline, mean (SD), (m=12, n=2441)</i> | 49.47 (22.27) | 49.75 (21.59) |
| <i>Combined pain score at one month, mean (SD), (m=10, n=1948)</i> | 34.19 (22.95) | 35.81 (23.91) |
| <i>Combined pain score at three months, mean (SD), (m=9, n=1673)</i> | 27.92 (23.03) | 32.12 (24.25) |
| <i>Combined pain score at six months, mean (SD), (m=8, n=1321)</i> | 27.35 (23.12) | 32.31 (23.90) |
| <i>Combined pain score at 12 months, mean (SD), (m=10, n=1816)</i> | 31.80 (25.81) | 33.32 (25.38) |
| Function | | |
| <i>RMDQ sum score at baseline, mean (SD), (m=9, n=2174)</i> | 8.99 (4.96) | 10.07 (5.44) |
| <i>RMDQ sum score at one month, mean (SD), (m=8, n=1760)</i> | 5.62 (5.02) | 6.65 (5.37) |
| <i>RMDQ sum score at three months, mean (SD), (m=8, n=1648)</i> | 4.81 (5.14) | 5.52 (5.34) |
| <i>RMDQ sum score at six months, mean (SD), (m=8, n=1348)</i> | 4.99 (5.44) | 6.26 (5.95) |
| <i>RMDQ sum score at 12 months, mean (SD), (m=7, n=1575)</i> | 5.44 (5.67) | 6.16 (5.92) |
| Secondary outcomes | | |
| <i>SF36 Physical Component Scale of SF36 at baseline, mean (SD), (m=5, n=1362)</i> | 40.69 (7.15) | 41.06 (7.59) |
| <i>SF36 Mental Component Scale of SF36 at baseline, mean (SD), (m=5, n=1362)</i> | 43.83 (9.05) | 45.08 (9.60) |
| <i>Medication use at baseline, n (% medication use) (m=3, n=668)</i> | 145 (21.7) | 216 (32.3) |

SD= standard deviation; m = number of studies; n = number of participants; * less than 3 studies or combining categories was not meaningful

Table 3: Moderator effects of SMT vs recommended interventions for pain. Within-study interaction (•) and 95% confidence intervals (CI) with the intervention effects of random-effect models adjusted for baseline using REML separating, between-study and within-study variation are presented.

| Combined Pain scale | Follow-up | | | |
|---|--------------------------------|--------------------------------|----------------------------------|----------------------------------|
| | 1 month • (95% CI) m; n | 3 months • (95% CI) m; n | 6 months • (95% CI) m; n | 12 months • (95% CI) m; n |
| Demographic moderators | | | | |
| Sex: (reference: male) | -1.63 (-5.02; 1.75) 9; 1859 | -2.76 (-6.81; 1.28) 8; 1592 | -5.11 (-9.69; -0.54) 7; 1270 | -6.69 (-10.71; -2.67) 9; 1740 |
| Age *: (reference: <65 years old) | -1.74 (-6.03; 2.55) 9; 1859 | -0.56 (-7.96; 6.84) 8; 1590 | -9.42 (-17.65; -1.20) 7; 1268 | 2.60 (-5.27; 10.47) 6; 1042 |
| Body mass index: (reference: <30) | -1.96 (-7.30; 3.38) 6; 1060 | 3.78 (-3.10; 10.65) 5; 924 | 4.36 (-2.28; 11.00) 6; 1056 | 6.01 (-0.84; 12.86) 6; 1042 |
| Ethnicity: (reference: other than white) | -1.96 (-10.08; 6.15) 4; 699 | 5.12 (-7.37; 17.60) 3; 492 | -0.08 (-13.39; 13.22) 3; 465 | 2.77 (-9.48; 15.02) 3; 469 |
| Lifestyle factors | | | | |
| Physical activity: (reference: 3 or less a week) (reference: 1 or less a week) | -0.46 (-7.45; 6.54) 4; 533 | -4.84 (-11.59; 1.92) 7; 721 | -4.67 (-11.47; 2.14) 4; 681 | -0.02 (-7.58; 7.54) 5; 661 |
| Smoker: smoker (reference: non-smoker) | -3.96 (-10.07; 2.16) 4; 533 | -2.06 (-8.31; 4.18) 7; 721 | 1.00 (-5.89; 7.60) 4; 681 | -3.22 (-10.35; 3.90) 5; 661 |
| Alcohol use | 3.19 (-3.20; 9.58) 5; 886 | 2.45 (-3.68; 8.58) 4; 866 | 6.02 (0.12; 11.92) 5; 891 | 4.85 (-1.33; 11.03) 4; 806 |
| Socio-demographics | | | | |
| Marital Status: (reference: not involved in relation) | 2.60 (-3.11; 8.31) 6; 1076 | 1.39 (-4.47; 7.35) 4; 802 | 1.84 (-4.19; 7.87) 5; 834 | -0.28 (-6.11; 5.57) 4; 764 |
| Employment status: (reference: not employed) | 5.69 (0.32; 11.06) 7; 1622 | 0.88 (-5.72; 7.49) 7; 1440 | 5.12 (-2.94; 13.19) 6; 1191 | 0.96 (-4.93; 6.86) 8; 1572 |
| Level of Education: (reference: low or middle) | -0.42 (-4.62; 3.77) 6; 1377 | -1.52 (-7.51; 4.48) 5; 1117 | -3.31 (-14.50; 7.88) 4; 625 | -2.54 (-9.27; 4.19) 5; 1066 |
| Income | ‡ | ‡ | ‡ | ‡ |
| Nature and severity of LBP | | | | |
| Duration of LBP *: (reference: < 1 year) | -1.69 (-10.37; 7.00) 5; 876 | 4.97 (-3.20; 13.13) 4; 700 | 10.76 (1.06; 20.47) 5; 875 | 5.26 (-2.92; 13.44) 5; 854 |
| Radiation: (reference: no leg pain) | -4.13 (-9.68; 1.43) 3; 649 | -2.56 (-9.18; 4.06) 4; 716 | 0.43 (-6.56; 7.41) 3; 636 | -4.41 (-11.33; 2.52) 4; 682 |

| | | | | |
|--|---|--------------------------------|--------------------------------|---------------------------------|
| Previous LBP treatment received: | 0.23 (-5.06; 5.53) 5; 878 (reference: no) | 2.42 (-9.09; 4.25) 4; 675 | -0.36 (-7.18; 6.45) 3; 626 | -0.95 (-8.15; 6.25) 3; 622 |
| Previous Physio for LBP: | -10.83 (-19.42; -2.25) 3; 448 (reference: no) | -3.38 (-11.51; 4.74) 4; 679 | 2.41 (-6.64; 11.46) 4; 639 | -1.55 (-10.13; 7.02) 4; 624 |
| Previous SMT for LBP: | -3.97 (-13.12; 5.19) 4; 629 (reference: no) | 5.34 (-3.25; 13.95) 4; 676 | 6.86 (-1.63; 15.35) 4; 636 | 15.59 (6.18; 24.99) 4; 621 |
| Previous medication for LBP: | 1.32 (-3.47; 6.13) 5; 887 (reference: no) | -2.99 (-8.44; 2.46) 6; 902 | -2.43 (-8.22; 3.37) 4; 790 | -1.69 (-11.33; 7.96) 6; 862 |
| Comorbidities | ‡ | ‡ | ‡ | ‡ |
| Psychological factors | | | | |
| Depression *: | 1.45 (-6.78; 9.68) 4; 1053 (reference: no depression) | -1.06 (-11.23; 9.11) 4; 860 | ‡ | -1.20 (-13.23; 10.83) 4; 817 |
| Treatment preference/expectations * | ‡ | ‡ | ‡ | ‡ |
| Primary/secondary outcomes at baseline as moderator | | | | |
| Baseline pain score per 10 points change * | -0.20 (-1.2; 0.80) 10; 1922 | -0.70 (-2.10; 0.80) 9; 1922 | -0.40 (-0.18; 1.10) 8; 1922 | -1.1 (-2.90; 0.70) 9; 1791 |
| Baseline function scales combined (z-score) * | -1.25 (-3.90; 1.39) 10; 1914 | -0.77 (-3.43; 1.87) 9; 1641 | -1.73 (-4.27; 0.82) 8; 1313 | -0.90 (-4.07; 2.26) 10; 1783 |
| MCS | -0.09 (-0.40; 0.21) 5; 1190 | -0.01 (-0.28; 0.26) 4; 1121 | 0.17 (-0.16; 0.49) 4; 681 | -0.19 (-0.48; 0.11) 4; 1046 |
| PCS | 0.19 (-0.36; 0.73) 5; 1190 | -0.07 (-0.52; 0.38) 4; 1121 | -0.40 (-1.07; 0.28) 4; 681 | 0.09 (-0.50; 0.69) 4; 1046 |

A negative interaction coefficient indicates a more positive / less negative effect of SMT versus recommended therapies for the index group (e.g. females) as compared to the reference group (e.g. males).

- (95% CI) = within-study interaction and confidence interval: the mean difference in pain score for the specific moderator for SMT vs recommended therapies on scale from 0-100; m=number of studies; n= number of participants

* confirmatory moderator analysis

‡ not enough data

Table 4 Moderator effects of SMT vs recommended interventions for function. Within-study interaction (•) and 95% confidence intervals (CI) with the intervention effects of random-effect models adjusted for baseline using REML, separating between-study and within-study variation are presented.

| Standardized mean difference of combined function scales | Follow-up | | | |
|---|----------------------------------|----------------------------------|---------------------------------|---------------------------------|
| | 1 month | 3 months | 6 months | 12 months |
| | • (95% CI) m; n | • (95% CI) m; n | • (95% CI) m; n | • (95% CI) m; n |
| Demographic moderators | | | | |
| Sex: (reference: male) | -0.03 (-0.16; 0.10) 9; 1876 | 0.06 (-0.09; 0.21) 10; 1837 | 0.01 (-0.15; 0.18) 8; 1439 | -0.02 (-0.17; 0.14) 9; 1775 |
| Age *: (reference: <65 years old) | -0.03 (-0.17; 0.12) 9; 1876 | -0.06 (-0.25; 0.13) 10; 1835 | -0.23 (-0.45; -0.01) 8; 1437 | -0.32 (-0.57; -0.07) 9; 1773 |
| Body mass index: (reference: <30) | -0.07 (-0.26; 0.12) 6; 1047 | -0.18 (-0.42; 0.07) 7; 1139 | -0.06 (-0.30; 0.17) 7; 1225 | 0.15 (-0.14; 0.44) 6; 1055 |
| Ethnicity: white vs other (reference: other than white) | -0.19 (-0.55; 0.17) 4; 691 | 0.07 (-0.39; 0.53) 5; 707 | -0.23 (-0.65; 0.19) 4; 630 | 0.03 (-0.38; 0.44) 3; 469 |
| Lifestyle factors | | | | |
| Physical activity: (reference: 3 or less a week) | -0.002 (-0.008; 0.002) 4; 511 | -0.002 (-0.009; 0.004) 6; 739 | -0.13 (-0.40; 0.14) 4; 659 | 0.00 (-0.01; 0.01) 5; 676 |
| (reference: 1 or less a week) | -0.11 (-0.33; 0.11) 4; 511 | -0.05 (-0.27; 0.18) 6; 739 | -0.13 (-0.34; 0.09) 4; 659 | -0.10 (-0.33; 0.14) 5; 676 |
| Smoker: smoker (reference: non-smoker) | 0.24 (0.00; 0.48) 5; 873 | 0.22 (-0.02; 0.47) 6; 1075 | 0.14 (-0.11; 0.38) 6; 1050 | 0.29 (0.02; 0.56) 4; 801 |
| DZ converted to a MD on the 24 point RMDQ scale | 1.08 | 1.11 | 0.72 | 1.54 |
| Alcohol use | ‡ | ‡ | ‡ | ‡ |
| Socio-demographics | | | | |
| Marital Status: (reference: not involved in relation) | -0.12 (-0.29; 0.05) 6; 1066 | -0.09 (-0.29; 0.12) 6; 1016 | -0.08 (-0.26; 0.10) 6; 1005 | -0.12 (-0.33; 0.10) 4; 777 |
| Employment status: (reference: not employed) | 0.10 (-0.08; 0.27) 7; 1657 | -0.17 (-0.39; 0.04) 8; 1665 | 0.06 (-0.16; 0.27) 7; 1377 | -0.06 (-0.36; 0.23) 8; 1606 |
| Level of Education: (reference: low or middle) | -0.17 (-0.37; 0.01) 6; 1398 | -0.11 (-0.29; 0.08) 7; 1363 | -0.07 (-0.27; 0.13) 5; 796 | -0.14 (-0.35; 0.05) 5; 1106 |
| Income | ‡ | ‡ | ‡ | ‡ |
| Nature and severity of LBP | | | | |

| | | | | |
|---|----------------------|----------------------|----------------------|---------------------|
| Duration of LBP *: >1 year | 0.07 (-0.29; 0.43) | 0.02 (-0.30; 0.34) | 0.19 (-0.02; 0.39) | 0.13 (-0.25; 0.52) |
| (reference: < 1 year) | 5; 861 | 6; 910 | 6; 1031 | 5; 848 |
| DZ converted to a MD on the 24 point RMDQ scale | 0.35 | 0.10 | 1.06 | 0.78 |
| Radiation: leg pain | -0.16 (-0.40; 0.80) | 0.04 (-0.18; 0.27) | -0.01 (-0.22; 0.21) | -0.08 (-0.33; 0.17) |
| (reference: no leg pain) | 3; 660 | 5; 911 | 4; 820 | 4; 681 |
| Previous LBP treatment received: (reference: no) | 0.09 (-0.11; 0.29) | 0.11 (-0.12; 0.34) | 0.02 (-0.21; 0.15) | 0.12 (-0.14; 0.39) |
| | 5; 884 | 5; 871 | 5; 812 | 4; 637 |
| Previous Physio for LBP: (reference: no) | -0.08 (-0.63; 0.48) | 0.04 (-0.33; 0.40) | 0.18 (-0.19; 0.56) | 0.11(-0.27; 0.50) |
| | 3; 426 | 5; 696 | 4; 615 | 4; 634 |
| Previous SMT for LBP: (reference: no) | -0.11 (-0.49; 0.26) | -0.07 (-0.46; 0.32) | 0.14 (-0.20; 0.49) | 0.52 (0.09; 0.95) |
| | 4; 616 | 6; 885 | 5; 795 | 4; 631 |
| DZ converted to a MD on the 24 point RMDQ scale | -0.49 | -0.36 | 0.74 | 2.93 |
| Previous medication for LBP: (reference: no) | -0.02 (-0.22; 0.19) | -0.11 (-0.33; 0.09) | -0.20 (-0.41; 0.004) | -0.11 (-0.39; 0.17) |
| | 5; 887 | 6; 903 | 4; 790 | 6; 877 |
| Comorbidities | ‡ | ‡ | ‡ | |
| Psychological factors | | | | |
| Depression *: (reference: no depression) | 0.28 (-0.03; 0.58) | 0.33 (-0.02; 0.69) | 0.13 (-0.26; 0.51) | 0.02 (-0.39; 0.43) |
| | 4; 1075 | 5; 1066 | 3; 505 | 4; 825 |
| Treatment preference/expectations * | ‡ | ‡ | ‡ | ‡ |
| Primary/secondary outcomes at baseline as moderator | | | | |
| Baseline function scales combined (z-score) | -0.04 (-0.17; 0.09) | +0.01 (-0.10; 0.13) | -0.04 (-0.17; 0.08) | -0.05 (-0.17; 0.07) |
| | 10; 1939 | 11; 1892 | 9; 1490 | 10; 18266 |
| Baseline pain dichotomized *: (reference: baseline painless than 50) | -0.20 (-0.36; -0.04) | -0.20 (-0.37; -0.03) | -0.22 (-0.39; -0.06) | -0.14 (0.33; 0.04) |
| | 10; 1932 | 11; 1882 | 9; 1506 | 10; 1806 |
| | -0.90 | -0.92 | -1.00 | -0.64 |
| MCS per 10 points change | -0.00 (-0.10; 0.10) | -0.03 (-0.16; 0.08) | 0.09 (-0.07; 0.25) | 0.00 (-0.12; 0.12) |
| | 5; 1204 | 6; 1358 | 5; 864 | 4; 1069 |
| PCS per 10 points change | 0.03 (-0.17; 0.23) | -0.06 (-0.18; 0.06) | -0.13 (-0.32; 0.07) | 0.00 (-0.22; 0.21) |
| | 5; 1204 | 6; 1358 | 5; 864 | 4; 1069 |

A negative interaction coefficient indicates a more positive / less negative effect of SMT versus recommended therapies for the index group (e.g. females) as compared to the reference group (e.g. males).

• (95% CI) = within-study interaction and confidence interval of the interaction term: the difference in Z score for the specific moderator for function for SMT vs recommended therapies; m=number of studies; n= number of participants

* confirmatory moderator analysis

‡ not enough data