Effect of spinal manipulative therapy on adults with low back pain meeting a clinical prediction rule. A systematic review

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FOREWORD

As a newly educated physical therapist I found low back pain to be one of the most difficult conditions to treat. I was very frustrated several times and I found it hard to help patients with low back pain. While watching other therapists like manual therapist and chiropractors I saw patients with low back pain get instantly much better after manipulation treatment. As a new manual therapy student I was therefore curios to find out more about low back pain and the effect of manipulative therapy in the treatment of low back pain.

It has been an interesting process with a lot of new knowledge that has developed me further as a clinician. I would like to thank all the people who have helped me through this process. First I want to thank my supervisor Kjartan Vibe Fersum for all your knowledge and good guiding through this writing process. I also want to thank the librarian Regina Küfner Lein for helping me with the searches in the different databases and the librarian Ingvild Kirkehei for assisting me in questions I had. In addition I want to thank to Kristin Thuve Dahm for being the second reviewer and for all the good discussions and advices you gave me.

Last but not least I want to thank my family who have always supported and encouraged me in following my dreams and for all the support through this demanding time.

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DEFINITION OF TERMS

AHCPR	Agency for Health Care Policy and Research
CBRG	Cochrane Back Review Group
CI	Confidence Interval
CPR	Clinical Prediction Rule
CPR+	Clinical Prediction Rule positive according to the criteria
CPR-	Clinical Prediction Rule negative according to the criteria
HVLA	High Velocity Low Amplitude (thrust manipulation)
LBP	Low Back Pain
NSAID	Non-steroidal anti-inflammatory drug
ODQ	Oswestry Disability Questionnaire
RCT	Randomized Controlled Trial
RMDQ	Roland Morris disability questionnaire
RoB	Risk of Bias
ROM	Range of Motion
SMT	Spinal Manipulative Therapy

CONTENT

ABSTRACT

Study design: Systematic review of interventions.

Background: Spinal manipulative therapy (SMT) is one of many therapies used to treat low back pain. Reviews have concluded that SMT is no more effective than other recommended therapies. Subgrouping patients using clinical prediction rules have been suggested to potentially increase the effect of SMT in the treatment of low back pain.

Objective: To review the effect of spinal manipulative therapy on adults with low back pain meeting a clinical prediction rule compared to those who do not meet a clinical prediction rule.

Methods: An experienced librarian and the master student searched for randomized controlled trials (RCTs) in multiple databases up to 27th of august 2014. RCTs that examined the effect of manipulation or mobilization in adults with low back pain and using a clinical prediction rule to subgroup the patients were included. The outcomes were pain and function. Two reviewers independently conducted the study selection, risk of bias assessment and data extraction.

Results: We identified 2 RCTs (total participants = 370). Both studies had a low risk of bias. One study found that patients who were positive on the clinical prediction rule and received manipulation experienced significantly better effects on pain and function at 1 week, 4 weeks and 6 months than patients who were rule negative and received manipulation. The results, in the other study, showed no significant differences in effects on pain and function between status on the rule and manipulation at 1 week, 2 weeks, 4 weeks and 12 weeks.

Conclusion: There are conflicting results whether patients who are rule positive have a better effect of manipulation than rule negative patients. More studies including both rule positive and rule negative patients are needed to find out more about the effect of manipulation in subgroups of LBP patients.

Key words: spinal manipulative therapy, spinal manipulation, low back pain, clinical prediction rule, systematic review

SAMMENDRAG

Studiedesign: Systematisk oversikt

Bakgrunn: Manipulasjon er en av mange intervensjoner brukt til å behandle korsryggryggplager. Systematiske oversikter har konkludert med at manipulasjon ikke virker bedre enn andre anbefalte behandlingstiltak. Sub-gruppering av pasienter ved å bruke en klinisk prediksjonsregel har blitt foreslått for potensielt å øke effekten av manipulasjon i behandlingen av korsryggplager.

Hensikt og problemstilling: Gjøre en systematisk gjennomgang av litteraturen for å avdekke om voksne med korsryggsmerter som er positive på en klinisk prediksjonsregel for manipulasjon har bedre effekt av manipulasjon enn de som er negative på en klinisk prediksjonsregel for manipulasjon.

Metode: En erfaren bibliotekar søkte sammen med masterstudenten etter randomiserte kontrollerte studier (RCT) i flere databaser frem til 27. august 2014. RCT studier som undersøkte effekten av manipulasjon og mobilisering av voksne med korsryggsmerter og som brukte en klinisk prediksjonsregel for å subgruppere pasientene ble inkludert. Utfallsmålene var smerte og funksjon. To reviewere utførte studieutvelgelse, kvalitetsvurdering og ekstrahering av data uavhengig av hverandre.

Resultat: Vi identifiserte 2 RCT studier (antall deltakere = 370). Begge hadde høy metodisk kvalitet. Den ene studien fant at pasienter som ble vurdert positive på regelen og fikk manipulasjon opplevde signifikant bedre effekt på smerte og funksjon ved 1 uke, 4 uker og 6 måneder enn pasienter som var vurdert negative på regelen og mottok manipulasjon. Resultatene i den andre studien viste ingen signifikante forskjeller på utfallsmålene mellom status på regelen og manipulasjon ved 1 uke, 2 uker, 4 uker og 12 uker.

Konklusjon: Det er motstridende resultat om pasienter som ble vurdert positive på regelen hadde bedre effekt av manipulasjon på korsryggsmerter enn pasienter som ble vurdert negative på regelen. Flere studier som inkluderer pasienter som er både positive og negative på regelen trengs for å undersøke effekten av manipulasjon i subgrupper av pasienter med korsryggsmerter.

Nøkkelord: spinal manipulasjon, manipulasjon, korsryggsmerter, klinisk prediksjonsregel, systematisk oversikt

1.0 INTRODUCTION

1.1 Background

Low back disorders are prevalent and induce large costs to the health services, the national insurance system and employers in Norway (Lærum et al., 2007). The lifetime prevalence is approximately 60-80 %. Half of the adult population had experienced low back pain during the last year, and approximately 40% the last month (Brage and Laerum, 1999; Lærum et al., 2013). A resent report describe that among the musculoskeletal injuries low back pain is the most common reason for sick leave (11%) and disability (9%) (Lærum et al., 2013). The total cost of low back pain is estimated to 13-15 billion per year (Lærum et al., 2007).
Also in the rest of the World low back pain is a common, disabling disorder, and a financial burden (Dagenais et al., 2008; Vos et al., 2012). Therefore, adequate treatment of low back pain is an important issue for patients, clinicians and policy makers (Rubinstein et al., 2013).

One of the interventions used for the treatment of low back pain is spinal manipulative therapy (SMT). There are no uniform definition of manipulation (Evans and Lucas, 2010); however, several studies define SMT as both mobilization and manipulation (Rubinstein et al., 2011; Rubinstein et al., 2013).

Several randomized controlled trials (RCT) have examined the effect of manipulation and the trials have been summarized in recent systematic reviews (Assendelft et al., 2003; Cherkin et al., 2003; Ferreira et al., 2003; Bronfort et al., 2004; Rubinstein et al., 2011; Rubinstein et al., 2013). The reviews concluded that SMT was no more effective for acute and chronic low back pain than inert interventions, sham SMT, adjunct therapy or other recommended therapies for reducing pain and improving function. The quality on the chronic low back pain trials was of high quality (Rubinstein et al., 2011), but the quality of the acute low back pain trials was of very low to moderate quality (Rubinstein et al., 2013).

Numerous authors have discussed the possible reasons for the lack of treatment results (Lamb et al., 2010; Foster et al., 2011; Rubinstein et al., 2013). Reasons like a natural course of improvement for acute low back pain, heterogeneity of patients included in trials and the variation in treatment effects, underestimating non-specific treatment effects like practitioners

attention, support and empathy, poor outcome measures have been mentioned. (Foster et al., 2011).

An argument for achieving better treatment results is to match groups of patients with the most appropriate treatment for their profile which is referred to as stratified care (Foster et al., 2009; Foster et al., 2013). Foster et al. (2013) consider stratified care as three approaches, namely those based on patients' prognosis (risk), those based on underlying causal mechanisms and those based on treatment responsiveness with some overlap between them. One example of stratified care based on treatment responsiveness is clinical prediction rules (Foster et al., 2013). A clinical prediction rule is a clinical tool that quantifies the individual contributions that various components of the history, physical examination, and basic laboratory results make toward the diagnosis, prognosis, or likely response to treatment in a patient. Clinical prediction rules attempt to standardize, simplify, and increase the accuracy of clinicians' diagnostic and prognostic assessments (McGinn et al., 2008; Haskins et al., 2012). However, systematic reviews have concluded that clinical prediction rules are not validated broadly enough to be implemented in clinical practice. Few clinical prediction rules have been tested in RCTs, there is a lack of validation studies and results have been contradictory (Beneciuk et al., 2009; May and Rosedale, 2009; Stanton et al., 2010; Haskins et al., 2012).

Rubinstein et al. (2013) recommend that future RCT should examine specific subgroups likely to respond to SMT, such as through the use of clinical prediction rules. Last review conducted on clinical prediction rules (Haskins et al., 2012) the search was performed in January 2010 and in addition investigated the clinical readiness of clinical prediction rules. None reviews we are aware of have investigated the effect of manipulation when using a clinical prediction rule.

1.2 Aim

The aim of this study was to systematically review RCTs on the effects of spinal manipulative therapy for low back pain in adults meeting a clinical prediction rule compared to those who do not meet a clinical prediction rule.

2.0 THEORY

Low back pain is as mentioned before a common and costly condition both in Norway and in the rest of the world, therefore effective treatments are needed (Lærum et al., 2007; Dagenais et al., 2008; Vos et al., 2012). In the theory section I will first describe what low back pain is. Then I will try to give an overview of spinal manipulative therapy and its implementation when used to treat low back pain and how the intervention might work. Lastly I will describe stratified care and methodological factors to consider in clinical prediction rule studies. The theory chapter will create the theoretical rationale behind this master's thesis.

2.1 What is low back pain?

Low back pain is defined as pain and discomfort that is localized below the costal margin and above the inferior gluteal folds, with or without referred leg pain. Including pain from L1 to S4 (van Tulder et al., 2006; Lærum et al., 2007).

There are a range of specific diseases and non-specific musculoskeletal disorders that can involve the lower back, most of which manifest as low back pain (Haldeman et al., 2012). Low back pain is thus considered to be a heterogenic condition (Kent and Keating, 2004; Haldeman et al., 2012) and the disorders have been classified in multiple ways over the years (Riddle, 1998; Jenkins, 2002; Haldeman et al., 2012).

The most widely accepted classification includes four clinical categories (Haldeman et al., 2012). One of the categories is low back pain with serious or systemic pathology (red flags) like cancer, inflammatory disorders, infections and fractures. Pathology in this category is rare and accounts for only 1-2% of patients with low back pain. Another category is low back pain with neurological deficit, often classified as specific low back pain. The primary neurological deficits that fall into this category include compression of nerve roots, the spinal cord or the cauda equina (Ibid). Modic change has also been classified into this category (Vibe Fersum et al., 2013). It has been estimated that 5-10% of patients presenting with low back pain fall into this category. A third category is non-specific spinal pain, which is the most common category, accounting for 90% or more of all people who experience low back pain. There is growing evidence that it is not possible to identify the structure, pathology or

source of pain in the majority of patients with these symptoms (Haldeman et al., 2012). In addition a number of systemic, abdominal and pelvic pathologies may present as low back pain and these pathologies comprise the fourth category (Ibid). In the diagnosis of low back pain it is recommended to perform a triage process where the therapist is screening for the small possibility of serious or specific pathology (O'Sullivan and Lin, 2014). The main goal is to distinguish between LBP amendable for manual therapy and low back pain which needs referral (Jenkins, 2002).

However, low back pain is not just about the back (O'Sullivan and Lin, 2014). In some cases the low back pain may have an additional psychosocial overlay that will prevent conservative treatment from being entirely effective (Jenkins, 2002; O'Sullivan and Lin, 2014). There is growing evidence that several provocative factors can influence on low back pain. These include cognitive factors (e.g. negative beliefs, stress, fear-avoidance and depression) and lifestyle factors (e.g. sedentary behavior, inactivity and sleep deficits) (Vibe Fersum et al., 2013; O'Sullivan and Lin, 2014). Also physical factors like pain provocative postures and movement patterns related to altered body schema, muscle guarding, pain behaviors and deconditioning are regarded as provocative factors (Vibe Fersum et al., 2013). It is therefore recommended to screen patients with non-specific LBP for psychosocial risk factors and addressing maladaptive beliefs and behaviors to better target care after the initial triage process (O'Sullivan and Lin, 2014). Lately there has been developed a multi-dimensional classification system screening for all the above mentioned categories and factors and thus accounting for all the aspects of low back pain and thereby interpreting an LBP disorder from a biopsychosocial perspective (O'Sullivan, 2005).

Low back pain can also be classified according to the stage of the disorder. Acute low back pain is defined as the duration of an episode persisting for no longer than 6 weeks, subacute pain 6 to 12 weeks or chronic low back pain lasting for 12 weeks or more. Recurrent pain is defined as a new episode after a symptom-free period of 6 months, but not an exacerbation of chronic low back pain (van Tulder et al., 2006).

Acute low back pain is usually self-limiting with a recovery rate of 90% within 6 weeks of the initial episode, and 2%-7% of people develop chronic pain. According to van Tulder et al. (2006) it is the recurrent and chronic pain that account for most of the workers' absenteeism (75% to 85%).

2.2 Spinal manipulative therapy

Spinal manipulative therapy is one of many therapies for the treatment of low back pain and is used worldwide by various practitioners like manual therapists, chiropractors and osteopaths (Rubinstein et al., 2013).

There is no uniform definition of manipulation. Several studies include both mobilization and manipulation as spinal manipulative therapy (SMT) (Rubinstein et al., 2011; Rubinstein et al., 2013) and others include only manipulation when terming it SMT (Bronfort et al., 2004). The terminology used to describe manual therapies has been identified as problematic (Flynn et al., 2008) since it can be confusing to the biomedical community who may not understand the difference in the terminology used by clinicians and researchers (Hebert and Perle, 2008). The authors recommend that in future work, researchers should clearly describe if manipulation, mobilization or both therapies are used (Ibid).

Mobilization use low-grade velocity, small-or large-amplitude passive movement techniques within the patient's joint range of motion and control that does not involve a thrust. Manipulation uses a high velocity impulse or thrust applied to a synovial joint over a short amplitude at or near the end of the passive or physiological range of motion, which can be accompanied with an audible click (Rubinstein et al., 2013). The presence or absence of an audible clicking sound during thrust manipulation does not seem to be related to outcomes in patients with low back complaints (Flynn et al., 2003; Flynn et al., 2006).

Evans (2002) suggests assessing mobilization and manipulation as separate clinical entities due to different biological effects. However, there are conflicting results about the effect of mobilization versus manipulation on low back pain. Bronfort et al. (2004) concluded in a systematic review that thrust manipulation provided more short-term pain relief than non-thrust mobilization in acute low back pain. Also Cleland et al. (2009) found a better effect of thrust manipulation compared to non-thrust mobilization in a subgroup of patients with low back pain who satisfied a clinical prediction rule. However, Cook et al. (2013a) found no difference between early use of thrust manipulation or non-thrust mobilization at the second visit follow-up or at discharge with any of the outcomes categories. There is, however; no evidence for the superiority of one manipulation technique over another (Fritz et al., 2007;

Cleland et al., 2009). Also, it seems like manipulation is a safe intervention to use (Cook, 2012).

2.3 How the intervention might work

Several hypotheses exist regarding the mechanisms behind the clinical effectiveness of spinal manipulation and mobilization (Bialosky et al., 2009). Roughly the theories can be divided into biomechanical and neurophysiological mechanisms (Rubinstein et al., 2013). The biomechanical theory is based on the thought that hypo-mobile or mal-aligned structures can be identified by clinical evaluative procedures and are followed by the application of specific techniques meant to "correct" the observed dysfunction thus suggesting a biomechanical mechanism (Bialosky et al., 2011). However, current literature does not support the validity of this model of clinical practice (Bialosky et al., 2008b). Research shows that individual therapists cannot agree on a specific location requiring spinal manipulative therapy (Seffinger et al., 2004). In addition when applied, spinal manipulative therapy forces are not specific to intended location (Ross et al., 2004), vary from practitioner to practitioner (Ngan et al., 2005), despite similar therapeutic effect, and only transient biomechanical effect are supported by studies which quantifies motion (Gal et al., 1997; Colloca et al., 2006), but not lasting positional change (Tullberg et al., 1998; Hsieh et al., 2002; Bialosky et al., 2009).

Many reports suggest that neurophysiological mechanisms may provide the most plausible explanations for the effectiveness of spinal manipulative therapy (Bialosky et al., 2008b; Bialosky et al., 2009; Bialosky et al., 2011). Bialosky et al. (2009) suggests a comprehensive model that categorizes neurophysiological mechanisms as those likely originating from a peripheral mechanism, spinal cord mechanisms, and/or supraspinal mechanisms. The model suggests that a mechanical force from for example spinal manipulative therapy initiates a cascade of neurophysiological responses from the peripheral and central nervous system which are responsible for the clinical outcomes (Bialosky et al., 2009).

Bialosky et al. (2008b) summarizes some effects that have been associated with spinal manual therapy like increased afferent discharge (Colloca et al., 2003), motor neuron pool depression (Dishman and Burke, 2003), changes in motor activity, such as reflexive muscle activation (Herzog et al., 1999) and decreased resting electromyographic signal intensity (DeVocht et al., 2005), and reduction of pain perception in response to a standard stimulus (Vicenzino et

al., 1996; George et al., 2006). The studies suggests that spinal manipulative therapy has a direct effect on the central nervous system and that clinical outcomes associated with spinal manipulative therapy may result from multiple neurophysiological mechanisms working alone or in combination (Bialosky et al., 2008b). These include gating of nociception at the spinal cord due to stimulation of the mechanoreceptors (Pickar and Wheeler, 2001), direct stimulation of a spinal reflex to alter muscle activity (Indahl et al., 1997), or stimulation of pain centers in the brain (Wright, 1995). In addition Teodorczyk-Injeyan et al. (2006) observed a significant reduction of blood and serum level cytokines in individuals receiving spinal manipulative therapy that was not observed in those receiving sham treatment or in a control group. The study suggests a potential mechanism of action of spinal manipulative therapy on musculoskeletal pain mediated by the peripheral nervous system (Bialosky et al., 2009).

Additionally effectiveness of spinal manipulative therapy may be related to nonspecific neurophysiological effects such as placebo, treatment expectation and psychological factors (Williams et al., 2007; Bialosky et al., 2008b; Bialosky et al., 2009). These neurophysiological effects are related to supraspinal descending inhibition due to associated changes in the opioid system (Sauro and Greenberg, 2005), dopamine production (de la Fuente-Fernandez et al., 2006) and central nervous system (Petrovic et al., 2002; Wager et al., 2004; Matre et al., 2006) which have been observed in studies unrelated to spinal manipulative therapy (Bialosky et al., 2009).

Expectation and conditioning are thought of as primary mechanisms in placebo hypoalgesia (Bialosky et al., 2011). If a patient expect or think the treatment will be beneficial studies have shown to enhance the hypoalgesic effect (Ibid). Placebo effect is also found to be maximized in studies where an instructional set is intended to enhance expectation e.g. if the patient is told the agent they have just received is known to powerfully reduce pain in some patients (Ibid). In addition placebo-related hypoalgesia is enhanced through learning and conditioning effect. Research has shown that placebo related hypoalgesia is improved when a painful stimulus is surreptitiously lowered immediately following the application of a placebo (Ibid). Placebo is also enhanced in participants who observe others report a hypoalgesia response to the same placebo. It therefore seems like past experience is significant in placebo-related hypoalgesia (Ibid). Also worth noticing is the results from the study of Bialosky et al. (2008a) where the researchers found a significant increase in pain perception to occur

following spinal manipulative therapy in the low back of participants receiving negative expectations, suggesting a patient with a negative experience and thus negative expectation will not likely benefit from spinal manipulative therapy. Bialosky et al. (2011) therefore suggest that manual therapists should ask the patient about prior experience with spinal manipulative therapy with the likely potential of an enhanced placebo response in patients who report prior successes.

Important to also know is that factors related to negative mood can alter placebo-related hypoalgesia. Specifically factors like, desire for pain relief, fear of pain and anxiety are all negatively correlated with placebo-related hypoalgesia (Bialosky et al., 2011). For example a Fear Avoidance Beliefs Questionnaire is included as one of the criteria to identify patients most likely to benefit from spinal manipulative therapy, where the patients most likely to benefit have a low score of fear-avoidance (Flynn et al., 2002). Also the UK BEAM Trial Team (2004) found that patients with fear avoidance beliefs were less likely to improve following spinal manipulative therapy. According to Bialosky et al. (2011) the mechanisms of the relationship between psychological factors and clinical outcomes related to manual therapy are not established and factors related to negative mood may serve as both a prognostic factor for a specific intervention and as a means to enhance a corresponding placebo response. Williams et al. (2007) found in a systematic review that there was some evidence that spinal manipulation improved psychological outcomes compared with verbal interventions. If the back pain is secondary to a psychological disturbance such as depression the authors speculate if it could be due to reducing distressing symptoms such as pain and fear and thus improve psychological outcome (Ibid).

Thus the mechanisms through which manual therapy inhibits musculoskeletal pain are likely multifaceted and related to the interaction between the intervention, the patient, the practitioner, and the environment (Bialosky et al., 2011). It is recommended that manual therapists should take steps to maximize placebo mechanisms through minimizing negative mood, maximizing realistic expectations, and drawing on patient preferences and past experience for evidence-based interventions (Ibid).

2.4 Effect of spinal manipulative therapy on low back pain

Numerous RCTs have been conducted both on acute and chronic low back pain and several systematic reviews have summed up the research on the effect of SMT on LBP.

In 2003 three systematic reviews of SMT for the treatment of LBP were published (Assendelft et al., 2003; Cherkin et al., 2003; Ferreira et al., 2003). All reviews concluded that SMT is only effective when compared to sham or ineffective treatments and had no significant benefits over other conservative treatment like physical therapy, exercises, analgesics and general practitioner care for both acute and low back pain (Assendelft et al., 2003; Cherkin et al., 2003; Ferreira et al., 2003). All reviews used a meta-analysis to analyze the treatment effects that is considered to be an advantage if certain criteria are followed. By summarizing the results of multiple studies, a meta-analysis can increase the sample size and thus the power to study effects of interests (Walker et al., 2008). A limitation of Assendelft et al. (2003) is that the meta-analysis did not distinguish between patients with and without the presence of leg pain. Since the prognosis is considered to be different in patients with and without radiating symptoms, this may have influenced the results. In addition the authors mention another limitation of the review which is the uneven quantity and quality of the original studies (Assendelft et al., 2003).

Bronfort et al. (2004) did a systematic review to find out about the efficacy of spinal manipulation and mobilization for low back pain and neck pain. A best evidence synthesis incorporating explicit, detailed information about outcome measures and interventions was used to evaluate treatment efficacy. Six (n=662) acute low back pain studies were included. The validity score of the included studies varied from 19-69 %. The results showed that there was moderate evidence that SMT provided more short-term relief than mobilizations and detuned diathermy, and limited evidence of faster recovery than a physical therapy treatment strategy (Ibid). For chronic LBP 11 (n=3068) RCTs were included. The results showed there was moderate evidence that SMT had an effect similar to NSAID, SMT/MOB was effective in the short term when compared with placebo and general practitioner care, and SMT/MOB was effective in the long term when compared with physical therapy. There was limited to moderate evidence that SMT was better than physical therapy and home back exercise in both the short and long term. There was limited evidence that SMT was superior to sham SMT in the short term and superior to chemonucleolysis for disk herniation in the short term. An

advantage with this study is that the studies had to have 10 or more subjects receiving SMT and/or MOB to be included in the review. A limitation is that of the 43 trials accepted into evidence, 29 (67%) had relatively low validity scores (6-44) (Bronfort et al., 2004).

The Cochrane collaboration published an update of the previous systematic review from Assendelft et al. (2003). The update was split into two parts according to the duration of the complaint, namely acute (Rubinstein et al., 2013) and chronic (Rubinstein et al., 2011) low back pain and focus on the effect SMT has on these conditions. In the review of acute low back pain 20 studies (2674 participants) were included and study sample size ranged from 36 to 323. In total, 6 trials (30% of all included trials) had a low risk of bias. The authors found there is low- to very low-quality evidence suggesting no difference in effect for SMT for acute low back pain compared with inert interventions, sham SMT or as adjunct therapy. Also, there was very low to moderate quality of evidence suggesting there was no difference in effect for SMT when compared with other recommended therapies. The evaluation is limited by the few number of studies (Rubinstein et al., 2013). An advantage of the updated review is that it followed the recently published methodological guidelines from the Cochrane Back Review Group (Furlan et al., 2009). In the review of effect of SMT on chronic LBP 26 RCTs (total participants = 6070) were included. High quality evidence suggests that there is no clinically relevant difference between SMT and other interventions for reducing pain and improving function in patients with chronic low back pain (Rubinstein et al., 2011).

SMT is recommended by many clinical practice guidelines, which is based on previous systematic reviews; however, not all clinical practice guidelines support SMT (Dagenais et al., 2010; Koes et al., 2010). In the acute phase most guidelines support the use of SMT as a therapeutic option; however, the Australian and Spanish guidelines do not support use of SMT in the acute phase. Also in the chronic phase most guidelines recommended SMT, only the New Zealand guideline did not recommend it (Dagenais et al., 2010; Koes et al., 2010). The guidelines recommended SMT for short-term symptomatic relief in addition to other interventions (Dagenais et al., 2010). Thus it seems like there are some discrepancies for recommendations regarding SMT (Koes et al., 2010). The reasons for these differences are not clear. Koes et al. (2010) speculate if the underlying evidence is not strong enough to result in similar recommendations regarding SMT.

To sum up, several systematic reviews concluded that SMT was no more effective in reducing pain and improving function than other interventions for both acute and chronic low back pain. The quality of the studies varied and the few number of studies limited the evaluation of the effect manipulation had on acute low back pain. Recommendations for the use of manipulation on low back pain also differ in the clinical guidelines. Rubinstein et al. (2013) recommend that future RCTs should examine specific subgroups.

2.5 Stratified care

An argument for achieving better treatment results in low back pain is to match groups of patients with the most appropriate treatment for their profile which is referred to as stratified care (Foster et al., 2009; Foster et al., 2013). Stratified care therefore represents a more targeted approach in the treatment of low back pain compared to the "one size fits all" approach, with a potential of a better treatment effect and reduced costs (Foster et al., 2011; Foster et al., 2013). Foster et al. (2013) consider stratified care as three approaches, namely those based on patients' prognosis (risk), those based on underlying causal mechanisms and those based on treatment responsiveness with some overlap between them (Figure 1). In this theory chapter I will focus on stratified care based on treatment responsiveness.

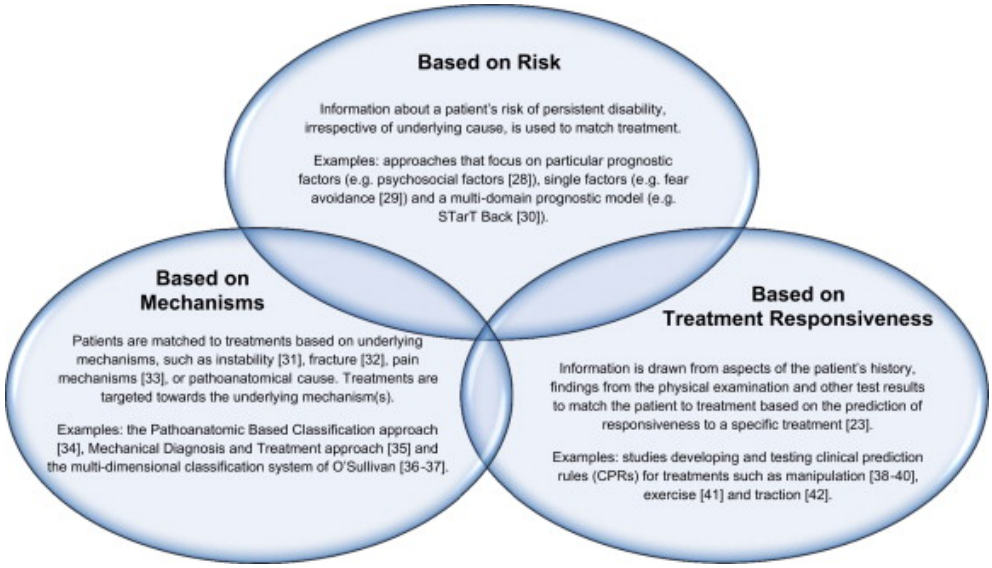

Figure 1: Stratified care approaches (Foster et al., 2013)

One example of stratified care based on treatment responsiveness is studies developing and testing clinical prediction rules (Foster et al., 2013).

2.5.1 Clinical prediction rule

A clinical prediction rule is a clinical tool that quantifies the individual contributions that various components of the history, physical examination, and basic laboratory results make toward the diagnosis, prognosis, or likely response to treatment in a patient. Clinical prediction rules attempt to standardize, simplify, and increase the accuracy of clinicians'

diagnostic and prognostic assessments (McGinn et al., 2008; Haskins et al., 2012). Low back pain is considered an ideal target for clinical prediction rules due to its heterogeneous population and numerous treatment alternatives. The need to subgroup, or classify, patients with nonspecific, heterogeneous diagnostic labels into smaller categories based on likely response to a specific treatment has been identified as a central aspect of clinical decision making in physical therapy (Fritz, 2009).

Flynn et al. (2002) developed a clinical prediction rule to identify a subgroup of patients with non-specific low back pain who were likely to benefit from spinal manipulation. The derivation study identified 5 variables (Table 1) and the presence of four of five variables in the prediction rule increased the likelihood of success with manipulation from 45% to 95% (Ibid). Later Fritz et al. (2005) derived a more pragmatic two-factor rule from the Flynn prediction rule (Table 1). The results showed a positive likelihood ratio of 7.2 for a positive outcome in patients with low back pain positive on both predictor variables and treated with manipulation (Ibid).

Table 1: Clinical prediction rules predictor variables in LBP

CPR to identify patients with LBP most likely to benefit from manipulation (Flynn et al., 2002)	**Abbreviated CPR to identify patients with LBP most likely to benefit from manipulation** (Fritz et al., 2005)
• Duration of symptoms <16 days • No symptoms distal to the knee • Fear-Avoidance Beliefs Questionnaire work subscale score <19 • At least one hip with >35° of internal rotation range of motion • Hypomobility in the lumbar spine	• Duration of symptoms <16 days • No symptoms distal to the knee

CPR = Clinical Prediction Rule. LBP = Low Back Pain

Several systematic reviews have investigated the clinical readiness of the different clinical prediction rules. All studies concluded that the current body of evidence does not enable confident direct clinical application of any of the identified clinical prediction rules. Few clinical prediction rules have been tested in RCTs, there is a lack of validation studies and

validation studies have shown contradictory results (Beneciuk et al., 2009; May and Rosedale, 2009; Stanton et al., 2010; Haskins et al., 2012).

2.5.2 Methodological factors to consider in clinical prediction rule studies

Clinical prediction rules are designed to improve decision making and it is therefore important that they are developed and validated according to rigorous methodological standards (Childs and Cleland, 2006). McGinn et al. (2000) suggested a clinical prediction rule should go through a 3-step process with developing and testing prior to widespread implementation in clinical practice. The first step is to develop the rule through a derivation study, then progressing to a process of validation and then subsequent investigation of its clinical impact (Childs and Cleland, 2006; Nee and Coppieters, 2011; Haskins et al., 2012). In this theory chapter I will just go through the methodological factors to consider in validation studies since this review only includes validation studies.

The validation process investigates a rule's performance and generalizability to other patient populations, clinicians and clinical settings (Haskins et al., 2012). Narrow validation of a clinical prediction rule is when a rule is tested in a similar patient population and clinical setting to the derivation study. The confidence in the rule increases as the rule is validated more broadly in various settings comprising different clinicians and patients with differing prevalence of disease or injury and with differing responsiveness to treatment (Kent et al., 2010; Haskins et al., 2012). Clinical prediction rules that demonstrate consistent and strong performance after a broad validation process are considered ready to be applied in clinical practice with confidence in their accuracy (Haskins et al., 2012).

To decide whether a treatment-related clinical prediction rule has a prescriptive validity a specifically designed RCT that compares the clinical prediction rule treatment to an alternate treatment is needed (Hancock et al., 2009a; Nee and Coppieters, 2011). Enrolment criteria and the clinical prediction rule treatment protocol need to be the same as in the original study. In addition the RCT should use standard methods that ensure a valid assessment of the effect of treatment e.g. adequate randomization and blinding of outcome assessors. However, there are additional issues to consider when assessing the prescriptive validity of a clinical prediction rule (Nee and Coppieters, 2011). Each patient's status on the rule needs to be concealed throughout the trial i.e. the treating clinician should not know whether the patient is

positive or negative on the clinical prediction rule. If the clinician knows the clinical prediction rule status it could reduce the ability to apply the assigned treatment consistently during the trial. Also outcome assessors should be unaware of each patient's status on the clinical prediction rule to avoid measurement bias (Ibid).

In order to say something about rule performance the study has to include both rule positive and rule negative patients (Haskins et al., 2012). Studies who only include patients who are positive on the rule can't tell anything about the predictive performance of the tool (Ibid). For a treatment-related clinical prediction rule to have prescriptive validity, the clinical prediction rule treatment effect needs to be significantly greater for patients who are positive on the rule than patients who are negative on the rule. Statistically this is known as testing for an interaction between the treatment group assignment and the status on the clinical prediction rule (Nee and Coppieters, 2011). A RCT that shows a clinical prediction rule treatment has prescriptive validity provides strong evidence that the clinical prediction rule treatment is a better option for patients who are positive on the rule relative to the alternate treatment. It is also important that researchers include a large enough sample to make sure the test for an interaction is valid (Hancock et al., 2009a; Nee and Coppieters, 2011).

3.0 MATERIALS AND METHODS

This systematic review followed the recently published method guidelines for systematic reviews in the Cochrane Back Review Group (Furlan et al., 2009) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

3.1 Criteria for considering studies for this systematic review

3.1.1 Inclusion criteria

Study design

Only randomized controlled studies were included.

Population

- Adult participants (≥ 18 year of age) with a mean duration of low back pain for 6 weeks or less.
- The population must be sub grouped at baseline according to a manipulation clinical prediction rule.
- The clinical prediction rule should contain 2 or more predictor variables.
- The studies should also include patients who are positive and negative on the clinical prediction rule to be able to say something about rule performance (Nee and Coppieters, 2011).

Intervention

Studies that used spinal manipulative therapy or mobilization as experimental intervention were included.

Comparison

No limits were set on the control group, or the setting (i.e., whether from primary, secondary or tertiary care).

Outcome

Only patient-reported outcome measures were evaluated.

The effect was evaluated from the change in pain, functional status and quality of life:

- Pain, measured by a visual analogue or other pain scale (e.g., visual analogue scale (VAS), numerical rating scale (NRS), Mc Gill pain score.

- Back-pain specific functional status, measured by a back pain specific scale (e.g. Roland-Morris disability questionnaire, Oswestry Disability Index)
- Perceived health status or quality of life (e.g., subscale from the SF-36, the EuroQol thermometer).

For a study to be included, the assessment of potential predictor variables was required to be performed by a physiotherapist to ensure their direct relevance to the primary research aim.

Only English and Scandinavian literature was reviewed.

3.1.2 Exclusion criteria

Study design

Studies using an inadequate randomization procedure (e.g., alternate allocation, allocation based on birth date) were excluded.

3.2 Search Methods for identification of studies

3.2.1 Electronic searches

The project leader (ML) searched electronically with assistance from an experienced librarian for RCTs in the following databases (last search date: 27th of august 2014); The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED, PEDro, SVEMED+ and Index to Chiropractic Literature using sensitive search strategies for identifying LBP, manipulation and clinical prediction rule studies. PubMed was also searched (in addition to MEDLINE) to identify recently published electronical articles not yet available in MEDLINE. A sensitive search strategy for clinical prediction rules (Ingui and Rogers, 2001) that has been used in previous systematic reviews (Beneciuk et al., 2009; May and Rosedale, 2009) was employed in combination with the search strategy recommended by the Cochrane Back Group (Furlan et al., 2009) for identifying articles relevant to LBP with some modifications as recommended by the experienced librarian. Medical subject headings (MeSH) and free text word were used in combinations like back pain, backache AND manipulation, manipulate AND prediction rule. Full search strategy for some of the databases is available in appendix 1-5.

3.2.2 Searching other resources

The reference list of all the included studies and relevant systematic reviews were also screened. Experienced researchers and authors of identified RCTs in the field of clinical prediction rule studies were contacted to check for any additional studies.

Identified studies were downloaded into an electronic reference management system (EndNote version X6) and duplicates were removed.

3.3 Data collection and analysis

3.3.1 Selection of studies

Two reviewers independently conducted the first-stage screening of titles and abstracts based upon the selection criteria. The studies decided by both reviewers to fulfill the selection criteria progressed to the second-stage of eligibility screening. Also studies identified by citation tracking and hand searching of relevant journals was progressed to the second-stage. The full text of included studies was obtained and examined by both reviewers. During this second stage of screening, agreement between the reviewers determined inclusion (Figure 2). Disagreements were resolved with a consensus meeting between the reviewers.

3.3.2 Data extraction and management

A standardized form was used to extract the following qualitative data from the full text articles: Study characteristics (e.g., country where the study was conducted, recruitment modality, RoB), patient characteristics (e.g., number of participants, age, sex), description of the experimental and control interventions, duration of follow-up, types of outcomes assessed, and the authors´ results and conclusions.

3.3.3 Assessment of Risk of Bias in Included Studies

To conduct the RoB assessment for RCTs the two reviewers used the 12 criteria recommended by the Cochrane Back Review Group were used (Furlan et al., 2009). Disagreement was resolved in a consensus meeting. The studies were rated as having a “low risk of bias” when at least 6 of the 12 Cochrane Back Review Group criteria have been met and the study has no serious flaws (e.g. 80% drop-out rate in 1 group). Studies with serious

flaws, or those in which fewer than 6 of the criteria are met were rated as having a “high risk of bias”.

4.0 RESULTS

4.1 Study selection

The database search strategy resulted in 224 studies. Another 4 studies were identified via hand-searching relevant journals and citation tracking of included studies. After removing duplicate records, 168 studies were screened via title and abstract. A total of 14 studies progressed to the second stage of screening. The full-text paper of these studies were found and reviewed with 2 studies composing the final included sample (Figure 2).

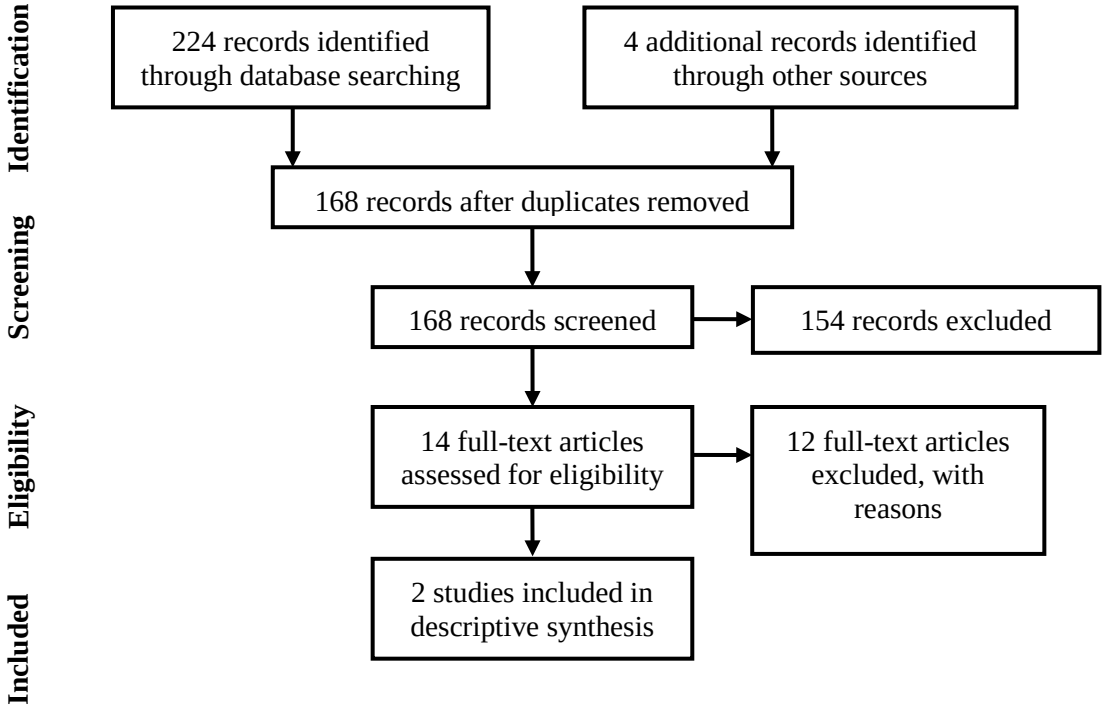

Figure 2: Study flow diagram. Summary of selection process.

4.2 Excluded studies

Most of the studies were excluded because they only included clinical prediction rule positive patients in the analysis (Cleland et al., 2009; Hallegraeff et al., 2009; Sutlive et al., 2009; Schenk et al., 2012; Cook et al., 2013b; Donaldson et al., 2013; Learman et al., 2014). Other reasons for exclusion were the study was not a clinical prediction rule manipulation study (Paatelma et al., 2008; Rabin et al., 2014), secondary analysis not relevant (Childs et al., 2006; Hancock et al., 2009b) and one study did not provide a subgroup of manipulation x rule status (Brennan et al., 2006).

4.3 Characteristics of included studies

One of the studies originated from USA and was published in 2004 and the other study from Australia was published in 2008. Both studies used the 5 variables clinical prediction rule derived by Flynn et al. (2002). A total of 370 patients from both genders were included in the trials. The mean age of the patients in Hancock et al. (2008b) was a bit higher than the patients in Childs et al. (2004). The duration of symptoms also differed in the two studies. In one of the studies the therapists used both thrust manipulation and mobilization as intervention, but in the other only thrust manipulation were used. Both studies measured pain using an 11-point scale where 0 equaled no pain and 10 equaled worst possible pain. Function was measured with a modified Oswestry Disability Questionnaire in one of the studies and a 24-point Roland Morris disability questionnaire in the other study. The follow up of pain and function measurement were almost similar (1, 4 and 24 weeks and 1,2,4 and 12 weeks), with one of the studies measuring slightly longer. Details of the characteristics of included studies are written in table 2 and more detailed in appendix 6 and 7.

Table 2: Study characteristics and results of included studies

Author/Country	Design/CPR	Setting	Participants	Intervention	Control	Result
Childs et al (2004) USA	RCT 5 variables 4/5 variables= CPR+[3]	Health care facilities within the US Air force	131 patients mean 33.9 years old 42% female median 27 days of symptoms	2 sessions of manipulation followed by 3 sessions of exercise (4 weeks)	5 sessions of exercise only (4weeks)	Patients who were CPR+ and received manipulation experienced significantly better outcomes (pain and function) at 1 week, 4 weeks and 6 months than patients who were CPR+ and received exercise or patients who were CPR-[4] and received exercise or manipulation
Hancock et al (2008) Australia	RCT 5 variables 4/5 variables = CPR+[3]	General practice clinics in Sydney	239 patients mean 40.7 years old 44% female mean 9 days of symptoms	Spinal manipulative therapy[1] 2 or 3 x per week (4 weeks)	Placebo therapy[2] 2 or 3 times per week (4 weeks)	The clinical prediction rule proposed by Childs et al 2004 did not generalize to patients presenting to primary care with acute low back pain who received a course of spinal manipulative therapy[1].

[1] Mobilization and thrust manipulation. [2] Detuned pulsed ultrasound, [3] Clinical prediction rule positive, [4] Clinical prediction rule negative

4.4 Risk of Bias in included studies

Quality scoring of the included studies is provided in table 3 and more detailed in appendix 6 and 7. Both studies were rated as having a low risk of bias as they fulfilled more than 6 of the 12 criteria from the Cochrane Back Review Group. However, one of the studies (Hancock et al., 2008b) had a slightly higher study quality than the other (Childs et al., 2004). Loss to follow up in Childs et al. (2004) was more than 30% in one of the groups; however, in Hancock et al. (2008b) loss to follow up was less than 2%.

Table 3: Risk of bias summary: review authors' judgments about each risk of bias item for the included studies.

RoB/Author	Childs et al (2004)	Hancock et al (2008)
1. Random sequence generation (selection bias)	+	+
2. Allocation concealment (selection bias)	+	+
3. Patients blinding – All outcomes? (performance and detection bias)	-	-
4. Therapist blinding – All outcomes? (performance and detection bias)	-	-
5. Outcome assessors blinding – All outcomes? (performance and detection bias)	-	-
6. Incomplete outcome data (attrition bias), All outcome - drop-outs?	-	+
7. Incomplete outcome data (attrition bias): All outcomes – Intention to treat analysis?	+	+
8. Selective reporting (reporting bias)	?	?
9. Similarity of baseline characteristics?	+	+
10. Co-intervention avoided or similar?	+	+
11. Compliance acceptable?	?	?
12. Timing outcome assessment similar?	+	+
Overall risk of bias	+	+

+ = Yes, - = No, ? = Unsure. RoB = Risk of Bias

4.5 Effect of interventions

Pain was measured by both studies; however, only Hancock et al. (2008b) presented the pain numbers (Table 4). The results show that there were no statistical significant differences between the SMT versus rule status in any of the follow up time points. The only statistical significant difference on pain was between clinical prediction rule positive and clinical prediction rule negative patients in the 2 weeks follow up i.e. positive status on the rule tended to predict better prognosis regardless of treatment received. Childs et al. (2004) found that patients who were clinical prediction rule positive and received manipulation experienced significantly less pain at 1 week, 4 weeks and 6 months than patients who were clinical prediction rule positive and received exercise or patients who were clinical prediction rule negative and received exercise or manipulation.

Table 4: Influence of manipulation, clinical prediction rule and interaction on pain

Author	Outcome measure	Comparison	Difference (95% CI)	P Value	Follow up Time point
Hancock et al (2008)	VAS[1]	SMT vs Sham	0.013 (-0.826 to 0.852)	0.976	1 week
	VAS	CPR+ vs CPR-	-0.693 (-1.462 to 0.076)	0.077	1 week
	VAS	SMT x rule status	0.308 (-0.781 to 1.396)	0.578	1 week
	VAS	SMT vs Sham	-0.455 (-1.330 to 0.420)	0.306	2 weeks
	VAS	CPR+ vs CPR-	-0.995 (-1.796 to -0.193)	0.015	2 weeks
	VAS	SMT x rule status	0.114 (-1.021 to 1.248)	0.843	2 weeks
	VAS	SMT vs Sham	-0.113 (-0.823 to 0.597)	0.754	4 weeks
	VAS	CPR+ vs CPR-	-0.540 (-1.191 to 0.110)	0.103	4 weeks
	VAS	SMT x rule status	-0.215 (-1.135 to 0.705)	0.645	4 weeks
	VAS	SMT vs Sham	-0.208 (-0.969 to 0.554)	0.592	12 weeks
	VAS	CPR+ vs CPR-	-0.367 (-1.066 to 0.333)	0.303	12 weeks
	VAS	SMT x rule status	0.051 (-0.934 to 1.036)	0.919	12 weeks

[1] 11 point scale; 0 = no pain, 10 = worst possible pain. Negative values represent improved outcomes. Results regarding the ability of the prediction rule to identify patients who respond to SMT are presented in the line SMT x rule status. SMT = spinal manipulative therapy. CI = confidence interval. VAS = visual analogue scale. CPR = clinical prediction rule. CPR+ = Clinical Prediction Rule positive. CPR- = Clinical Prediction Rule negative.

Function is presented in both studies. The results in Childs et al. (2004) demonstrated that patients who were positive on the rule and received manipulation experienced greater improvement in both the 1- and 4-week and the 6-month follow up compared to those who were negative on the rule and received manipulation (Table 5). In Hancock et al. (2008b) the results showed no statistically significant effects between status on the rule and manipulation (Table 6).

In the study of Hancock et al. (2008b), positive status on the rule tended to predict better prognosis regardless of treatment received and this was statistically significant for function at 2 and 12 weeks.

Furthermore, Childs et al. (2004) found that patients who were positive on the rule and received manipulation also experienced greater improvement in 1- and 4-week function outcomes than patients who were positive on the rule but received the exercise intervention. The difference was also maintained at the 6-month follow-ups. The same authors also found that patients who received manipulation, regardless of rule status, experienced greater improvements in function than those who did not receive manipulation (Childs et al., 2004).

Among patients who were positive on the rule, the number needed to treat for benefit for a successful outcome was 1.3 (95% CI 1.1 to 1.9) at 1 week with manipulation and 1.9 (95% CI 1.4 to 3.5) at 4 weeks with manipulation (Childs et al., 2004).

None of the studies measured quality of life.

Table 5: Influence of manipulation, clinical prediction rule and interaction on function

Author	Outcome measure	Comparison	Difference (95% CI	P value	Follow up Time point
Childs et al (2004)	Modified ODQ[1]	Manipulation vs exercise	9.2 (4.4 to 14.1)	<0.001	1-week
	Modified ODQ	Manipulation x rule status	15.0 (8.5 to 21.5)	<0.001	1-week
	Modified ODQ	Manipulation (CPR+) vs exercise (CPR+)	20.4 (13.0 to28.8)	<0.001	1-week
	Modified ODQ	Exercise (CPR+) vs exercise (CPR-)	-1.9 (4.9 to -8.6)	>0.2	1-week
	Modified ODQ	Manipulation vs exercise	8.3 (2.4 to 14.2)	0.006	4-week
	Modified ODQ	Manipulation x rule status	15.2 (7.1 to 23.3)	<0.001	4-week
	Modified ODQ	Manipulation (CPR+) vs exercise (CPR+)	14.6 (5.4 to 23.8)	0.003	4-week
	Modified ODQ	Exercise (CPR+) vs exercise (CPR-)	6.5 (-1.8 to 14.8)	0.127	4-week
	Modified ODQ	Manipulation vs exercise	10.1 (4.3 to 15.9)	0.001	6-month
	Modified ODQ	Manipulation x rule status	10.3 (2.2 to 18.4)	0.014	6-month
	Modified ODQ	Manipulation (CPR+) vs exercise (CPR+)	12.9 (3.5 to 22.3)	0.008	6-month
	Modified ODQ	Exercise (CPR+) vs exercise (CPR-)	6.8 (-1.5 to 15.2)	0.112	6-month

[1] 0% = no disability, 100% max disability. Higher values represent larger improvements in function. Results regarding the ability of the prediction rule to identify patients who respond to SMT are presented in the line manipulation x rule status. ODQ = Oswestry Disability Questionnaire. CPR+ = Clinical Prediction Rule positive. CPR- = Clinical Prediction Rule negative.

Table 6: Influence of manipulation, clinical prediction rule and interaction on function

Author	Outcome measure	Comparison	Difference (95% CI)	P value	Follow up Time point
Hancock et al (2008)	RMDQ[1]	SMT vs Sham	-1.753[2] (-3.853 to 0.348)	0.102	1 week
	RMDQ[1]	CPR+ vs CPR-	-1.802 (-3.749 to 0.144)	0.069	1 week
	RMDQ	SMT x rule status	1.763 (-0.970 to 4.496)	0.205	1 week
	RMDQ	SMT vs Sham	-2.669 (-4.782 to -0.556)	0.014	2 weeks
	RMDQ	CPR+ vs CPR-	-2.139 (-4.101 to -0.178)	0.033	2 weeks
	RMDQ	SMT x rule status	2.378 (-0.381 to 5.136)	0.091	2 weeks
	RMDQ	SMT vs Sham	-1.501 (-3.307 to 0.306)	0.103	4 weeks
	RMDQ	CPR+ vs CPR-	-1.625 (-3.301 to 0.052)	0.057	4 weeks
	RMDQ	SMT x rule status	1.081 (-1.268 to 3.431)	0.366	4 weeks
	RMDQ	SMT vs Sham	-1.751 (-3.622 to 0.120)	0.066	12 weeks
	RMDQ	CPR+ vs CPR-	-2.164 (-3.901 to -0.428)	0.015	12 weeks
	RMDQ	SMT x rule status	2.314 (-0.120 to 4.747)	0.062	12 weeks

[1] 24 point RMDQ (0 = low disability, 24 = high disability) [2] Negative values represent improved outcomes. RMDQ = Roland Morris disability questionnaire. CPR+ = Clinical Prediction Rule positive. CPR- = Clinical Prediction Rule negative.

5.0 DISCUSSION

The aim of this study was to systematically review RCTs on the effects of spinal manipulative therapy for low back pain in adults meeting a clinical prediction rule compared to those who do not meet a clinical prediction rule.

5.1 Summary of results

Two studies fulfilled the inclusion criteria (Childs et al., 2004; Hancock et al., 2008b) and showed conflicting results. Childs et al. (2004) were the first study to validate a clinical prediction rule developed by Flynn et al. (2002). The results showed that patients who were positive on the clinical prediction rule and received manipulation experienced significantly better effects on pain and function at 1 week, 4 weeks and 6 months than patients who were rule negative and received manipulation. However, the results in the other study (Hancock et al., 2008b) showed no significant differences in effects on pain and function between status on the rule and manipulation in any of the follow up time-points (1 week, 2 weeks, 4 weeks and 12 weeks).

Several authors have discussed the reasons for the lack of agreement between the studies. One of the reasons mentioned is the difference in treatment provided in the two studies (Hancock et al., 2008a; Hancock et al., 2008b; Hebert and Perle, 2008; Haskins et al., 2012). The therapists in Childs et al. (2004) used only high velocity-thrust manipulation whereas the therapists in Hancock et al. (2008b) used high velocity thrust-manipulation in only 5% of the cases and mobilization in the rest. This could mean the rule does not generalize to treatments mixing manipulation and mobilization (Hancock et al., 2008b; Cleland et al., 2009). Evans (2002) suggests assessing mobilization and manipulation as separate clinical entities due to different biological effects. There are conflicting results about the effect of mobilization versus manipulation on low back pain. Bronfort et al. (2004) concluded, in a systematic review, there was moderate evidence that thrust manipulation provided more short-term pain relief than non-thrust mobilization in acute low back pain. Also Cleland et al. (2009) found a better effect of thrust manipulation compared to non-thrust mobilization in a subgroup of patients with low back pain who satisfied a clinical prediction rule. However, Cook et al. (2013a) found no difference between early use of thrust manipulation or non-thrust mobilization at the second visit follow-up or at discharge with any of the outcomes categories.

Hancock et al. (2008b) speculate it is possible the rule is useful for the high-velocity manipulation technique used in Childs et al. (2004); however, this needs to be demonstrated in a new setting with different patients and clinicians before being recommended for clinical practice.

Hancock et al (2008a) and (2008b) also speculates if the differences could be due to different patients, settings or co-interventions in the two studies. If so the clinical prediction rule have failed to generalize to a different setting than in the original study and thus failed to be validated broadly. However, Hebert and Perle (2008) argue that Hancock et al. (2008b) failed to replicate the study of Childs et al. (2004) due to a different study protocol and therefore the result do not test the validity of the prediction rule. Further investigation using the same study protocol as Childs et al. (2004) in different settings is required to determine if the CPR does generalize beyond a narrow validation (Hancock et al., 2008a; Hebert and Perle, 2008; Kent et al., 2010). Another explanation for the disagreement between the studies is that subgroup analyses within trials can generate spurious results. The original positive result in Childs et al. (2004) may have been a type 1 error meaning it was detected an effect that was not present (Brookes et al., 2001; Hancock et al., 2008b). It is important that future trials have enough power to do reliable subgroup analyses (Brookes et al., 2001).

An interesting finding in the study of Hancock et al. (2008b) was the statistical significant difference between CPR+ and CPR- patients on pain in the 2 week follow up (-0.995; 95% CI -1.796 to -0.193; p = 0.015) and on function in the 2-week (-2.139; 95% CI -4.101 to -0.178; p = 0.033) and 12-week (-2.164; 95% CI -3.901 to -0.428; p = 0.015) follow up i.e. positive status on the rule tended to predict better prognosis regardless of treatment received. Cook et al. (2013b) had similar results. Also in this study individuals with LBP who received both manipulation and mobilization and met the CPR for manipulation were likely to respond favorably compared to those who did not meet the CPR. The authors concluded that meeting the clinical prediction rule was prognostic for all outcome measures and should therefore be considered a universal prognostic predictor (Cook et al., 2013b). As discussed in Cook et al. (2013b), these findings is supported by the suggestion of Kent et al. (2010) who, after use of a novel formula, identified that the CPR for lumbar manipulation was both prognostic and prescriptive of a positive response to a specific treatment.

The study of Hancock et al. (2008b) included only acute low back pain patients. Acute low back pain is usually self-limiting with a recovery rate of 90% within 6 week of the initial episode (Deyo and Weinstein, 2001; van Tulder et al., 2006). This could mean that patients in both groups improved as a natural course of the condition regardless of what treatment they got and therefore causing the non-significant effect of manipulation compared to placebo treatment. Placebo is traditionally considered an inert intervention; however, the pain research literature suggests that placebo is an active hypoalgesic agent (Bialosky et al., 2011). To control for placebo and the natural course of the disease, future studies could include a no-treatment control group were patients got advice to just stay active and did not receive treatment (Ibid). However, this kind of study with 3 groups and subgroups would demand a large sample size and the costs would also be high.

5.2 Methodological quality of the evidence

Both of the included studies were rated as having a low risk of bias as they fulfilled more than 6 of the 12 criteria from the Cochrane Back Review Group. However, one of the studies (Hancock et al., 2008b) had a slightly higher study quality than the other (Childs et al., 2004). Loss to follow up in Childs et al. (2004) was more than 30% in one of the groups, but in Hancock et al. (2008b) loss to follow up was less than 2%. This could also explain the differences in the results (Hancock et al., 2008b). Also the results in the short term assessment (1 week and 4 weeks) would be more reliable than the results in the long term follow up (6 months) due to the drop out of more than 30% in the long term follow up.

Hancock et al. (2008b) considered the patients in their trial to be blinded to treatment allocation. However, we considered the patients as not being blinded since the treatments given differed so much (manipulation versus detuned ultrasound), it is therefore possible to assume that the patients were aware if they got manipulation or not. The same authors also considered the assessors in their trial to be blinded on both treatment allocation and status on the clinical prediction rule (Hancock et al., 2008b). However, we considered the assessors as not being completely blinded in the risk of bias evaluation. The reason was that the patients reported and rated outcomes (pain and function) and as we assumed the patients could possibly know which treatment group they belonged to we considered them to not being blinded as outcome assessor. Also the assessors on the CPR could be questioned if they were completely blinded on the rule as the treating therapist collected data on three of the criteria

and a researcher blinded to the patients' treatment group collected the last 2 criteria. The question is if bias could occur when different people are getting parts of the data? The authors think the assessors of the clinical prediction rule were blinded as the researchers who collected part of the clinical prediction rule were blinded to allocation and the physiotherapists collecting 3 of the criteria did not know the status on the other items. In addition they did not know about the clinical prediction rule or how it was scored since it was not commonly used in Australia (personal communication, Mark Hancock).

Both studies had relatively large confidence intervals. Hancock et al. (2009a) suggests that estimates of treatment effect modification require narrow confidence intervals to be convincing and the results of the included studies should therefore be interpreted with care. More reliable results could be achieved by larger sample sizes in one study or by summarizing the results of multiple studies in a meta-analysis and thereby increase the sample size and thus the power to study effects of interests; however, the latter requires similar methodology and definitions and more studies (Walker et al., 2008; Hancock et al., 2009a).

5.3 Factors to consider in the treatment of LBP

Non-specific LBP is a heterogeneous condition and the anatomical basis is considered unidentifiable (Deyo, 2002) and a pathoanatomical diagnosis is generally not helpful for guiding treatment (Delitto et al., 1995; Bialosky et al., 2014). SMT is one of the treatments used to treat LBP. Conflicting evidence exists regarding the effectiveness of spinal manipulation and mobilization (SMT) (Bronfort et al., 2004; Cleland et al., 2009; Cook et al., 2013a). Clinical prediction rules that identify those likely to respond favorably to manipulation have been proposed and tested in validation studies; however, also these studies have conflicting results (Childs et al., 2004; Hancock et al., 2008b). A better understanding of the mechanisms of spinal manipulative therapy may strengthen or expand existing clinical prediction rules (Bialosky et al., 2008b; Bialosky et al., 2014).

Traditionally the decision to incorporate spinal manipulative therapy into a plan of care was based on a biomechanical theory where the thought was to correct the hypo-mobile or mal-aligned structures identified on examination (Bialosky et al., 2008b; Bialosky et al., 2011; Bialosky et al., 2012). Also the clinical prediction rule for manipulation has a reflection of

this thought, as one of the criteria in the rule is to have a hypo-mobile segment. However, many research reports suggest that neurophysiological mechanisms may provide the most plausible explanation of the effectiveness of spinal manipulative therapy (Bialosky et al., 2009; Bialosky et al., 2010; Bialosky et al., 2011). The comprehensive model by Bialosky et al. (2009) that categorizes neurophysiological mechanisms suggests that a mechanical force from spinal manipulative therapy initiates a cascade of neurophysiological responses from the peripheral and central nervous system evoking responses between the spinal cord and the cortex, which are responsible for the clinical outcomes. A likely explanation for a successful outcome could be pain inhibition and changes in motor neuron pool activity (Bialosky et al., 2010). However, also nonspecific neurophysiological effects such as placebo, treatment expectation and psychological factors may influence on the outcome (Williams et al., 2007; Bialosky et al., 2008b; Bialosky et al., 2009). To identify those patients most likely to benefit from manipulation and to maximize the treatment effect it is important to be aware of these mechanisms related to manipulation, placebo effects and psychological factors. Studies have shown if a patient expects or think the treatment will be beneficial the hypoalgesic effect have enhanced (Bialosky et al., 2011). In addition placebo effect is found to be maximized in studies where the instructional set is intended to enhance expectation e.g. if the patient is told the agent they have just received is known to powerfully reduce pain in some patients (Ibid). However, research have also shown if a patient has a negative expectation to manipulation an increase in pain perception can occur suggesting a patient with negative experience and thus negative expectation will not likely benefit from manipulation (Bialosky et al., 2008a). Also factors related to negative moods like desire for pain relief, fear of pain and anxiety are all negatively correlated with placebo-related hypoalgesia (UK BEAM Trial Team, 2004; Bialosky et al., 2011). Interestingly Williams et al. (2007) found in a systematic review that there was some evidence that spinal manipulation improved psychological outcomes compared with verbal interventions. If the back pain is secondary to a psychological disturbance such as depression the authors speculate if it could be due to reducing distressing symptoms such as pain and fear and thus improve psychological outcome (Ibid).

Identifying fear of pain is already catered for in the clinical prediction rule developed by Flynn et al. (2002). Based on the findings mentioned above one could argue that the therapist should also ask the patient about prior experience with spinal manipulative therapy in order to identify the patients with previous positive experience. Also by using an instructional set that enhance expectation the hypoalgesic effect of manipulation could further be improved. In

addition it seems like patients with negative experience with manipulation or factors related to negative mood should rather receive other therapies (Bialosky et al., 2011).

5.4 Limitations in this review

Only English and Scandinavian languages were used. This could be a limitation. However, few studies in the search were a different language than these.

Ingui and Rogers (2001) recommend several filters to retrieve clinical prediction rule studies. They recommend each researcher depending on the goals and time constraints to chose one of the filters. In this review the most sensitive filter were not chosen due to limited time. Thus studies could possibly have been lost. However, after asking several experienced researches in the field of clinical prediction rules (Mark Hancock, Rob Haskins, Rob Herbert and John Childs) none of them knew of any other studies meeting the inclusion criteria in this study.

In addition we used a slightly different search strategy than recommended by Cochrane in the search for low back pain studies after recommendation from the experienced librarian. However, this does not have to be a disadvantage as one study found several mistakes in the search strategies from Cochrane reviews (Mathisen, 2011).

Another possible limitation of this review is publication bias (Dickersin, 1990). No effort was made to identify unpublished research, which is more likely to have negative outcome (Bronfort et al., 2004).

The result of this systematic review were also limited by the few number of studies found and future reviews will likely have an important influence on the findings.

Finally, it must be declared, the primary author of this systematic review is a manual therapist who uses manipulation in the clinical practice. Most likely this have not affected the results of this review; however, we cannot completely rule it out.

6.0 PERSPECTIVES

Only two studies fulfilled the inclusion criteria in this trial (Childs et al., 2004; Hancock et al., 2008b) and the studies showed conflicting results. The use of different interventions has been mentioned as one of the reasons for the lack of agreement between the studies (Hancock et al., 2008a; Hancock et al., 2008b; Hebert and Perle, 2008; Haskins et al., 2012). The intervention in one of the studies was manipulation (Childs et al., 2004) whereas in the other it was a mix of manipulation and mobilization (Hancock et al., 2008b). There is conflicting evidence whether manipulation and mobilization should be assessed as separate clinical entities. Evans (2002) suggests that the two interventions should be assessed separately due to different biological effects; however, there are conflicting results about the effect of mobilization and manipulation. Some studies have found manipulation to be more effective than mobilization (Bronfort et al., 2004; Cleland et al., 2009) whereas another study did not support these findings (Cook et al., 2013a).
Even though there are conflicting evidence about the effectiveness of manipulation and mobilization, and if they should be assessed as separate clinical entities, it would have been interesting to separate the two interventions in future studies to get a clearer picture.

More studies are also needed in order to increase the statistical power and get a more complete picture about the effectiveness of lumbar manipulation in adult patients with low back pain meeting a clinical prediction rule. Considering clinical prediction rule studies are analyzing subgroups, large enough sample sizes should be included in future studies to get a more reliable result (Hancock et al., 2009a). Several authors have described methodological considerations that should guide researchers in studies of clinical prediction rules, future studies should follow these guidelines in order to make it possible to compare the results and make sure the methodology has a high standard (Childs and Cleland, 2006; Hancock et al., 2009a; Kent et al., 2010; Nee and Coppieters, 2011). Several of the excluded studies in this review included only clinical prediction rule positive patients (Cleland et al., 2009; Hallegraeff et al., 2009; Sutlive et al., 2009; Schenk et al., 2012; Cook et al., 2013b; Donaldson et al., 2013; Learman et al., 2014). However, in order to say something about clinical prediction rule performance both patients who are positive on the rule and negative on the rule should be included in future studies (Haskins et al., 2012).

Low back pain is considered to be a heterogenic condition and several factors can influence on low back pain. Manipulation is one of the therapies used in the treatment of low back pain; however, research have shown that manipulation is not more effective than other therapies (Rubinstein et al., 2013). In order to achieve better treatment effect a clinical prediction rule was developed to identify patients more likely to respond favorably to manipulation (Flynn et al., 2002).

However, the validation studies of the rule identified in this review showed conflicting results (Childs et al., 2004; Hancock et al., 2008b). The clinical prediction rule developed by Flynn et al. (2002) includes both biomechanical factors (lumbar spine hypomobility and hip internal rotation range of motion) and a psychological factor (fear avoidance beliefs) (Bialosky et al., 2012). Considering the heterogenic condition of low back where several factors can influence, one could argue to include more factors in the search of identifying patients most likely to benefit from manipulation. Some researchers have suggested a better understanding of the mechanisms of spinal manipulative therapy may strengthen or expand the clinical prediction rule for manipulation (Bialosky et al., 2008b; Bialosky et al., 2014). Research has shown that placebo is an active hypoalgesic agent and expectation and conditioning are thought of as primary mechanisms in placebo hypoalgesia (Bialosky et al., 2011). It would therefore be beneficial to identify those patients with an earlier positive experience of pain relief after manipulation and the effect of manipulation could also be further maximized with an instructional set which would enhance the expectation (Ibid). In the future it could have been interesting to test the additional criteria together with the existing criteria to see if it would improve the effect of spinal manipulative therapy. However, it is also important in the clinical setting to include clinical reasoning to identify patients most likely to respond to spinal manipulative therapy, since it is not sure all patients who will benefit, fit into the limited scheme of a specific system of classification (Stanton et al., 2011). Also it is unknown whether the use of a clinical prediction rule to inform who should receive manipulation would actually result in better outcomes than what would otherwise occur if clinicians used their traditional clinical reasoning strategies to make the decision. This is why impact analysis is important; however, these studies don’t yet exist (Haskins et al., 2012).

7.0 CONCLUSION

There are conflicting results whether patients who are rule positive have a better effect of manipulation than rule negative patients. More studies including both rule positive and rule negative patients are needed to find out more about the effect of manipulation in subgroups of LBP patients.

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APPENDICES

Appendix 1: Search history CENTRAL

Appendix 2: Searc history MEDLINE

Appendix 3: Search history EMBASE

Appendix 4: Search history CINAHL

Appendix 5: Search history AMED

Appendix 6: Detailed characteristics of included studies and Risk of Bias evaluation Childs et al 2004

Appendix 7: Detailed characteristics of included studies and Risk of Bias evaluation Hancock et al 2008

Cochrane CENTRAL Wiley searched 25th of august 2014

ID	Search Hits
#1	MeSH descriptor: [Back] explode all trees 503
#2	MeSH descriptor: [Buttocks] this term only 69
#3	MeSH descriptor: [Leg] this term only 2598
#4	MeSH descriptor: [Back Pain] 1 tree(s) exploded 2918
#5	MeSH descriptor: [Back Injuries] explode all trees 766
#6	MeSH descriptor: [Low Back Pain] this term only 2086
#7	MeSH descriptor: [Sciatica] this term only 229
#8	(low next back next pain) 4586
#9	(lbp) 610
#10	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9) 8955
#11	MeSH descriptor: [Musculoskeletal Manipulations] explode all trees 1947
#12	MeSH descriptor: [Chiropractic] explode all trees 150
#13	manip* 6898
#14	MeSH descriptor: [Osteopathic Medicine] explode all trees 26
#15	osteopath* 492
#16	chiropract* 1020
#17	(#11 or #12 or #13 or #14 or #15 or #16) 8453
#18	(#10 and #17) 851
#19	predict* and rule* 1623
#20	(#18 and #19) 28$

$ = 17 records are from cochrane reviews, 10 records form Trials and 1 form other reviews.

MEDLINE OVID searched 1946 to 27th of august 2014

1 exp Back Pain/ (29216)
2 dorsalgia.tw. (61)
3 backache.tw. (2015)
4 ((back or lumbar) adj pain).tw. (31312)
5 Sciatica/ (4167)
6 sciatica.tw. (3265)
7 coccyx/ (851)
8 (coccyx or coccydynia).tw. (556)
9 (spondylosis or lumbago).tw. (3483)
10 (Facet adj joint* adj2 pain).tw. (202)
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 (51224)
12 exp Musculoskeletal Manipulations/ (12390)
13 (manipulation or manipulate).tw. (73716)
14 chiropractic/ or Orthopedics/ or osteopathic medicine/ (21627)
15 12 or 13 or 14 (104401)
16 11 and 15 (2308)
17 predict*.tw. and rule*.mp. (13150)
18 16 and 17 (29)

EMBASE OVID searced 1974 to 27th of August 2014

1 dorsalgia.mp. (109)
2 back pain.mp. (56584)
3 exp BACKACHE/ (69799)
4 (lumbar adj pain).mp. (1604)
5 sciatica.mp. (4470)
6 exp ISCHIALGIA/ (5824)
7 spondylosis.mp. (7301)
8 lumbago.mp. (1529)
9 coccygeal bone/ (1105)
10 (coccyx or coccydynia).tw. (777)
11 exp Low Back pain/ (36526)
12 (Facet adj joint* adj2 pain).tw. (266)
13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (90346)
14 exp CHIROPRACTIC/ (3626)
15 exp Orthopedic Manipulation/ (2077)
16 exp Manipulative Medicine/ (26555)
17 exp Osteopathic Medicine/ (3217)
18 manipulation.mp. (77496)
19 manipulate.mp. (13309)
20 exp Orthopedics/ (21365)
21 osteopathy.mp. (2094)
22 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 (132688)
23 predict*.tw. and rule*.mp. (15991)
24 13 and 22 and 23 (49)

CINAHL EBSCO searched 1981 to 27th of August 2014

S14	S6 AND S12 AND S13	42
S13	TI (predict* and rule*) OR AB (predict* and rule*)	1,322
S12	S7 OR S8 OR S9 OR S10 OR S11	35,691
S11	TI (manipulation or manipulate) OR AB (manipulation or manipulate)	5,630
S10	(MH "Osteopathy+")	1,716
S9	(MH "Orthopedics")	6,659
S8	(MH "Manual Therapy+")	24,442
S7	(MH "Chiropractic")	9,602
S6	S1 OR S2 OR S3 OR S4 OR S5	16,415
S5	TI Facet N1 joint* N2 pain OR AB Facet N1 joint* N2 pain	47
S4	TI lumbar N1 pain OR AB lumbar N1 pain	375
S3	TI (dorsalgia or backache or coccyx or coccydynia or sciatica or spondylosis or lumbago) OR AB (dorsalgia or backache or coccyx or coccydynia or sciatica or spondylosis or lumbago)	989
S2	(MH "Sciatica")	647
S1	(MH "Back Pain+")	15,362

AMED OVID (Allied and Complementary Medicine) searched 1985 to 27th of August 2014

1 exp backache/ (5606)
2 dorsalgia.tw. (3)
3 back pain.mp. (5921)
4 (lumbar adj pain).mp. (68)
5 sciatica.mp. (238)
6 ischialgia.mp. (2)
7 spondylosis.mp. (123)
8 lumbago.mp. (44)
9 exp Low back pain/ (3886)
10 (Facet adj joint* adj2 pain).tw. (11)
11 (coccyx or coccydynia).mp. (15)
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (6938)
13 exp musculoskeletal manipulations/ (4784)
14 chiropractic/ or exp Orthopedics/ (13542)
15 osteopathy.mp. (1628)
16 (manipulation or manipulate).mp. (3552)
17 13 or 14 or 15 or 16 (20661)
18 12 and 17 (1276)
19 predict*.tw. and rule*.mp. (133)
20 18 and 19 (10)

CHARACTERISTICS OF INCLUDED STUDIES

Author: Childs et al 2004

Methods	Design
Participants	• Country: USA • Number of participants: 157 eligible, 131 randomized • Setting: Health care facilities within the US Air force • Age: 18-60, mean 33.9 years old • Sex: Both • Inclusion: Age 18 to 60, primary symptom of LBP, with or without referral into the lower extremity, and an ODQ score of at least 30%. • Exclusion: ”red flags” for a serious spinal condition (e.g. Tumor, compression fracture or infection), those who had signs consistent with nerve root compression (positive straight leg increase <45 degrees or diminished reflexes, sensation, or lower-extremity strength), those who were pregnant, those who had previous surgery to the lumbar spine or buttock • Criteria consistent with those used in Flynn (2002), were designed to include patients without a contraindication to manipulation CPR • 5 criteria according to Flynn (2002) measured at baseline • Classified as positive if the patients met at least 4 of 5 criteria • Classified as negative if patients met 3 or fewer criteria
Intervention	Patient randomly assigned to one of two intervention protocol 1. Manipulation plus exercise for 4 weeks. First two sessions patients received HVLA thrust manipulation and a ROM exercise only. Same technique used by Flynn (2002). The next 3 sessions were exercise. 2. Exercise only for 4 weeks, 5 sessions. Consisted of a low-stress aerobic and lumbar spine-strengthening program as recommended by AHCPR clinical practice guidelines. Patients began with a goal of 10 minutes of aerobic exercise on a stationary bike or treadmill at a self-selected pace. The exercise program progressed according to recommended criteria Manipulation: HVLA thrust Mobilization: No Treated by physical therapists
Outcome	Evaluation of treatment outcome was obtained after 1 week, 4 weeks and 6 months. 1. **Pain:** 11-point pain-rating scale ranging from 0 (no pain) to 10 (worst imaginable pain) to assess current pain intensity and the best and worst level of pain during the last 24 hours 2. **Function:** Modified ODQ (0% = no disability, 100% max disability)
Notes	

Risk of bias		
Item	Authors’ judgment	Description
1. Method of randomization adequate?	Yes	Random-number generator generated a randomization list
2. Allocation concealment?	Yes	Sealed envelopes
3. Blinding?	No	Patient aware of treatment

All outcomes-patient		
4. Blinding? All outcomes - providers	No	Providers aware of treatment given
5. Blinding? All outcomes - assessors	No	• Patients reported and rated outcomes: assessors were not blinded. • Physical examination and clinical ratings were performed and rated by assessors who were blinded to treatment assignment. To further minimize bias, examiners were not instructed in the rule's criteria and were unaware of the patient's status on the rule. • Only patient reported outcomes are used in the review
6. Incomplete outcome data addressed? All outcomes - drop-outs (80%)	No	More than 30% drop out in one group (exercise, 65,6%) after 6 months.
7. Incomplete outcome data addressed? All outcomes – ITT analysis	Yes	Included all 131 patients in the analysis by carrying forward the last observation according to ITT principles
8. Free of selective reporting?	Unsure	Did not find a protocol
9. Similarity at baseline characteristics?	Yes	Baseline variables did not differ between treatment groups
10. Co-interventions avoided or similar?	Yes	Patients in both groups were given advice to maintain usual activity within the limits of pain and received an exercise instruction booklet
11. Compliance acceptable?	Unsure	Not mentioned in the article
12. Timing outcome assessments similar?	Yes	Assessment 1 week, 4 weeks and 6 months following randomization in both groups.

CHARACTERISTICS OF INCLUDED STUDIES

Author: Hancock et al 2008

Methods	Design
Participants	• Country: Australia • Number of participants: 240 randomized, 1 excluded after randomization, suspected serious spinal pathology (n= 239). • Setting: Private clinics across Sydney • Age: mean 40,7 years old • Sex: 44% female • Inclusion: Primary complaint of pain in the area between the 12th rib and buttock crease causing moderate pain and moderate disability (measured by adaptation of items 7 and 8 of the SF-36) • Exclusion: Current episode not preceded by a pain-free period of at least 1 month in which no care was provided; known or suspected serious spinal pathology; nerve root compromise; currently receiving non-steroidal anti-inflammatory drugs or SMT; surgery within the preceding 6 months; contraindication to paracetamol, diclofenac or SMT. CPR • 5 criteria according to Flynn (2002) measured at baseline • Classified as positive if the patients met at least 4 of 5 criteria • Classified as negative if the patients met 3 or fewer criteria
Intervention	Patient randomly assigned to one of four intervention protocol 1. Placebo SMT and placebo diclofenac group 2. Placebo SMT and active diclofenac group 3. Active SMT and placebo diclofenac group 4. Active SMT and active diclofenac group Intervention group: Both SMT groups Control group: Both placebo SMT groups Placebo SMT consisted of detuned pulsed ultrasound SMT = manipulation and mobilization: Manipulation used in 5 % of the cases, mobilization used in 95% of the cases Treated by 15 physiotherapists who had as a minimum, university-based post-graduate training in manipulative therapy and who regularly used manipulative therapy in their clinical practice
Outcome	Evaluation of treatment outcome was obtained after 1, 2, 4 and 12 weeks 1. **Pain:** Measured using an 11-point scale (0=no pain, 10=worst possible pain). 2. **Function:** Measured using the 24-point Roland Morris disability questionnaire (0 = low disability, 24 = high disability)
Notes	

Risk of bias		
Item	Authors' judgment	Description
1. Method of randomization adequate?	Yes	Randomization was performed using randomly permuted blocks of 4, 8 and 12
2. Allocation concealment?	Yes	Sealed opaque envelopes
3. Blinding? All outcomes-patient	No	The treatments given differed so much (manipulation vs detuned ultrasound) that it is possible to assume that the patient were aware if they got manipulation or not.
4. Blinding? All outcomes - providers	No	Providers aware of treatment given
5. Blinding? All outcomes - assessors	No	Patients reported and rated outcomes: assessors were not blinded. A researcher blinded to patients' treatment group collected data on two of the five CPR. The treating physiotherapist collected data on the other three criteria, therefore the CPR assessors was not completely blinded.
6. Incomplete outcome data addressed? All outcomes - drop-outs (80%)	Yes	Less than 2% drop-outs at all time points
7. Incomplete outcome data addressed? All outcomes – ITT analysis	Yes	All data were analyzed by intention to treat
8. Free of selective reporting?	Unsure	
9. Similarity at baseline characteristics?	Yes	Differences in baseline pain and function scores between the SMT group and the placebo group were small and statistically non-significant
10. Co-interventions avoided or similar?	Yes	The sham ultrasound aimed to match the treatment duration and patient/therapist contact with active SMT. Active and placebo SMT sessions were matched in time (30-40 min for the initial session and approximately 20 min for follow-up sessions)
11. Compliance acceptable?	Unsure	Not mentioned in the article
12. Timing outcome assessments similar?	Yes	Assessment 1, 2, 4 and 12 weeks in both groups