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THE BURDEN OF BACK PAIN
Evaluation of costs and health outcomes

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The Burden of Back Pain – Evaluation of Costs and Health Outcomes

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If pain must come, may it come quickly.
Because I have a life to live, and I need
to live it in the best way possible.

PAULO COELHO

By the River Piedra I sat down and wept

POPULÄRVETENSKAPLIG SAMMANFATTNING

Idag vet vi att nästan alla människor någon gång i livet kommer att drabbas av ryggsmärta. För de flesta avtar smärtan efter bara några veckor och den får en relativt liten påverkan på deras liv. Återgången till det normala sker relativt snabbt och utan några större insatser. Men för en av tio kommer smärtan att orsaka svåra problem med omfattande påverkan på vardagen. Aktiviteter som att gå, sitta, tvätta sig och eller delta i sociala sammanhang blir svåra, i vissa fall till och med övermäktiga att utföra. Smärtan benämns långvarig eller kronisk om den håller i sig mer än tre månader. Långvarig smärta kan ha en stor inverkan på en individs fysiska hälsa, men även ge mentala och sociala problem. Sammantaget räknas ryggsmärta globalt som den främsta orsaken till funktionshinder och funktionsnedsättning.

Att välja behandling för ryggsmärta kan vara komplicerat då det finns över 200 olika behandlingsalternativ. Majoriteten av dessa alternativ bekostas inte av offentliga medel utan det är individen själv som betalar för behandlingen. Långvarig ryggsmärta kan därför bli mycket kostsam för individen. Även primärvården erbjuder en rad olika behandlingsalternativ vid ryggsmärta. Det råder stor osäkerhet kring hur effektiva behandlingarna är och de flesta terapeuter måste själva avgöra vilken behandling de tror är effektivast. Bristen på nationella riktlinjer medför också att behandlingsinsatsen beror på vilken klinik eller vårdcentral patienten besöker. Osäkerheten och bristen på kunskap medför en risk för att skattepengar används ineffektivt, då patienter erbjuds mindre effektiva eller onödigt kostsamma behandlingar.

Syftet med denna avhandling är att tydliggöra några av ovanstående problem och beskriva hur långt forskningen har kommit vad gäller olika behandlingsalternativ. Jag har försökt att sammanställa all kunskap som finns om behandlingar som patienter erbjuds inom primärvården. Vidare undersöker jag kostnaderna för sjukskrivningar orsakade av ryggsmärta och presenterar nya data över hur patienter mår efter besök i primärvården.

En delstudie undersöker kunskapen om de olika behandlingarna som erbjuds inom primärvården. Den visar att det finns goda möjligheter att få lindring genom smärtstillande medel, spinal manipulation, multimodal behandling samt ultraljud. Forskargruppen identifierar dock generellt sett stora kunskapsbrister på området och ett omfattande behov av mer forskning. Kostnadsstudien visade att en individ med ryggsmärta i genomsnitt kostar över 50 000 kr per år till följd av sjukskrivning och förtidspension. Kostnaderna är högre för kvinnor än för män och låg utbildningsnivå eller fysiskt arbete leder till högre kostnader. Slutligen visar resultaten att patienter som besökt kiropraktor mådde bättre en månad efter sin första behandling. Alla patienter som fått behandling i primärvården (kiropraktik, sjukgymnastik eller en kombination av dessa) mådde bättre efter tre och sex månader. Dock framkom inga skillnader mellan de olika behandlingsalternativen och det går inte att säga om någon av dessa behandlingar är bättre än bara information och rådgivning för patienter med långvarig ryggsmärta. Fortsatt forskning kring ryggsmärta är nödvändig för att patienter ska kunna erbjudas det effektivaste omhändertagandet.

ABSTRACT

Background: Back pain is a leading cause of disability in the world. Beyond the negative impact on people's health and quality of life, back pain is associated with substantial costs both within and outside the health care sector. While there are many alternative strategies for the treatment and management of back pain, there is a lack of knowledge about their effectiveness, costs and cost-effectiveness. Such information could guide decision-makers regarding which treatment strategies to use for back pain. The aim of the thesis was to explore the costs of back pain, and to explore the effectiveness, costs and cost-effectiveness of different treatments for low back pain.

Methods: Studies I and II used a clinical trial design, where data from multiple study centres were combined and analysed in order to increase understanding of changes in patient-reported outcome and costs over time. Study III was a systematic mapping of systematic reviews on the effectiveness of various primary care treatments for chronic low back pain (CLBP). Study IV was a register study where data from multiple national registers were combined and productivity losses for patients with back pain were analysed.

Results: There were significant productivity losses due to long-term sickness absence and disability pension among individuals of working age who had undergone a first specialist health care visit for back pain. Productivity losses may be affected by sociodemographic factors and it was indicated that individuals with back pain with an additional diagnosis might have higher productivity losses than individuals with only a back pain diagnosis.

There was evidence that some primary care treatments (non-steroidal anti-inflammatory drugs, opioids, spinal manipulation, multidisciplinary biopsychosocial rehabilitation, and therapeutic ultrasound) had positive effects on pain and/or function in patients with CLBP. However, there are considerable knowledge gaps for most treatments.

There were statistically significant improvements in health outcomes (back pain-related functional limitation, pain intensity, and health-related quality of life) from a 4-week treatment with chiropractic care for patients with non-specific acute or chronic back pain.

There were no statistically significant differences in back pain-related functional limitation, pain intensity, health-related quality of life, costs or quality-adjusted life years when physiotherapy, chiropractic care, and the combination of physiotherapy and chiropractic care were compared with advice among patients with non-specific CLBP over a 6-month period.

Conclusion: Back pain is associated with large productivity losses for individuals in the working age. Individuals with a first specialist health care visit for back pain have considerable greater productivity losses than those without back pain. Women tend to have higher productivity losses than men, and individuals with at least one other diagnosis tend to have higher productivity losses compared to those with only a back-pain diagnosis.

Chiropractic care of patients with acute or chronic back pain may, over a 1-month period, improve health outcomes (back pain-related functional limitation, pain intensity, and health-related quality of life). There were no statistically significant differences when physiotherapy, chiropractic care, and combination treatment were compared with advice, over a 6-month period, in the treatment of patients with CLBP in Sweden. Due to a high dropout rate and low power, these results should be interpreted with caution, and differences between the treatment groups cannot be ruled out. Some primary care treatments had positive effects on pain and/or function for patients with CLBP. However, these effects were usually not clinically important, and there are considerable knowledge gaps for most back pain treatments.

In conclusion, there is a great need for high-quality, large-scale studies to further study the effectiveness, costs and cost-effectiveness of primary care treatments for CLBP.

LIST OF SCIENTIFIC PAPERS

I. Gedin, F., Dansk, V., Egmar, A.C., Sundberg, T. and Burström, K. Patient-reported improvements of pain, disability, and health-related quality of life following chiropractic care for back pain – A national observational study in Sweden. Journal of Bodywork and Movement Therapies. 2019;23:241-246.
II. Gedin, F., Skeppholm, M., Sparring, V., Tessma, M. and Zethraeus, N. Effectiveness and costs of physiotherapy and chiropractic care compared with information and advice in the treatment of non-specific chronic low back pain – A pragmatic multi-centre randomized controlled trial in Sweden. Manuscript.
III. Gedin, F., Sundberg, T., Sparring, V., Skeppholm, M., Heintz, E. and Zethraeus, N. Primary care treatments for non-specific chronic low back pain – A systematic mapping. Submitted.
IV. Gedin, F., Alexandersson, K., Zethraeus, N. and Karampampa, K. Productivity losses among people with back pain and among population-based references – a register study. BMJ Open. 2020;10(8)e036638.

RELATED WORK

Gedin, F., Skeppholm, M., Burström, K., Sparring, V., Tessma, M. and Zethraeus, N. Effectiveness, costs and cost-effectiveness of chiropractic care and physiotherapy compared with information and advice in the treatment of non-specific chronic low back pain: study protocol for a randomised controlled trial. Trials. 2017;18:613.

CONTENTS

LIST OF ABBREVIATIONS

AMSTAR	A MeaSurement Tool to Assess systematic Reviews
COI	Cost-of-illness
CLBP	Chronic low back pain
DP	Disability pension
EQ-5D	EuroQol Five Dimensions questionnaire
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HUI	Health utilities index
LISA	Longitudinal integration database for health insurance and labour market studies
MIDAS	MicroData for Analysis of the Social Insurance database
NRS	Numeric rating scale
ODI	Oswestry Disability Index
PCRU	Primary care rehabilitation unit
PROM	Patient-reported outcome measure
QALY	Quality-adjusted life year
SA	Sickness absence
SALAR	Swedish Association of Local Authorities and Regions
SBU	Swedish Agency for Health Technology Assessment and Assessment of Social Services
SEK	Swedish Krona
SF-36	The Short Form (36) Health Survey
WHO	World Health Organization
YLDs	Years lived in disability

PREFACE

As a grandchild of two Serbian immigrants suffering from low back pain, I have seen the inequality of pain. As a student in public health doing an internship in a war-torn country, I have seen how pain can affect a community. In this thesis, I will present the perspective of a health economist.

Suffering from persistent back pain is a tremendous waste. Health economists could describe this in various ways, for example loss of productivity or a decrease in health-related quality of life. However, what we mean by such academic terms is waste. Waste is always unnecessary and provides no benefits, neither for the individual, nor for health care or society. We might describe our findings in monetary values, but behind the euros, dollars or Swedish crowns are real people with real disabilities.

At some point in life, you have probably had some sort of back pain. It affects almost everyone at some point, making it a global public health problem. Providing an economic perspective on this global public health problem has been my aim. To fulfil the aim of the thesis, I have used several approaches/methods (observations, registers, literature and clinical trial), some with success and some with less success. Ultimately, I think I have contributed to the current knowledge.

I hope that you, after having read this thesis, will have increased your understanding of how much back pain costs in terms of productivity losses, the need for more research even for treatments deemed effective in treatment guidelines, and the benefits of primary care interventions.

1 BACKGROUND

Pain is a human emotion, much like hunger, fear or satisfaction. It is one of the most essential alarm mechanisms that the body has against physical harm and a driver for self-awareness. By signalling to the brain when something is wrong or unpleasant, the nerve system ensures that the body avoids harmful elements, preventing potential body damage (1). Adjunct professor Bud Craig from the Barrow Neurological Institute describes pain as follows: "Human feeling of pain is both a distinct sensation and a motivation – that is, a specific emotion that reflects homeostatic behavioural drive, similar to temperature, itch, hunger and thirst." (1) This reveals how important pain is for wellbeing. Pain is also an important diagnostic symptom in medicine. Differing pain sensations can provide important insights when diagnosing, treating or rehabilitating a patient and are used in nearly all medical professions. However, pain is also one of the most disabling and costly conditions of our time (2).

In the summer of 2020, the International Association for the Study of Pain released their revised definition of pain. The new definition places great emphasis on the individual experience of pain based on biological, psychological, and social factors. It highlights that everyone learns about pain throughout their life and that although a person can adapt to long-term pain, it may still have an adverse effect on function and quality of life (3).

There are different diseases and conditions that can lead to back pain, which can be classified in four sub-categories: back pain due to 1) severe, but rare conditions (for example tumours and infections), 2) rheumatic diseases, 3) degenerative conditions (for example herniated discs and arthritis), and 4) non-specific back pain (pain without any known pathology). The last category is the most common and accounts for approximately 75% of all back pain cases (4). Back pain is usually described in stages: the acute and the chronic. The first 12 weeks with pain make up the acute stage; after 12 weeks, the pain has entered a chronic stage (5).

Low back pain is one of the most common types of back pain, and is usually defined as pain primarily located between the lower rib margins and just above the gluteus (6).

Back pain is a complex condition and there are multiple components that can contribute to its development. The biopsychosocial model is a theoretical model which integrates the biological, psychological and social components that lead to pain and increased pain sensation. Each component can impact pain on its own, but pain can become disabling if all components interact. All evidence-based medicine uses the biopsychosocial model when diagnosing and treating pain (7).

Back pain is a common disability. In 2018, about 47% of people in Sweden reported having back pain and about 8% experienced severe pain (8). Severe back pain is more common among women (10%) than men (6%) and the prevalence of severe symptoms increases with age (8). The Stockholm Public Health Survey Report from 2015 suggested that the gap found between men and women was more related to gender differences than biological sex in the sense that women, e.g., tend to have professions associated with more monotonous work tasks and involving lifting that could lead to back pain (9). In 2014, approximately 4% of the adult Swedish population reported having had frequent pain during the last six months, that either decreased their work ability or prevented them from other daily activities. In Region

Stockholm, about 80,000 persons had decreased work capacity due to back and/or neck pain. Frequent and severely debilitating low back pain was more common among workers than among officials (9).

Ethnicity and culture are complex concepts in back pain research. Studies have shown that the prevalence of low back pain is higher among the Sami than the general population, and that the prevalence among women is higher than among men (10). Again, this is work-related. Among reindeer herders, the prevalence of pain in hands, elbow or lower back is significantly higher than in other blue-collar occupations (10). Clinical studies have observed differences in acute pain response based on ethnicity, but the relevance of this for individuals with chronic pain is unclear. People with a non-Nordic background living in Sweden have a higher occurrence of back pain. This is probably not due to a tendency for non-Nordic people to develop pain, but rather a higher exposure to risk factors for pain (11).

1.1 BURDEN OF BACK PAIN

In the World Health Organization's (WHO) study on global burden of disease, low back pain was behind nearly 11% of the overall years lived in disability (YLDs), making it the leading cause of YLDs in the world. Low back pain caused 2% more YLDs than the second largest contributor, major depressive disorder (2). Since 1990, the prevalence of low back pain has increased by 54% (12).

Low back pain is not common during the first years in life, but the prevalence increases during the teenage years, with a prevalence of approximately 40% in the age group 9–18 years (13). Almost everyone will at some point in time experience back pain (14); the lifetime prevalence of low back pain is estimated to be around 70% to 80% (5, 15, 16). A significant proportion of patients with back pain (10–20%) develop chronic low back pain (CLBP) lasting at least 3 months (17). Among those seeking care for their back pain, around 60% have had pain for more than 12 months (18). CLBP have been associated with persistent or recurring pain, disability, and a significant impact on health and quality of life (5, 6). In addition to the health aspects, CLBP is associated with considerable increase in costs both in and outside the health care sector. Direct medical costs, e.g., for interventions and visits to primary care, and indirect costs (production losses) due to absenteeism from work are sizeable (19). CLBP is responsible for a majority of the disease burden related to low back pain and health care systems should therefore prioritise identification of effective and cost-effective treatment strategies to decrease the disease burden of CLBP.

Musculoskeletal disorders account for the second largest cost in terms of sick leave in Sweden (20). A study from Hubertsson et al. showed that low back pain was the most common reason for granting sick leave to patients with musculoskeletal disorders (21). The indirect costs related to low back pain are sizeable and have been estimated to account for 84% of the total cost, which was approximately 1,860 million EUR in Sweden in 2001 (22). It has also been estimated that a patient with CLBP costs primary care 227,000 SEK a year and that an episode of low back pain usually costs around €2,753 (23, 24).

1.2 TREATMENT OPTIONS FOR CHRONIC LOW BACK PAIN

There is a wide range of treatment options for the treatment and management of CLBP (25). Various pharmacological and non-pharmacological treatments, like physical activity, spinal manipulation and multidisciplinary rehabilitation, are widely used – alone or in combination (26, 27). According to a survey by the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU, 2016), treatments for acute back pain in Sweden are often given by physiotherapists, chiropractors or naprapaths. These occupational groups usually combine different interventions, with information and advice to stay active given to all patients with CLBP (28). Physiotherapists typically use treatment based on training and exercise, which is less frequently used by chiropractors and naprapaths. Chiropractors and naprapaths use manual therapies, which physiotherapists in general do not use. In the survey by the SBU, 69% of the physiotherapists stated that they frequently used "circulation training" compared with 36% of the chiropractors (28). Moreover, the survey showed that around 13% of the physiotherapists regularly used spinal manipulation, whereas the corresponding figure among chiropractors was 96% (28). These results may reflect what treatments patients with CLBP usually receive. However, due to the lack of clinical guidelines for CLBP in Sweden, there is a need to further investigate what treatments are given to patients with CLBP (29).

Serious harm is rare in clinical trials on pharmaceutical treatments for back pain (30). In observational studies, it has been shown that opioids has been linked to overdoses and addiction (31). Harm in non-pharmaceutical treatment for back pain is poorly reported and should be assessed in clinical trials (30). However, no serious adverse effects have been reported for any of the treatments (30).

1.2.1 Evidence on effectiveness

A systematic review investigated the effectiveness of motor control exercise for patients with CLBP (32). In total, 29 studies were included with a total population of 2,431 participants. The trials compared motor control exercise to other supervised exercises, minimal interventions, manual therapy, a combination of exercise and electro physical agents and home exercises. The review found, that the evidence for motor control exercise to be clinically important is low to moderate, if compared to minimal intervention. There is moderate evidence that motor control exercise have similar outcomes as other exercises and manual therapies (32).

Rubinstein et al. (2019) analysed 47 randomised controlled trials (RCTs) with a total combined study population of 9,211 people with CLBP (33). The results of the systematic review and meta-analysis showed that there was moderate evidence that spinal manipulation was as effective as other recommended treatments for short pain relief and slightly better at improving function (33). The evidence on spinal manipulation compared with sham was inconclusive (33).

Enthoven et al. (2016) investigated the evidence for use of non-steroidal anti-inflammatory drugs (NSAIDs) among patients with CLBP with or without pathological findings. The systematic review included 13 studies with a total sample size of 1,354 participants. The review found that there was low quality evidence that NSAIDs were more effective in reducing pain

and disability than placebo, and that the effect size was small. The review did not find any significant differences between different types of NSAIDs (34).

A systematic review by Kamper et al. (2015) on multidisciplinary treatment for CLBP, included 41 studies with a total sample size of 6,858 participants. Most of the studies compared multidisciplinary treatment to usual care and physiotherapy. Results from the systematic review showed moderate evidence that patients with CLBP receiving multidisciplinary treatment were more likely to have less pain and disability than patients receiving usual care or physiotherapy. The effect size was modest and it was not clear if the effect was reasonable, given the additional time and resources spent in the multidisciplinary treatment group. The authors concluded that only patients with significant psychosocial impact should be referred to multidisciplinary treatment (27). The SBU (2015) commented on the systematic review and stated that multidisciplinary treatment had moderate effects on disability and pain intensity, as compared with physical therapy. However, the findings were to a large extent influenced by results from one particular study, which showed a remarkably high effect for the multidisciplinary treatment compared with physiotherapy. This may have been due to publication bias. When that study was excluded, the SBU could not find any significant differences between physiotherapy and multidisciplinary treatment (35).

1.2.2 Evidence on cost-effectiveness

In a Swedish RCT, Skargren et al. (1998) compared the outcomes and costs of chiropractic care and physiotherapy as a primary care treatment for patients with back and neck pain during a one year follow-up. In total, 323 participants aged 18–60 years were randomised to chiropractic care or physiotherapy. The outcomes were the Oswestry Disability Index (ODI), pain intensity, general health, recurrence rate, and direct and indirect costs. The result did not detect any statistically significant differences in costs or health outcomes for the total population. However, the subgroup analyses indicated that patients with acute back pain gained more from chiropractic care, at a similar cost, whereas patients with chronic back pain gained more from physiotherapy, with a slightly reduced cost (36).

In a Swedish study from 2019, Saha et al. estimated the cost-effectiveness of structured physiotherapy including a work place intervention compared with structured physiotherapy alone, delivered in primary care (37). A total of 352 people were recruited from 20 clinics and randomised to one of the treatment alternatives. The study showed that structured physiotherapy including a work place intervention was cost-effective if the willingness-to-pay was greater than €23,606 (2013 price year).

A randomised controlled trial in Finland investigated the effectiveness and costs of combined manipulation treatment, stabilising exercises, and physician consultation compared with physician consultation alone for patients with CLBP (38). In total, 204 patients were followed during one year. The combined intervention was more effective in reducing pain and disability. There were no significant differences in costs between the treatment groups (38). In a follow-up study two years later it was indicated that physician consultation was cost-effective compared with the other treatment alternatives (39).

In a randomised controlled trial from UK (40), patients seeking primary care for low back pain were randomised to one of four treatment arms: best care in general practice (this was given to

all participants and included "active management" (advice) and a "back book"), exercise, spinal manipulation or a combination of exercise and spinal manipulation. A total of 1,332 study participants were recruited and followed during one year. The study measured quality of life, disability, pain intensity and costs. Over one year, the mean treatment costs were £346 for best care, £486 for exercise, £541 for manipulation, and £471 for combination treatment. After relating the costs to the benefits of the different treatments, the authors concluded that spinal manipulation could be a cost-effective addition to "best care" for back pain in general practice. The results also indicated that manipulation alone probably gave better value for money than manipulation followed by exercise (41).

An economic analysis alongside a RCT study by Whitehurst (2007) aimed to assess the cost-effectiveness of a brief pain management program compared with physical therapy for patients with low back pain. The study could not detect any significant difference between the groups in outcomes or costs. The conclusion was that physical therapy indicated slightly better results than the brief management program (42).

Haas et al. (2015) performed a systematic review on pharmacological management of CLBP. The review included seven trials which were deemed as having low quality. Therefore, the review could not provide any conclusions on the cost-effectiveness of pharmacological management of CLBP (43).

To summarise, there is insufficient research on the cost-effectiveness of treatments for low back pain to draw any conclusions on cost-effectiveness. A systematic search for economic evaluations of preventive treatments for acute back and neck pain yielded only four studies with a high to moderate GRADE (Grading of Recommendations, Assessment, Development and Evaluations) score (28).

1.2.3 Health outcome measures of back pain

To assess the health consequences of different treatments for back pain, it is important to use outcome measures that reflect multiple aspects of health that are important for the individual and that are affected by the treatments. Health outcome measures should reflect the impact on back pain-related functional limitation, pain intensity, and health-related quality of life (HRQoL). There are many outcome measures that can be used to capture these aspects.

1.2.3.1 Back pain-related functional limitation

ODI is a back pain-specific questionnaire, which measures back pain-related functional limitation (44). Together with the Roland-Morris disability questionnaire, ODI is the most frequently used questionnaire for spinal disorders, both in research and in the clinical setting (45). It has been debated which of these questionnaires is better for rating back pain, with suggestions made that ODI is better for more severe spinal disorders and that the Roland-Morris disability questionnaire is more suitable in case of less severe causes (44). However, when compared directly, the questionnaires were equally valid in measuring non-specific back pain (46).

The ODI questionnaire consists of ten questions on pain intensity, personal care, lifting, walking, sitting, standing, sleeping, sex life, social life, and travelling. Each question has six response choices and the score for each question ranges from 0 (no problems) to 5 (worst

problems imaginable). A total score for ODI is computed as the sum of the scores for each question, and ranges between 0 (no problems) and 50 (worst problems imaginable). The total ODI score is normalised to 0–100 by multiplying the (unadjusted) total score by 2. ODI has shown high reliability, validity and responsiveness, and is easy to administer and sensitive to clinical changes from treatment in patients with chronic low back pain (45, 47, 48).

1.2.3.2 Unidimensional pain rating

Rating scales for pain has been used extensively, dating back to the 1950s (49). There are four main types of scales: the verbal rating scale, the visual analogue scale, the face pain rating scale and the numeric rating scale (NRS) (50). All scales measure pain in a unidimensional way (49). According to a review from 2015, the NRS is a good unidimensional scale for estimating pain.

The NRS usually consists of a horizontal line running between the numbers 0 to 10 and marked with evenly placed boxes or vertical lines numbered 1 to 9 (50). The patient is asked to rate their pain intensity on the scale with 0 being no pain and 10 being the worst imaginable. The patient rates their pain by selecting a number on the scale (50). The NRS is easy to administrate and has a high responsiveness (45, 51). There is support for its validity (52) and the scale has excellent test-retest reliability (53).

1.2.3.3 Health-related quality of life

The EuroQol Five Dimensions questionnaire (EQ-5D), the Short Form (36) Health Survey (SF-36) and the Health Utilities Index (HUI) are all generic instruments measuring health-related quality of life (HRQoL). The EQ-5D questionnaire consists of five questions with three levels of severity (54). The dimensions and levels result in 243 possible EQ-5D health states. There are different country-specific value sets that can be used to assign a value for each health state (55). The Swedish value set is different from the UK value set; the Swedish one is experience-based and the lowest possible value is never worse than dead (56). EQ-5D is a valid instrument among patients with pain (45, 57). There are two versions of the EQ-5D instrument, the EQ-5D-3L and the EQ-5D-5L. The version 5L uses two more levels than the 3L with the aim of providing more sensitivity. However, there is no Swedish value set for the 5L version. The EQ-$5D_{index}$, which can be derived from the Swedish or UK value sets, is used to obtain a quality of life weight to calculate QALYs in health economic evaluations (58).

1.3 ECONOMIC EVALUATION

Drummond defines economic evaluation as “the comparative analysis of alternative courses of action in terms of both their costs and consequences” (Drummond et al., 2015). Economic evaluation is thus a method for analysing the costs and consequences of two or more alternatives (e.g., different health care interventions). The economic evaluation can serve as support for decisions aiming at improving efficiency in the allocation of limited resources, and has an important role in guiding decisions and policy in health care and society. An efficient allocation of limited resources implies that resources are used in a way that optimises outcomes. When a new drug enters the market, economic evaluations can reveal if it is good value for money and if it is cost-effective compared with existing alternatives.

Economic evaluations that are applied to health care programmes are usually divided into cost-minimisation analyses, cost-effectiveness analyses, cost-utility analyses and cost-benefit analyses. One of the most common analyses used is the cost-effectiveness analysis, where costs are measured in monetary terms and effectiveness is measured in health units. The aim of a cost-effectiveness analysis is to maximise health given a budget or a cost constraint. It is important to use a health outcome measure that combines effects on both quality and quantity of life. The most commonly used outcome measure that combines quality and quantity of life is the quality-adjusted life years (QALYs) (58). A treatment is defined as cost-effective (compared with an alternative) if it is less costly while providing the same or better health outcomes (the treatment is then said to dominate the alternative), or if the added cost of the treatment is reasonable given the health improvements, in which case the incremental cost per gained QALY is estimated. A drug or intervention can be defined as cost-effective if the cost per gained QALY is below a certain threshold value. This threshold value should correspond to what a society is willing to spend in order to gain a QALY. The Swedish Transport Administration have set the value of a life at SEK 40.5 million in cost-benefit analyses of road investments. If we use this figure, the threshold value per QALY gained is approximately SEK 1,000,000, which is in line with previous studies (59, 60). As a comparison, Neumann et al. (2014) recommended US$ 100,000 (SEK 950,000; US$ 1 = SEK 9.5) or US$ 150,000 (SEK 1,400,000) per gained QALY in the USA.

1.3.1 Costs in economic evaluation

Costs in an economic evaluation can be defined as the value of limited resources used to improve health. The cost of an intervention should reflect the opportunity cost of the resources used for the intervention, i.e., the value of (health) benefits forgone due to not using these resources for the next best alternative (e.g., another intervention). The estimation of costs in an economic evaluation involves three steps. The first is to identify the relevant costs of an intervention and the alternative(s). Relevant costs should be those that are expected to differ between the treatment alternatives. The second step is to measure and quantify the costs in physical units. These physical units could be primary care visits or the number of pain medication tablets required. The final step is to value and assign a price for each physical unit (58). Resources should be valued at their opportunity costs; unit costs are often used as an approximation (e.g., the unit cost for a primary care visit). Costs can be divided into direct medical costs (e.g., costs for inpatient and outpatient care), direct non-medical costs (e.g., costs for social services) and indirect costs (productivity costs/productivity losses, e.g., due to disability pension and sick leave).

Which costs to include depends on which perspective the economic evaluation takes. The two most common perspectives are the health care sector perspective and societal perspective. If a health care perspective is used, only costs that are associated with the health care sector should be included. These are direct medical costs, for example for medication and inpatient and outpatient care. When using the societal perspective, all costs should be included, irrespective of who bears the costs (e.g., patients, municipality, government), which implies that both direct and indirect costs for sick leave and productivity losses should be included (61). A societal perspective in economic evaluation is recommended by Gold et al. (1996) as a reference case in order to increase the quality and comparability of different economic evaluations (62). However, Sanders et al. (2016) recommend having both perspectives as reference cases. A

societal perspective can be used as a reference case for a decision-maker whose aim is to decide on the broad allocation of resources for all individuals in society (63). Other perspectives, like the health care sector perspective, can complement the societal perspective, e.g., in the case when a decision-maker cares only about costs arising in the health care sector.

Economic evaluations are an important part in the allocation of resource to evidence-based treatments for back pain. To obtain valid and reliable cost-effectiveness results in the area of back pain, a pragmatic RCT design has been suggested as the best way to reflect the clinical situation upon which the decision will be applied. It is also important to use a sufficiently long follow-up period and a well-defined study population (43, 64). This would enable performance of cost-effectiveness analyses based on data characterised by both high internal validity and high external validity. An advantage to using a pragmatic RCT as the basis for an economic evaluation is that patient-level trial data provides an unbiased estimate on the effectiveness of interventions as reflected in clinical practice. Furthermore, an RCT provides an opportunity for collecting data on resource use, to estimate costs and cost-effectiveness (65).

1.4 RATIONALE OF THE THESIS

Given the limited health care resources and stretched health care budgets, health care systems should strive to achieve efficient use of scarce resources. Economic evaluation can be used to support decisions aiming at improving efficiency and constitutes important input for guiding clinical decisions (58). To be useful for decision-makers, the economic evaluation should be based on a societal perspective, including both costs within and outside the health care system (62, 66). The societal perspective may also be complemented by a health care sector perspective, as suggested by Sanders et al. (2016).

There are currently no national treatment guidelines for non-specific back pain in Sweden (29). A lack of reliable evidence was the reason that back, neck or shoulder pain were not included in the national guidelines on musculoskeletal disorders in 2012 (29). For the same reason, back pain was absent also from the updated national guidelines from 2020 (67). Back pain is one of the leading causes of disability and causes major costs to the society in terms of productivity losses and use of health care resources (22-24). It is therefore important to increase the knowledge on costs, effectiveness and cost-effectiveness of some of the most frequently used treatments. This would guide treatment recommendations, improving the efficiency in the use of limited resources and improve health outcomes and the quality of life among individuals with back pain.

2 RESEARCH AIMS

The aim of the thesis was to explore the costs of back pain, and to explore the effectiveness and cost-effectiveness of various treatments for low back pain. In order to achieve this overarching aim, four sub-studies were conducted with the following specific aims:

Study I: To explore patient-reported outcomes (PROMs) for patients with back pain seeking chiropractic care in Sweden.

Study II: To evaluate the effectiveness, costs and cost-effectiveness of physiotherapy, chiropractic care and the combination of physiotherapy and chiropractic care, compared with information and advice in the treatment of patients with CLBP in Sweden.

Study III: To identify, critically assess, and summarize existing evidence and knowledge gaps regarding the effectiveness of primary care treatments for non-specific CLBP.

Study IV: To explore the occurrence of sickness absence (SA) and disability pension (DP), and to estimate productivity losses among individuals with back pain compared with among matched references.

3 MATERIALS AND METHODS

In order to fulfil the aim of this thesis, four sub-studies were conducted with different study designs (Table 1). Studies I and II used a design where data from multiple study centres were combined and analysed in order to explore changes in PROMs and costs over time. Study III was a systematic mapping of systematic reviews on the effectiveness of different primary care treatments for CLBP. Study IV was a register study, where data from multiple national registers were combined and analysed to explore the costs of productivity losses among patients with back pain.

Table 1. Overview of the studies included in the thesis.

	Study I	Study II	Study III	Study IV
Study focus	Explore the changes in PROMs after a primary care treatment	Evaluate the effectiveness, cost and cost-effectiveness of primary care treatments	Summarise knowledge and knowledge gaps in primary care treatments	Estimate productivity losses of back pain due to sickness absence and disability pension
Study setting	Chiropractic clinics in primary care in Sweden	Primary care rehabilitation units in Region Stockholm and Region Jönköping in Sweden	Treatment domains relevant for primary care in Sweden	Inpatient and specialised outpatient health care in Sweden
Study design	Prospective observational study	Pragmatic randomised controlled trial	Systematic mapping of systematic reviews	Explorative prospective cohort study
Study participants	Patients with non-specific back pain (n=138)	Patients with CLBP (n=88)	Patients with CLBP (n=61,870)	Patients receiving their first back pain diagnosis (M54) in 2010 (n=23,176), and a matched reference group (n=115,880)
Data collection	Paper-and-pencil questionnaires at baseline, and after 2 and 4 weeks	Computer-based patient questionnaires at baseline, and after 3 and 6 months	Systematic reviews with low to moderate risk of bias	Register data (LISA, MiDAS, National Patient Register)
Outcomes	ODI, EQ-5D, NRS	ODI, EQ-5D, NRS, self-rated health, direct and indirect costs	Level of evidence according to GRADE	Sickness absence, disability pension, productivity loss

3.1 PRIMARY CARE REHABILITATION UNITS FOR CLBP

Musculoskeletal disorders caused more than 30% of the total Swedish health insurance costs in 2009 (68). The increasing costs and a political goal of getting people back to work led the Swedish government and the Swedish Association of Local Authorities and Regions (SALAR) (69) to sign an agreement, vowing to focus on evidence-based rehabilitation for patients with chronic pain (68).

In 2008, SALAR implemented a health care reform which implied extensive changes to the primary health care system, based on the so-called *rehabilitation guarantee*. The *rehabilitation guarantee* was a reaction to the agreement between SALAR and the Swedish government on providing evidence-based rehabilitation. This meant that all patients with chronic back pain were guaranteed multidisciplinary treatment, in order to improve health and decrease productivity loss (70). The health care reform involved the implementation and establishment of primary care rehabilitation units (PCRUs), with the aim to provide multidisciplinary treatment at a primary care level. However, following recommendations made by the Swedish National Audit Office, the *rehabilitation guarantee* was abolished in 2016 and multidisciplinary treatment is no longer the primary treatment for patients with chronic back pain. During the years 2008 to 2016, the *rehabilitation guarantee* led to some improvement among chronic back pain patients regarding quality of life, but had little to no effect on sickness absence (71). This were also seen in Region Skåne, where multimodal care was evaluated as cost-effective, given that the work rate decreased (72).

In 2020, there were 74 PCRUs in Region Stockholm (73). All PCRUs must employ physiotherapists, occupational therapists and a speech therapist. A PCRU can also employ chiropractors and naprapaths. Out of the current 74 PCRUs, 53 have chiropractors and eight have naprapaths (73). PCRUs are the primary public option for CLBP patients, who are a prioritised patient group for the PCRUs (74).

In 2016, a report from SALAR revealed several deficiencies and unjustified differences in the care of patients with various pain disorders. The report found that primary health care lacked the competence and structure to properly deal with patients with chronic pain and that the lack of a national quality registry made systematic improvements difficult (69).

3.2 STUDY I

3.2.1 Study design

Study I was a prospective national observational study involving 23 chiropractic clinics throughout Sweden. Observational study designs can be used to answer a range of research questions, for example regarding prevalence, incidence, causes of a disease, prognoses or treatment effectiveness (75). When it comes to evaluating treatment effects, observational studies may be questioned, as observational studies have lower internal validity (76). However, such studies are inexpensive compared with clinical trials and can therefore be used in areas where funding is scarce (76). Another benefit is that observational studies can have higher external validity than clinical trials with small sample sizes (76).

3.2.2 Sample size

The study used a convenience sample of at least 20 patients per participating clinic, for feasibility reasons. The number of patients was estimated based on the average number of new patient visits to a chiropractor for back pain during the recruitment period.

3.2.3 Sampling and recruitment

The chiropractic clinics were contacted by the researchers by phone and were given information about participating in the study. About 30 chiropractic clinics were contacted and 23 agreed to participate. The clinics were located throughout Sweden, but as some clinics declined to participate, they were not evenly distributed.

Adult patients (over 18 years) who were for the first time seeking care for back pain of any pain duration at one of the 23 participating chiropractic clinics, and able to answer a questionnaire in Swedish, were invited to participate in the study by the treating chiropractor. Exclusion criteria were ongoing chiropractic care or severe causes of back pain such as tumours, infections or fractures. A convenience sample of at least ten back pain patients from each participating chiropractic clinic was deemed feasible, i.e., this was the lowest number of new patients that each participating chiropractic clinic was expected to see during the study period.

3.2.4 Data collection

Data were collected by paper-and-pencil questionnaires that had been pilot-tested prior to data collection (77). Patients filled out the baseline questionnaire at the first visit to the chiropractic clinic, which took place after a chiropractic examination, but before chiropractic treatment was initiated. The patients were instructed to put the completed questionnaire in an opaque, sealed envelope, without showing the answers to the study chiropractor, after which the envelope was distributed to the external study administrators, who also sent out the follow-up questionnaires by post. Patients with acute back pain received follow-up questionnaires after two and four weeks, whereas chronic back pain patients received one follow-up questionnaire after four weeks. The follow-up after four weeks was the main measurement for all patients, whereas the two-week follow-up was included to detect potential short-term effects among patients with acute back pain.

The questionnaire contained PROMs that are well-established in clinical care and research (78), including back pain-specific instruments and generic instruments (79). The outcomes were NRS, ODI, and the EQ-5D. The questionnaire also included patient characteristics.

3.2.5 Data analysis

The main analysis of PROMs was from baseline to four weeks, with additional analyses of acute back pain patients at the two-week follow-up. Data on patient characteristics were sex, age (categorised into age groups: 18–44 years; 45–64 years; and 65 years and above), occupational status (categorised into blue-collar workers and white-collar workers), sick leave before first visit (yes, no), co-morbidity at baseline (yes, no), and treatment by other practitioner(s) (yes, no).

Assumptions for performing parametric tests were made for the whole study population, for the total patient group, and subgroups. Assessing significant differences between patient characteristics was done using Pearson's chi-squared test. Wilcoxon's signed-rank test was used to test the change in EQ-$5D_{index}$ from baseline to follow-up, as it did not fulfil the assumption of normal distribution, whereas the Student's paired sample t-test was used for NRS, ODI and EQ VAS from baseline to follow-up. For acute back pain patients, ANOVA was used to test the change in NRS from baseline to both two and four weeks within all subgroups, and post-hoc testing (Tukey's) for multiple comparisons of means was performed. Only available responder data was analysed, i.e., imputation procedures were not performed for missing data due to no response at follow-up. Statistical significance was set to 5% (80).

3.3 STUDY II

3.3.1 Study design

Study II was a multicentre four-armed pragmatic RCT. The study was prospectively registered in the ISRCTN Registry (2017-02-20: ISRCTN15830360) and the study protocol was published in a peer-reviewed journal before the study was completed and data were analysed (81).

Traditional RCTs are used for providing data on medical treatment safety and efficacy (58). Measuring the same outcome in two or more study groups makes it possible to estimate an intervention's efficacy in comparison to placebo or another intervention. A high internal validity is achieved through randomisation of study participants. RCTs are increasingly used to collect data for economic evaluations. Such studies are called "piggyback" evaluations, as the economic evaluation is piggybacked onto the RCT (82). The advantages of piggybacking are that costs and outcomes are at a patient level, that the costs for collecting economic data are modest and that collecting economic data in a RCT could provide a fast-track source of relevant evidence with high internal validity. The major drawback of using a RCT for economic evaluations is the lack of generalisability. Most RCTs do not identify their study population randomly, but rather through a selection process. The selection is based on a set of criteria like age and disease severity in order to increase treatment effect or decrease the sample size. Protocol-driven resource use, increased compliance and frequent monitoring leading to "case finding" also create potential problems (64, 82).

RCTs are often of an exploratory nature, with the purpose of estimating the efficacy of existing interventions in ideal or experimental settings. An alternative would be to adapt an RCT specifically for economic evaluations. The alternative to the exploratory design (*can* it work?) is the pragmatic design (*does* it work?). The intention of a pragmatic designed trial is to offer both high internal validity and high external validity. A pragmatic RCT still uses a randomisation process, but has fewer restrictions on how study participants are recruited. The aim is to provide results that more closely reflect "real world" outcomes of using the intervention in clinical practice (58).

3.3.2 Setting and recruitment of PCRUs

The study was conducted at nine PCRUs in Region Stockholm and one in Region Jönköping County. About 20 PCRUs were invited, by phone or via mail, to participate in the study. If a PCRU was interested in participating, an information meeting was scheduled with the staff of that PCRU and someone from the research team.

3.3.3 Setting and participants

Participants were included or excluded based on the criteria in Table 2.

Table 2. Inclusion and exclusion criteria for recruitment of participants in Study II.

Inclusion criteria	Exclusion criteria
• Between 18 and 60 years • Pain located below the costal margin and above the inferior gluteal folds • Reoccurring low back pain for at least 3 months • Can stand or walk independently • Swedish speaking and literate	• Pain attributable to a known specific pathology (e.g., pain related to fractures, fibromyalgia, or tumour) • Pregnancy or less than 6 months postpartum or post weaning • Having been treated for low back pain by a chiropractor and/or physiotherapist in the preceding month

Study participants were recruited through the reception of each PCRU. Patients seeking care for back pain by phone were invited to participate in the study and received verbal information. After enrolment, study participants were randomised using a computer-generated block randomisation list, allocating each participant to one of the four treatment arms. All researchers involved in the study were blinded to block size(s) and the randomisation list. Opening envelopes was only permitted at the time of intervention allocation.

3.3.4 Data collection

Data were collected at baseline (after randomisation and before treatment began), and at follow-up, 3 and 6 months after baseline. Each participant filled out a computer-based questionnaire at each measurement occasion. If needed, a second and a third reminder was sent 2 and 7 days after the follow-up occasion. All data were obtained through the computer-based questionnaire and from the chiropractor and/or physiotherapist reporting the number and content of treatments.

Baseline data was collected during the first visit or at 1–4 days before the first visit at the PCRU. The questionnaire included data on personal characteristics (age, sex, education, smoking status, physical activity, use of painkillers, and pain duration), outcome measures (back pain-related functional limitation, pain intensity, general health, HRQoL, working status) and resource consumption (pharmaceuticals, health care visits, clinical examinations, surgery, and hospital days). Another questionnaire covering outcome measures (back pain-related functional limitation, pain intensity, general health, HRQoL, working status) and resource consumption (pharmaceuticals, health care visits, clinical examinations, surgery and hospital days) was sent out 3 and 6 months after baseline. At each follow-up occasion (and at baseline), the participants were asked to recall their resource consumption during the last three months.

Data on physical activity were also collected at follow-up. The Schedule for enrolment, interventions, and assessments is can be seen in table 3.

Table 3. Schedule of enrolment, interventions, and assessments of study participants in Study II.

	STUDY PERIOD				
	Enrolment	**Allocation**	**Post-allocation**		
TIME POINT	***Post first visit***	***Post first visit***	***Baseline***	***3 months***	***6 months***
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS:					
Advice			←	—	→
Chiropractic			←	—	→
Physiotherapy			←	—	→
Combination			←	—	→
ASSESSMENTS:					
Age, Sex, Education, Use of painkillers , Smoking, Pain duration			X		
Physical activity and Working status			X	X	X
ODI, NRS & EQ-5D			X	X	X
Direct and Indirect costs			X	X	X

3.3.5 Study treatments

During the first visit, all participants met a chiropractor and/or a physiotherapist for an initial clinical examination. The treatment duration, number of visits and the content of the treatment was at the discretion of the chiropractor and/or physiotherapist. Regardless of treatment allocation, participants were given verbal advice and written information on how to manage CLBP, and advice about the importance of staying active and avoiding rest (83). The treatment alternatives is presented in table 4.

Table 4. Treatment alternatives.

Information and advice (advice): Participants were given verbal advice and written information on how to manage CLBP and advice about the importance of staying active and avoiding rest.
Physiotherapy: The treatment usually involves stabilisation training, functional training, mobility training, postural control and exercise (28).
Chiropractic care: The treatment usually involves spinal manipulation defined as a high-velocity, low-amplitude movement at the limit of joint range, taking the joint beyond the passive range of movement (28).
Chiropractic care and physiotherapy (combination treatment): The treatment involves a combination of chiropractic care and physiotherapy, as defined above.

3.3.6 Data analysis

The main analysis was conducted as an intention-to-treat (ITT) analysis for all participants included in the study (84). The primary analysis was evaluation of the between-group differences in changes of ODI scores at 6 months. All statistical tests were carried out at the 5% significance level (2-sided). One-way ANOVA was used to analyse the differences between groups in the outcome variables at baseline and 6 months. Patterns of missing data and dropouts were examined and appropriate multiple imputations were used, depending on the nature of the missing data.

3.3.7 Cost-effectiveness analysis

The average number of quality-adjusted life years (QALYs) for each treatment was based on HRQoL values derived from the EQ-5D-3L and was calculated as the area under the curve during the 6-month period. For estimation of QALYs, adjustments were made for potential differences in baseline HRQoL between the treatment groups. This was done in a regression analysis (OLS model) with QALYs as the dependent variable, and three dummy variables for each treatment alternative (with advice being the reference treatment) and baseline HRQoL as independent variables (not specified in the study protocol).

To estimate direct costs, the quantities of consumed resources were multiplied by their unit costs. Unit costs of pharmaceuticals were collected from the price database available at the

Dental and Pharmaceutical Benefits Agency and unit costs for health care visits were based on prices for primary health care in Region Stockholm (85-87). Unit costs for clinical examinations and hospital days were based on unit costs in Region Stockholm and Region Skåne (Table 5) (88). Unit cost for surgery was based on Region Stockholm price adjustments for spinal surgery (87). A sensitivity analysis on total direct costs during 6 months was performed, in which unit costs were changed (± 50%). All costs were estimated in Swedish kronor (SEK) and for the year 2020.

Table 5. Medical care resources and unit costs (2020 costs in SEK).

	Resource	Unit cost	Reference
Medical visits			
	Physician	1,800	85
	Orthopaedist	1,800	85
	Nurse	800	85
	Psychologist	425	85
	Physiotherapist	420	85
	Chiropractor	420	85
	Naprapath	420	85
	Occupational therapist	420	85
	Dietician	420	85
Pharmaceuticals			
	Paracetamol	2	86
	Opioid	1.67	86
	Ibuprofen	1.8	86
	Ketoprofen	2.37	86
	Acetylsalicylic acid	2.65	86
	Diclofenac	1.95	86
	Celecoxib	4.50	86
Clinical examinations			
	Magnetic resonance imaging	1,700	88
	X-ray	618	88
	Computed tomography	1,648	88
	Ultrasound	1,000	88
	Blood sample	200	88
	Tissue sample	4,326	88
	Spinal surgery	50,000	87

3.4 STUDY III

3.4.1 Study design

Study III was a systematic mapping of systematic reviews (89). Systematic reviews and meta-analyses are effective methods for reviewing a treatment's effectiveness, compared with other inactive or active controls, and its level of evidence (90, 91). There is a growing number of systematic reviews with meta-analyses being published in peer-reviewed journals. In the Medline database alone, more than 8,000 systematic reviews are registered annually (92). Systematic mapping reviews have found that somewhere between 50% and 65% of the

assessed reviews had a high risk of bias (93, 94). A systematic review with high risk of bias can potentially be as misleading as a poorly performed clinical trial (95).

Mapping reviews allow researchers to systematically incorporate moderate to high quality systematic reviews on a specific research topic, to better understand the current knowledge (89). Systematic mapping reviews use the same systematic literature search strategies as regular systematic reviews, where the aim is to find the most relevant, recent, and high-quality reviews (95). When assessing relevance, mapping reviews use the same standard format of population, intervention, control and outcome as other systematic literature reviews (96). However, as a systematic review can become out-of-date after as little as 5 years, inclusion should be dependent on time of publication, with a focus on recent publications (95, 97-99).

All studies should ideally be free from bias. This is especially true for systematic reviews as they are often used as a basis for national treatment guidelines. Nonetheless, many of the systematic reviews are poorly performed and at risk of producing biased conclusions (92). There are a number of quality assessment tools available to decrease the risk of bias (100). The AMSTAR checklist (A MeaSurement Tool to Assess systematic Reviews) is one of the most widely used instruments to assess the risk of bias in systematic reviews and is used by the SBU, for example (96, 101).

3.4.2 Locating existing systematic reviews

Electronic searches for systematic reviews were conducted in PubMed and the Cochrane Database of Systematic Reviews. The search strategy also included screening of reference lists in the identified relevant articles, as well as manual searches. The first literature search was conducted in January 2017, followed by a second literature search in September 2019. The search algorithm was developed by the research group together with a search specialist from the Karolinska Institutet University Library. The first phase of the process was to review the records based on the inclusion and exclusion criteria. Two authors independently reviewed all records and full-text articles using the software Rayyan (102). If at least one of the authors found an abstract relevant, it was included and ordered in full text. In the second phase, the full-text articles were assessed for eligibility. Any disagreements were resolved in discussion with a third reviewer.

3.4.3 Assessing the relevance of existing systematic reviews

Systematic reviews of RCTs, published in English in peer-reviewed journals between 1 January 2007 and 30 September 2019, and investigating the effectiveness of treatments in one or more of the pre-defined treatment domains, were included. The population, intervention, control, and outcome (PICO) specified below was used to include relevant articles (please see table 6).

Table 6. Inclusion criteria.

Population	Individuals ≥ 18 years of age with non-specific CLBP, with or without radiating leg pain
Intervention	Non-surgical primary care treatments for non-specific CLBP
Control	No treatment, placebo/sham treatment, or other relevant non-surgical interventions in the treatment domains above
Outcome	Pain, HRQoL, or function

Systematic reviews that included a mix of RCTs and other study designs but did not report RCT results separately, and systematic reviews that mainly included subgroups based on one specific age, gender, or ethnicity, were excluded.

3.4.4 Assessing the quality and data handling

The AMSTAR checklist was used to assess the quality of the systematic reviews, in terms of risk of bias (101). In line with a previous mapping study (93), the AMSTAR checklist was modified in order to better fit the aim of the study. Question five was divided into two sub-questions, 5a ("Was a list of studies (included) provided?") and 5b ("Was a list of studies (excluded) provided?"). Based on the modified checklist and pre-specified criteria, each systematic review was classified as having a low, moderate, or high risk of bias using the definitions provided in Table 7. If the answer to any of the questions in the modified AMSTAR checklist was not reported or unclear, a conservative approach was used, and that question was interpreted as having a "No" answer. Any uncertainties regarding questions were discussed among the three reviewers in order to reach a consensus.

Table 7. Pre-specified criteria for low, moderate and high risk of bias. Modified list of questions based on AMSTAR.

Risk of bias	AMSTAR question	
	1	Predetermined research question and inclusion criteria established.
	2	At least two independent data extractors and consensus procedure reported.
	3	At least two databases were used in the literature search.
	5a	A list of included studies provided.
	6	Characteristics sex, age, and pain duration included in each study reported.
	7	Assessment of the overall scientific quality of each included study provided.
	8	The scientific quality of included studies used appropriately in formulating conclusions.
	9	The justification for combining or not combining results reported. Methods for pooling results reported.
	10	Potential publication bias reported. This item can be absent if publication bias was unlikely but not reported.
	11	Any conflict of interest reported. This item can be omitted if conflicts of interest were unlikely.
Low		Answer "Yes" to all questions 1, 2, 3, 5a, 6–11.
Moderate		Answer "Yes" to all questions 2, 5a, 6–8.
High		Answer "No" to any of the questions listed under Moderate risk of bias.

Questions 4 and 5b were not part of the risk of bias assessment and are not presented in the table.

Individual RCTs found within each systematic review were not assessed. RCTs were only assessed if there were clear inconsistencies or uncertainties about the characteristics of the study population and the results or conclusions in the systematic reviews. When more than one systematic review of the same treatment and outcomes was identified, the review with the lowest risk of bias was included (95), and if the risk of bias was the same, the most recent was included.

3.5 STUDY IV

3.5.1 Study design

Study IV is a population-based explorative prospective cohort study, using microdata from four Swedish nationwide administrative registers of people having had specialised outpatient or inpatient health care due to back pain.

Cost-of-illness (COI) studies describe the total costs (direct and indirect) that a disease or injury inflicts on a society or health care (103). Indirect costs are often the largest cost component in COI studies. Productivity losses are costs that derive from an individual's inability to perform their work due to a disease or disability. Productivity losses can be estimated in two ways: absenteeism, meaning that an individual is unable to work, or presenteeism, meaning that an individual's productivity at work is reduced (104).

To estimate indirect costs (productivity losses), most health economists use the human capital approach and lost gross income (salaries plus social and employer benefits) to estimate the reduction in the value of labour production during the time of sick leave and absence from work. Some argue that the human capital approach may overestimate the costs (58), and have instead proposed the friction cost method. However, Rice argues that the human capital approach underestimates costs, as retired elderly people tend to be valued very low when using market values and that the value of one's work may not be reflected in wages (103). A COI study gives information about the potential value of eradicating a disease, which can be used as a basis for guiding resources and research activities to fields with the highest potential benefits and to monitor changes in the burden of diseases over time. However, the value of COI studies when prioritising among interventions and health care programmes has been questioned (103).

3.5.2 Sampling and recruitment

The inclusion criteria for the back pain group were:

- Aged 19–60 years in 2010, having lived in Sweden in 2005–2009.
- Having been diagnosed with back pain (International Statistical Classification of Diseases and Related Health Problems (ICD-10) code M54 (105)) as main diagnosis in inpatient or specialised outpatient health care in 2010.
- No previous inpatient or specialised outpatient health care for back pain as main or secondary diagnosis according to the National Patient Register (available for inpatient health care since 1987 and for specialised outpatient health care since 2001).

A matched reference group was drawn from the general population in Sweden among all those who in 2010 were 19–60 years, had lived in Sweden in 2005–2009, and had no main or secondary diagnoses of back pain (ICD-10 code M54), in the past, present or the 12 months following the study, according to the National Patient Register. For each identified individual with back pain, five references were included, matched with regard to sex, age, type of living area, and country of birth.

Individuals with back pain were followed prospectively for 12 months from the date of the first inpatient stay or specialised outpatient health care event for back pain in 2010 (index date, T_0). The matched references were also followed for 12 months after the index date. Individuals were censored at the year of death if that occurred before the end of the 12-month follow-up.

Individuals with at least one visit to inpatient or specialised outpatient care during 12 months before T_0 for other diagnoses than M54 were defined as having multi-morbidity, except in the case of health care visits for uncomplicated delivery (O80) or burn-out (Z73.0).

3.5.3 Data collection and outcomes

Four nationwide registers used were managed by the following three authorities:

- Statistics Sweden: Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA), for information on age, sex (female/male), type of living area (big city/medium-sized city/rural area), country of birth (Sweden/Nordic countries

except Sweden/EU25 except Nordic countries/Rest of the world), educational level (elementary school/high school/university or college), occupation (white collar/blue collar/missing), and family situation (married or cohabitating without children at home/married or cohabitating with children at home/single without children at home/single with children at home).

- Swedish Social Insurance Agency: MicroData for Analysis of the Social Insurance database (MiDAS): dates, main diagnosis, and grade (full- or part-time) of SA and DP.
- National Board of Health and Welfare: National Patient Register (dates and diagnoses for inpatient and specialised outpatient health care), and Cause of Death Register (year of death).

Information on long-term SA (SA spells >14 days) and on DP were used to calculate the number of SA/DP net days during the 12 months from T_0 and forward.

In Sweden, both SA and DP can be granted for full-time (100%) or part-time (75%, 50%, or 25%) of ordinary work hours (106). This means that it is possible to have both partial SA and DP at the same time. Therefore, we calculated the number of net days, e.g., two absence days at 50% were combined into one net day. As a SA spell could go on for years before DP was granted, long-term SA and DP days were combined (hereinafter referred to as SA/DP).

The societal costs related to productivity losses for people with back pain and for the reference group were estimated using the human capital approach (58, 107). Productivity losses were estimated by multiplying the percentage of work time lost due to SA/DP per year by the age-adjusted mean annual income (451,664 SEK (108)) for each individual, including social security contributions from employers (31.42%) (109). The income was inflated to 2018 prices, using a harmonised index for consumer prices (110).

3.5.4 Data analysis

Descriptive analyses were conducted for the sociodemographic and multi-morbidity characteristics, as well as to estimate the mean number of SA/DP days and productivity losses during the 12 months following the index date T_0, for both the back pain patients and the reference group.

Since SA/DP is associated with a variety of sociodemographic factors (111-115), analyses of SA/DP were stratified based on the following variables: sex, age, type of living area, country of birth, educational level, occupational group, and family situation.

In addition, SA/DP during the 12-month follow-up was estimated for each of the following six different multi-morbidity diagnostic groups: Other musculoskeletal disorder (other M than M54), Depressive disorders (F32–F34), Other mental disorders (other F and Z73.0), Neoplasms (C00–D48), Diseases of the circulatory system (I00–I99), and Other (all others, excluding E10–E14, Z73.0, and O80).

The Pearson's chi-squared test was used to explore possible differences in the distribution of demographic and multi-morbidity characteristics between the back pain and the reference groups (between-group comparison) (116).

Another between-group comparison was performed to identify the difference in costs between the back pain group and the references with regard to demographic, socioeconomic, and multi-morbidity characteristics; this comparison was performed using a two-tailed t-test with unequal variances (statistical significance: $\alpha < 0.0001$). Two in-group comparisons were performed – one regarding differences in productivity losses between women and men in the back pain group, and the other exploring the impact of multi-morbidity on productivity losses, when already diagnosed with back pain. These comparisons were performed using a two-tailed t-test with unequal variances (statistical significance: $\alpha < 0.0001$).

3.6 ETHICAL CONSIDERATIONS

Study I was approved by the Regional Ethical Review Board in Stockholm, Sweden (Dnr 2012/2142-31/2) as were Studies II and IV (Dnr: 2016/1318-31-31, Dnr: 2007/762-31). In order to enable collection of data from a primary care setting, Study II received approval from Region Stockholm to collect personal data (SLSO 17-1976). For Study III, no ethical approval was sought, as the study design (systematic literature review) did not involve any participation of study participants.

Detailed information on background, purpose, study procedure, data and data processing for Studies I and II was given to all potential participants before they entered the trials. They were informed that participation was voluntary and that they were free to leave the study at any time. The information to potential study participants was adjusted in 2018 following the introduction of GDPR, and the changes were approved by the Regional Ethical Review Board in Stockholm, Sweden (Dnr: 20182295-32).

All participants in Studies I and II received care from a licensed health care professional. The treatment strategies evaluated are commonly and regularly used in Swedish primary health care. Potential risks of participating in the studies were likely to be small, but minor short-term pain and discomfort could be experienced after chiropractic care and physiotherapy.

Study IV was approved by the Regional Ethical Review Board in Stockholm, Sweden (Dnr: 2007/762-31). All data were cleaned and anonymised by a statistician before any of the researchers performed any data analysis. The raw data were never transmitted electronically.

4 FINDINGS

The findings in this thesis are divided into four sub-sections, starting with a comparison of the patient demographics of Studies I and II in relationship to Study IV (register data). The next sub-sections focus on the effectiveness and costs of the treatments for back pain and the level of evidence found in Study III. In the last sub-section, the results of the cost-effectiveness analysis in Study II are presented. However, the main findings of the thesis are summarised first.

4.1 MAIN FINDINGS

The study populations in Studies I, II and IV consisted of patients from primary care. On average, the patients in Study II had a higher socioeconomic status than those in Studies I and IV. There were some differences between Studies I and II in baseline PROMs, but these differences were not clinically important.

The changes in PROMs at 6 months (from baseline to follow-up) in Study II were greater than the changes in Study I were at 1 months. However, no statistically significant differences or clinically important differences could be detected between the groups in any of the outcome measures in Study II. The findings of the mapping review showed that there was some evidence (moderate to high) that NSAIDs, opioids, spinal manipulation, multidisciplinary biopsychosocial rehabilitation (MBR), and therapeutic ultrasound had some effects on PROMs in the treatment of patients with CLBP. However, the results indicated no clinically important differences between treatment groups.

Productivity losses were estimated in both Study II and Study IV. In Study IV, a back pain patient with a back pain diagnosis from specialised health care had a yearly indirect cost of SEK 52,118 on average. In Study II, the average value of labour production varied between about SEK 189,000 and 220,000 during six months in the different treatment groups, whereas the productivity loss estimated based on sick leave varied between about SEK 14,000 and SEK 26,000. The total direct costs over 6 months varied between about SEK 3,000 in the combination group and SEK 11,000 in the advice group.

The cost-effectiveness analysis was based on results that were neither statistically significant nor clinically important (between the treatment groups). Therefore, the cost-effectiveness results should be interpreted with caution. However, the point estimates of the differences in costs and effects between the treatment groups, as presented in Study II, indicated that combination treatment might be cost-effective, given that the willingness-to-pay for a gained QALY is SEK 900,000 (81).

4.2 DEMOGRAPHICS AND BASELINE OUTCOMES

Study IV shows that the typical back pain patient who sought specialist care in 2010 was a woman with a high school education, working in a blue-collar occupation. When compared with a matched reference group, there was a higher proportion of individuals with lower socioeconomic status in regard to education and occupation in the back pain group.

Study I had a higher proportion of men (51%) and blue-collar workers (47%) on average compared with Study IV. However, there were some differences between the acute and the chronic back pain groups in Study I. In the chronic back pain group, there were 63% women, compared with 40% in the acute back pain group. The acute back pain group had a higher proportion of white-collar workers: 34% compared with 25% in the chronic back pain group. There were more students, unemployed or retired patients in the chronic back pain group: 28% compared with 19% in the acute group. In Study I, there was a higher fraction of women when compared with Studies II and IV. Participants in Study II had a higher socioeconomic status in general than participants in Studies I and IV. For a comparison of patient characteristics between the different studies, see Table 8.

Table 8. Demographics of study sample in Studies I, II and IV.

		Study I	Study II	Study IV
		n = 138	n = 88	n = 23,176
Sex		n (%)	n (%)	n (%)
	Women	68 (49)	53 (60)	12,161 (52.47)
	Men	70 (51)	35 (40)	11,015 (47.53)
Age				
	19–29 years	14 (10.3)	7 (8)	3,909 (16.87)
	30–39 years	31 (22.4)	20 (22.7)	5,386 (23.24)
	40–49 years	40 (29.3)	33 (37.5)	6,870 (29.64)
	50–60 years	29 (20.7)	28 (31.8)	7,011 (30.25)
	61 years or older*	24 (17.2)	NA	NA
Educational level				
	Elementary school	NA	9 (10.2)	4,344 (18.74)
	High school	NA	39 (44.3)	11,957 (51.59)
	University/College	NA	40 (45.5)	6,875 (29.66)
Occupational group				
	White collar	41 (30)	43 (49)	7,295 (31.48)
	Blue collar	64 (47)	31 (35)	12,603 (54.38)
	Missing	30** (22)	14 (16)	3,278 (14.14)

** Individuals over 60 years of age included only in Study I.*

*** Students, unemployed or retired*

Participants in Study I reported higher HRQoL and lower pain intensity than participants in Study II. Participants in Study II where also worse off in terms of disability than participants with back pain in Study I (table 9). However, Study I showed that participants with acute back pain had the highest levels of disability of all groups.

Table 9. Mean values of PROMs at baseline in Studies I and II.

Study I		Baseline		Study II	Baseline		
	n	mean	(SD)		n	mean	(SD)
Acute back pain				Chronic low back pain			
$EQ\text{-}5D_{index}$	79	0.65	(0.26)	$EQ\text{-}5D_{index}$	88	0.56	(0.28)
ODI	79	23.96	(14.97)	ODI	88	22.93	(12.06)
NRS	79	4.81	(2.05)	NRS	88	5.36	(2.07)
Chronic back pain							
$EQ\text{-}5D_{index}$	56	0.69	(0.19)				
ODI	52	19.61	(11.66)				
NRS	56	4.59	(2.44)				

4.3 CHANGES IN PROMs

Exploration of the changes in PROMs after chiropractic care in Study I revealed that study participants with back pain had statistically significant improvements in all PROMs (ODI, HRQoL, and NRS) after 4 weeks as compared with at baseline (please see table 10). The largest differences were found among those with acute back pain. A larger difference for participants with acute back pain was expected, also without treatment, as most patients with acute pain recover within 6 weeks (78, 117).

Table 10. Mean changes in PROMs for chronic back pain patients from baseline to four weeks (standard deviation (SD) within parentheses).

Study I	Change over 1 month	
Chronic back pain	Mean (SD)	P value
ODI	2.88 (7.70)	0.01
HRQoL	0.04 (0.14)	0.02
NRS	0.90 (2.06)	0.00

Table 11 shows that all treatment groups (except physiotherapy) had a more than 10-point change in the primary outcome measure ODI, indicating that the change (between baseline and follow-up at 6 months) was clinically important. Chiropractic care showed a larger improvement in ODI after 6 months than after 1 month (12.56 vs 2.88 at 1 months), in both cases compared with at baseline. The same trend could be seen in the NRS. An interesting finding was the change in HRQoL among study participants in the physiotherapy treatment arm. Physiotherapy had the lowest positive change in both ODI and NRS among all four groups; however, physiotherapy had the second highest positive change in HRQoL after 6 months.

The change in PROMs between baseline and follow-up at 6 months were neither statistically significant nor clinically important between any of the treatment groups. The largest difference

was seen in ODI between chiropractic care and physiotherapy, with a difference of 6.43 in favour of chiropractic care. For HRQoL, the largest difference was between chiropractic care and advice, with a 0.12 difference in favour of chiropractic care. For the NRS, the largest difference was found between chiropractic care and physiotherapy with a 0.73 difference in favour of chiropractic care.

Table 11. Overview of changes in PROMs over 6 months and the current level of evidence on the treatment explored

		Study I	Study II		Study III
ODI		Change after 1 month	Change after 6 months	95% confidence intervals	Level of evidence**
	Advice	NA	10.86*	5.75 to 13.84	Low
	Physiotherapy	NA	6.13	1.37 to 11.20	Moderate
	Chiropractic	2.88	12.56*	7.38 to 16.76	Moderate
	Combination	NA	11.58*	5.48 to 17.92	Moderate
HRQoL					
	Advice	NA	0.06	-0.10 to 0.27	Missing
	Physiotherapy	NA	0.17	0.10 to 0.23	Moderate
	Chiropractic	0.04	0.18	0.01 to 0.34	Missing
	Combination	NA	0.13	0.12 to 0.27	Missing
NRS					
	Advice	NA	1.97*	0.39 to 4.05	Low
	Physiotherapy	NA	1.67	0.74 to 2.85	Moderate
	Chiropractic	0.90	2.70*	1.80 to 4.12	Moderate
	Combination	NA	2.13*	0.92 to 3.08	Moderate

* *Indicating a clinical important difference. Note that there is no clinical important difference in PROMs between any of the treatment groups.*
***For the primary treatment alternative for that specific treatment group*.

Study III showed that there was moderate evidence for some of the treatments most commonly used by physiotherapists (motor control exercise) and chiropractors (spinal manipulation). Study III showed moderate evidence that motor control exercise may or is likely to have a positive effect on pain and function compared with minimal intervention in the short, medium, and long term. There was also moderate evidence that it is likely or very likely that motor control exercise provides the same effect on reducing pain and improving function and HRQoL as manual therapies. Spinal manipulation is likely to reduce pain compared with other active treatments (exercise and physical devices) in the short, medium and long term, and is likely to improve function compared with other active treatments (exercise and physical devices) in the short and medium term.

There was also moderate evidence for the use of combined interventions for CLBP. However, knowledge gaps exist within all treatment groups. There was no evidence for the effectiveness of spinal manipulation or combined interventions compared with placebo or sham. There was also no evidence for combined chiropractic interventions to be more effective than other

alternatives. The knowledge gaps for physiotherapy were the effectiveness of exercise therapy, which is a more general exercise treatment than motor control exercise. There was generally low or very low evidence on how the different treatment alternatives affected HRQoL.

Advice was the treatment arm with the most knowledge gaps. There was low to very low evidence for any of the potential treatment alternatives (walking, patient education or back school). The point estimates for treatment arm advice suggested that it was slightly more effective than physiotherapy in increasing function and slightly better than physiotherapy in decreasing pain. However, when it came to HRQoL, the advice arm was not effective compared with the other treatment arms.

A high percentage of systematic reviews had a high risk of bias (66%) and these were excluded. The questions that most systematic reviews with a high risk of bias failed on were having at least two independent data extractors (AMSTAR question 2), unclear or lacking reports on population characteristics (AMSTAR question 6) and failure to appropriately formulate a conclusion based on the findings (AMSTAR question 8).

4.4 COSTS

Study IV showed that the total annual productivity loss was SEK 52,118 higher in the back pain group than the reference group. The difference in productivity loss between the back pain group and the reference group varied between subgroups. For example, the difference was SEK 60,230 for women, and SEK 63,706 and SEK 68,333 for individuals living in rural areas or born in other Nordic countries than Sweden, respectively. In Study II, the costs due to sickness absence varied between about SEK 14,000 and SEK 26,000 in the various treatment groups, which is less than half the costs of the total productivity losses in Study IV (SEK 85,709) (see Tables 12 and 13).

Table 12. Annual total costs of productivity losses per individual, among 23,176 people with incident back pain in 2010 and 115,880 matched references, in relation to sociodemographic characteristics.

	Mean cost per person and year (SEK)			
	Back pain	References	Difference	T-test (P value)
Sex				
Women	99,610	39,379	60,230	< 0.0001
Men	69,494	27,802	41,693	< 0.0001
Age				
19–29 years	41,693	13,901	27,792	< 0.0001
30–39 years	59,069	17,376	41,693	< 0.0001
40–49 years	84,547	31,267	53,280	< 0.0001
50–60 years	129,715	61,382	68,333	< 0.0001
Educational level				
Elementary school	127,402	78,758	48,643	< 0.0001
High school	89,184	33,590	55,594	< 0.0001
University/College	53,280	16,214	37,066	< 0.0001
Type of living area				
Big cities	71,808	31,267	40,541	< 0.0001
Medium-sized cities	90,336	33,590	56,755	< 0.0001
Rural areas	101,923	38,218	63,706	< 0.0001
Country of birth				
Sweden	82,234	30,115	52,118	< 0.0001
Nordic countries (except Sweden)	127,402	59,069	68,333	< 0.0001
EU 25 (excluding Nordic countries)	94,973	46,330	48,643	< 0.0001
Rest of the world	93,811	45,168	48,643	< 0.0001
Occupational group				
White collar	46,330	12,739	33,590	< 0.0001
Blue collar	89,184	27,802	61,382	< 0.0001
Missing	159,830	114,662	45,168	< 0.0001
Total population	85,709	33,590	52,118	< 0.0001

Table 13. Labour production (based on working status) and indirect costs (based on hours absent from work) during 6 months of follow-up.

	Advice n = 18	Physiotherapy n = 24	Chiropractic care n = 24	Combination n = 22
Labour production (SEK)				
0–3 months	105,540	97,153	113,927	110,433
4–6 months	88,066	91,561	106,239	106,239
0–6 months	193,606	188,714	220,166	216,671
Indirect costs (SEK)				
0–3 months	10,237	12,267	12,700	6,953
4–6 months	4,006	9,253	13,717	7,121
0–6 months	14,243	21,520	26,417	14,074

Study II showed that total direct costs over 6 months varied between SEK 3,081 in the combination group and SEK 11,135 in the advice group (table 14). The differences were not statistically significant between any of the treatment groups.

Table 14. Direct costs during 6 months in SEK

	Advice	Physiotherapy	Chiropractic care	Combination
Medical visits				
Physician	1,584	1,026	324	234
Orthopaedist	0	0	0	108
Nurse	0	304	0	48
Psychologist	0	55	51	0
Physiotherapist	542	962	403	496
Chiropractor	869	248	1,420	1,247
Naprapath	239	248	25	416
Occupational therapist	0	0	76	235
Total costs medical visits	3,235	2,843	2,299	2,784
Pharmaceuticals				
Paracetamol	59	218	81	44
Opioid	0	9	12	7
Ibuprofen	22	63	49	2
Ketoprofen	0	0	31	0
Acetylsalicylic acid	0	7	0	29
Diclofenac	28	38	1	11
Celecoxib	0	12	0	0
Total costs pharmaceuticals	109	347	174	92
Clinical examinations				
Magnetic resonance imaging	374	442	595	204
X-ray	238	0	0	0
Blood sample	179	0	102	0
Total costs clinical examinations	791	442	697	204
Spinal surgery	7,000	0	0	0
Total direct costs	**11,135**	**3,632**	**3,170**	**3,081**

4.5 COST-EFFECTIVENESS

One aim of this thesis was to evaluate the cost-effectiveness of different primary care treatments for CLBP. However, the point estimates were neither statistically significant nor clinically important. Therefore, the cost-effectiveness results from Study II should be interpreted with caution. The QALYs for each treatment is presented in table 15.

Table 15. QALYs based on the Swedish and the UK value sets.

Treatment	QALY* (95% confidence intervals)	QALY** (95% confidence intervals)
Advice	0.410 (0.399 to 0.428)	0.355 (0.323 to 0.408)
Physiotherapy	0.414 (0.400 to 0.430)	0.367 (0.303 to 0.398)
Chiropractic care	0.411 (0.396 to 0.426)	0.357 (0.339 to 0.421)
Combination	0.418(0.400 to 0.434)	0.377 (0.357 to 0.404)

** QALYs during 6 months after baseline based on a regression model, adjusting for differences in baseline HRQoL. The Swedish experience-based value set was used to convert EQ-5D health states to HRQoL values(56).*
*** QALYs during 6 months after baseline based on a regression model, adjusting for differences in baseline HRQoL. The UK value set was used to convert EQ-5D health states to HRQoL values (55).*

Using the point estimates for the costs and QALYs indicated that advice and physiotherapy were dominated by combination treatment, and that the combination treatment, from a societal perspective, was cost-effective compared with chiropractic care given a threshold value, or a willingness-to-pay for a QALY, of SEK 900,000. The incremental cost-effectiveness ratio, when comparing combination treatment with chiropractic care was SEK 486,571 (3,406/0.007). Combination treatment was cost-effective from a societal perspective also if indirect costs were estimated based on hours of sick leave or when QALYs were based on the UK value set.

Table 16. A sensitivity analysis on total costs during 6 months in which unit costs are changed (± 50%).

	Advice	Physiotherapy	Chiropractic care	Combination
Medical visits				
Physician +	11,927	4,145	3,332	3,198
Physician -	10,343	3,119	3,008	2,964
Orthopaedist +	11,135	3,632	3,170	3,027
Orthopaedist -	11,135	3,632	3,170	3,027
Nurse +	11,135	3,784	3,170	3,105
Nurse -	11,135	3,480	3,170	3,057
Physiotherapist +	11,406	4,112	3,371	3,328
Physiotherapist -	10,864	3,151	2,968	2,833
Chiropractor +	11,569	3,755	3,879	3,704
Chiropractor -	10,700	3,508	2,460	2,457
Naprapath +	11,254	3,755	3,182	3,288
Naprapath -	11,015	3,508	3,157	2,873
Occupational therapists +	11,135	3,632	3,207	3,198
Occupational therapists -	11,135	3,632	3,132	2,963
Pharmaceuticals				
Paracetamol +	11,164	3,740	3,210	3,103
Paracetamol -	11,105	3,523	3,129	3,058
Opioid +	11,135	3,636	3,176	3,084
Opioid -	11,135	3,627	3,164	3,077
Ibuprofen +	11,146	3,663	3,194	3,082
Ibuprofen -	11,124	3,600	3,145	3,079
Ketoprofen +	11,135	3,632	3,185	3,081
Ketoprofen -	11,135	3,632	3,154	3,081
Acetylsalicylic acid +	11,135	3,635	3,170	3,095
Acetylsalicylic acid -	11,135	3,628	3,170	3,066
Diclofenac +	11,149	3,650	3,170	3,086
Diclofenac -	11,121	3,613	3,169	3,075
Medical tests/investigations				
Magnetic resonance imaging +	11,322	3,853	3,467	3,183
Magnetic resonance imaging -	10,948	3,411	2,872	2,979
RTG +	11,254	3,632	3,170	3,081
RTG -	11,016	3,632	3,170	3,081
Blood test +	11,224	3,632	3,221	3,081
Blood test -	11,045	3,632	3,119	3,081
Surgery +	14,635	3,632	3,170	3,081
Surgery -	7,635	3,632	3,170	3,081
Without surgery	4,135	3,632	3,170	3,081
Total direct costs (base case)	11,135	3,632	3,170	3,081

From a health care perspective and when including only direct costs, combination treatment dominated all other treatments (lower costs and more QALYs). These results were not sensitive to changes in the unit prices for the resources (Table 16). Only when the price of a naprapath was increased by 50% or when the price of magnetic resonance imaging was decreased by 50% was chiropractic care associated with the lowest direct costs.

5 DISCUSSION

The thesis showed that back pain, for individuals of working age making their first specialist health care visit, was associated with significant productivity losses due to long-term sickness absence and disability pension. Productivity losses may be affected by sociodemographic factors and it was indicated that individuals with back pain with an additional diagnosis may have greater productivity losses than individuals with only a back pain diagnosis. In addition, the thesis demonstrated that there was evidence for some primary care treatments (NSAIDs, opioids, spinal manipulation, MBR, and therapeutic ultrasound) to have positive effects (although not clinically important) on pain and/or function in patients with CLBP. However, there were considerable knowledge gaps for the majority of treatments. Furthermore, the thesis showed significant (and clinically important) improvements in health outcomes on back pain-related functional limitation, pain intensity, and health-related quality of life over a 4-week period treatment with chiropractic care for patients with non-specific acute and chronic back pain.

As indicated in the pragmatic RCT, there were no statistically significant nor clinically important differences in back pain-related functional limitation, pain intensity, or health-related quality of life, when physiotherapy, chiropractic care, and the combination of physiotherapy and chiropractic care, were compared with advice to patients with non-specific CLBP over a 6-month period. There were small and not statistically significant differences in QALYs and costs between the treatment groups. Due to the low sample size and high dropout rates these results should be interpreted with caution.

Back pain is a complex condition and the new definition of pain places greater emphasis on its individuality as well as the biological, physiological and social factors that impact on pain perception (3, 6). This thesis contributed to the understanding of how certain social determinants of health may impact a back pain diagnosis. Productivity losses were higher among women than men, among blue collar workers than white collar workers and for individuals with a lower level of education, which has been seen in multiple studies (114, 115, 118). However, the important contribution of Study IV was the estimation of a monetary value on the burden of back pain due to long-term sick leave and disability pension in a Swedish context.

This thesis showed that minimal treatment alternatives such as advice to stay active, walking or information templets had a very low level of evidence as compared with other treatments. In a synthesis of the existing national treatment guidelines (USA, UK and Denmark) published in *The Lancet* in 2018, it was found that the first-line treatment for back pain should be "Advice to remain active" and "Education" (119). It may seem surprising that most national treatment guidelines recommend treatments with very low evidence. One reason could be that treatment guidelines are based not only on the level of evidence, but also on clinical experience. The results from Study II also indicated that the difference between advice and the other treatments was not statistically significant or clinically important. Future research should prioritise treatments that are considered to be minimal interventions, like staying active or walking, in order to understand their effectiveness. Otherwise, there is a risk of recommending ineffective treatments and wasting valuable health care resources.

One of the treatments where the evidence were rated as moderate to high was MBR. In the systematic review, the authors defined the treatment as "A multi-disciplinary rehabilitation technique with at least one physical dimension and one of the other dimensions (psychological or social or occupational)" (27). The results included in this thesis indicated that combined treatment could be cost-effective. Although this treatment should perhaps not be defined as multi-disciplinary, it does include some elements of psychological and social components. The booklet used to standardise advice mentions mental tools for dealing with your back pain, such as continuing to go to work and not avoiding social events (83). It would be interesting to study if different forms of multi-disciplinary treatments affect back pain patients differently and if there is a dose-response correlation.

A majority of the systematic reviews that were assessed in full had a high risk of bias. This is not unique for systematic reviews on CLBP. There has been an increase of published systematic reviews and unfortunately a high proportion are of poor quality (92). Unreliable reviews are equally misguiding as poor RCTs or observational studies (95). It is important to recognise the growing need for evaluations of systematic reviews, as health care staff, policymakers and clinical practice guideline developers can be misled by unreliable results.

One question that can be asked in the study of a condition for which there is a lack of pathological findings and objective outcome measures like biomarkers is "Does the treatment work?" (6). This thesis will not be able to answer that question. The natural history of acute back pain is that it goes away naturally, which explains the progression in the acute back pain group (117). However, individuals with chronic back pain do not usually experience any substantial improvements after the first 6 weeks (117). All treatment groups in Study II had greater improvements in function, pain intensity, and HRQoL after 6 months than the chronic back pain group at one month. This may indicate that there is a natural progression of back pain can that increase over time.

5.1 METHODOLOGICAL CONSIDERATIONS

The strength of this thesis was the combination of different levels of data. In Studies I and II, the patients followed and data collected were specific to the aim. A systematic literature review was performed to identify and assess the current knowledge. Ultimately, it was possible to dig into register data and make an assessment of the productivity losses using a national population sample. Combining all these results in a thesis yields a deeper understanding of the field and provides a context for the results of each of the sub-studies. One perspective that is absent from this thesis is that based on qualitative methods. Working closely with the staff at the PCRUs provided opportunities to discuss, not just aspects in the first and second sub-studies, but also the day-to-day work that they perform, which should be documented for future research projects.

Study participants in the RCT were not blinded to the treatment they received, as it was not possible given the pragmatic design. It has been argued that there is no correlation with higher effects for individuals who are blinded compared with those that are (120). The results indicated that blinding could be less important in clinical trials than previously believed.

5.1.1 Setting

Three out of four of the sub-studies in this thesis explored or assessed treatments in a primary care setting. This is not by chance, as there has been a growing need for research in this context and testing of not only pharmacological interventions, but also non-pharmacological interventions provided in primary care settings (121, 122). Primary care is also the setting where most of these patients are treated. However, starting new projects at a PCRU can be challenging, as most have little or no experience of research and there is little financial support for conducting research in the current reimbursement system.

5.1.2 Strengths and limitations of each sub-study

In Study I, we used a national sample of 20 chiropractic clinics located all around Sweden, in both rural and urban areas. The number of staff ranged from 1 chiropractor to more than 10 health care professionals. The work experience of the chiropractors varied and ranged from 1 year up to more than 25 years of experience. This was one of the major strengths of Study I, as it provided a representative view of the general chiropractic clinic. Another strength was the use of the validated PROMs EQ-5D, ODI and NRS (45, 54, 56, 123). These PROMs are frequently used in back pain research, as well as in the national registries in Sweden. However, there are some limitations to the method that should be taken into consideration when interpreting the findings, such as the lack of a control group and the high dropout rate. Without a proper control group, it is not possible to draw any conclusions on the effectiveness of a treatment or intervention.

It has been suggested that in order to provide data suitable for analysing the cost-effectiveness of an intervention, pragmatic RCTs are preferable to more traditional RCT (58, 82, 124). By using a pragmatic design, the results may more readily be generalised to clinical practice. The reason is that study participants in a pragmatic trial may to a greater degree reflect the group of patients that will be treated in clinical practice compared with study participants in a "traditional" RCT, who are selected based on restrictive inclusion and exclusion criteria. A limitation of using a pragmatic RCT is the need for larger sample sizes, as the effects of an intervention will be less precise and less effective.

In Study II, the drawbacks of Study I were corrected, with a study protocol being published a pragmatic RCT carried out (81). This was a strength and guided the project from the start. As previously stated, publishing a study protocol has many benefits. Publishing a protocol means sharing your work with researchers outside your research team and allows for an early peer-review of your work, decreasing the risk of major limitations to the study design. A study protocol increases the transparency of the study methods used to collect and analyse data and provides the opportunity for other researchers to review the study before data collection. Furthermore, a protocol reduces the risk of flexibility in the analysis and reporting of results. It may also reduce the risk of publication bias, which implies that negative findings may to a greater extent be published (125). Systematic reviews can now investigate if the number of published articles correlates with the number of preregistrations. Even if the research group tried to be as detailed as possible in the study protocol, there were some deviations from the

protocol, which was reported in Study II. For example, a regression model was used to correct for the baseline quality of life when estimating QALYs. This was not stated in the protocol.

An important limitation of Study II was the low sample size, which was far from reaching the required sample size to detect an effect in ODI. Based on power calculations, it was estimated that approximately 600 participants were needed (150 per treatment group) (81). This means that the study had a low power to detect any potential real difference in ODI and the other health outcome measures. Thus, it cannot be ruled out that there were differences in health outcomes between the treatment groups. Study II should be viewed as a pilot study and can be used as a basis to inform future studies investigating the effectiveness, costs and cost-effectiveness of different back pain treatments. The difficulty in recruiting study participants within a primary care setting can be seen in multiple studies, not just among back pain individuals, but also in studies on tobacco cessation programs and knee osteoarthritis (126-128). Bornhöft et al. describes the difficulty to motivate nurses to recruit study participants (127). A thesis on partnership between primary health care and academia described that collaborating with primary care was not a simple or linear process. In order to succeed, researchers need to carefully manage the partnership and place greater resources on collaboration planning (129). The PCRUs that participated in Study II had high staff turnover, which made recruitment of patients difficult. In a qualitative study on perceived barriers to implementing a tobacco prevention program in primary health care in Sweden, the staff describe a high staff turnover rate, lack of resources and structure (130). These findings are similar to the problems mentioned by the PCRU staff.

The dropout rates were a limitation in both Studies I and II. Dropout is common in RCTs and similar rates can be seen in other studies carried out in primary care (126-128, 131). High dropout rates means losing valuable information, which can create biased results as well as making the results less precise and widen the confidence intervals (132). In the studies included in this thesis, multiple imputation was used to address missing data which can reduce the risk of bias as well as increase the precision (132). However, multiple imputation does not solve the basicproblem and it is important to be transparent about the dropout rates and the limitations associated with it.

Study III used a new type of design for literature reviews. This design comes with both strengths and limitations. Grant and Booth write that the strengths of mapping reviews are their ability to identify and contextualise gaps in the evidence base (89). The perceived limitation of mapping reviews is related to the synthesis of results (89). A systematic mapping study is at risk of oversimplifying or masking considerable variation (heterogeneity) between studies (89).

A strength to Study III was its broad research strategy, which did not discriminate between treatments. As there were no national guidelines on which treatments should and should not be part of primary care, a broader search strategy was needed to capture all the relevant treatment alternatives. With the help of a panel of health care providers with clinical experience, the research group could produce categories into which the treatments found in the search could be searched. Another major strength corresponded to what Grant and Booth write about systematic mapping reviews. Study III provided an informative map on the current level of

evidence for treatment alternatives for CLBP. The lack of national guidelines, the inconsistencies in the treatment of CLBP patients at PCRUs in Sweden (28) and the inability within health care to effectively treat CLBP create a urgent need to evaluate current knowledge and find directions for future researcher.

A limitation of Study III was the use of an old version of the AMSTAR checklist. This could be seen as an example of bad planning. However, the reason that the newest version of the AMSTAR checklist was not used was simply that is was not available when the study began. The new version AMSTAR 2 was developed because of the increase in the use of non-randomised trials in systematic reviews (133). As systematic reviews using non-randomised trials for evaluating effectiveness were not included in Study III, the decision was made not to use AMSTAR 2. An interesting note is that the SBU still uses the old version of the AMSTAR checklist in its mapping reviews (134). Another limitation was that the RCTs within the systematic reviews were not assessed. This ties back to the perceived limitations of a mapping design as described by Grant and Booth (89). Given its design, a mapping study should not be too detailed and cannot examine, for example, heterogeneity to the same extent as a systematic review. This can create some problems as a mapping review can be seen as an uncomplete systematic review or an overly complicated attempt at producing a guideline. Study III was seen as both during the peer-review process.

In Study IV, a large study sample extracted from Swedish national registries was used. Having access to such data provided an excellent opportunity to estimate the cost of productivity losses for this specific study population. The data had some strengths: it was free from dropout and there was no selection bias, as the whole population is part of the register. Another strength was the use of matched references, which is not always used in evaluations of costs (22-24). Without a reference group, there is a risk of overestimating the true cost of a disease, as there is usually no population were productivity losses are zero. A limitation was the lack of sick leave data for the first 14 days, which may imply an underestimation of the total productivity loss due to sickness absence. Another limitation was the lack of data from primary care, which makes the sample different from those in the other three studies in this thesis. It is fair to say that the population in study IV was probably worse off with less severe back pain than the study populations in studies I, II or III.

6 CONCLUSIONS

Back pain is associated with significant productivity losses for individuals of working age. Individuals with a first specialist health care visit for back pain had considerable higher productivity losses than those without back pain. It was indicated that productivity losses might be affected by sociodemographic factors and that individuals with back pain with an additional diagnosis might have higher productivity losses than individuals with only a back pain diagnosis.

There was evidence that some primary care treatments (NSAIDs, opioids, spinal manipulation, MBR, and therapeutic ultrasound) had positive effects on pain and/or function for patients with chronic low back pain. However, these effects were usually not clinically important and there are considerable knowledge gaps for most back pain treatments.

Chiropractic care of patients with acute back pain may, over a 1-month period, improve health outcomes (back pain-related functional limitation, pain intensity, and health-related quality of life).

No statistically significant differences in back pain-related functional limitation, pain intensity, health-related quality of life, costs, or QALYs were found when physiotherapy, chiropractic care, and combination treatment were compared with advice over a 6-month period, in the treatment of patients with CLBP in Sweden. Due to the high dropout rate, the results should be interpreted with caution, and due to the low power of the study, it cannot be ruled out that there were differences between the treatment groups in these outcome measures. In conclusion, there is a great need for high-quality, large-scale studies to further study the effectiveness, costs and cost-effectiveness of primary care treatments for CLBP.

7 POINTS OF PERSPECTIVE

There is a continued need for economic evaluations of primary care treatment for back pain in Sweden. Even though this thesis provides some preliminary results on costs and effects, there is still a great need for more research in the field. This thesis found no difference between advice, physiotherapy, and chiropractic care or combination treatment. Future research should try to replicate Study II, with a sufficient sample size to test the validity of the results. It is important that future research encompasses HRQoL. There is a large knowledge gap in the literature on the effectiveness of primary care treatments as regards HRQoL which is crucial for economic evaluations.

It is strongly recommended that future systematic reviews follow the standard quality criteria for systematic reviews. The most common reasons for high risk of bias among the systematic reviews identified in this thesis were that they failed to include two reviewers when assessing the studies, that they lacked a clear description of the study population and that they failed to formulate appropriate conclusions based on the scientific evidence. Future systematic reviews should focus on treatments for which the most recent systematic review (with low to moderate risk of bias) will soon be outdated (e.g., exercise, NSAIDs, walking). It is suggested that future clinical research should focus on the treatments found to be effective and with a moderate or high level of evidence. Furthermore, future studies should consider researching the effectiveness and costs of advice as well as other minimal treatment options, as these are widely used and recommended in many treatment guidelines but need more evidence.

The productivity loss due to sickness absence and disability pension among patients with back pain are high when compared with those without a back pain diagnosis. The high costs, together with the high prevalence of back pain, makes this patient group important to prioritise. Allocating resources to primary care for research and health care should be a priority. There is also an urgent need for national treatment guidelines in order to standardise treatment modalities for back pain patients.

This thesis indicated that the combination of physiotherapy and chiropractic care could be a cost-effective treatment for patients with CLBP. Combination treatment had the lowest direct costs of all four treatment alternatives studied herein. Based on the results, collaboration between physiotherapists and chiropractors in the treatment of CLBP patients in primary care may be encouraged. However, there are considerable knowledge gaps, and there is a great need for large-scale studies to further study the effectiveness, costs and cost-effectiveness of combination treatment and other primary care treatments for CLBP.

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9 REFERENCES

1. Craig AD. A new view of pain as a homeostatic emotion. Trends in neurosciences. 2003;26(6):303-7.

2. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet (London, England). 2012;380(9859):2163-96.

3. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. 2020.

4. Swedish Council on Health Technology A. SBU Systematic Review Summaries. Occupational Exposures and Back Disorders. Stockholm: Swedish Council on Health Technology Assessment (SBU)

5. Balagué F, Mannion AF, Pellisé F, Cedraschi C. Non-specific low back pain. Lancet. 2012;379(9814):482-91.

6. Hartvigsen J, Hancock MJ, Kongsted A, Louw Q, Ferreira ML, Genevay S, et al. What low back pain is and why we need to pay attention. Lancet (London, England). 2018;391(10137):2356-67.

7. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. Psychological bulletin. 2007;133(4):581-624.

8. Public Health Agency of Sweden. Nationella folkhälsoenkäten, nationella och regionala resultat: Folkhälsomyndigheten; 2018 [Available from: http://fohm-app.folkhalsomyndigheten.se/Folkhalsodata/pxweb/sv/B_HLV/?rxid=19215807-23cd-44cf-8f63-b1eed980d297.

9. Backhans M, Forsberg JS, Lager A. Folkhälsorapport. Stockholms läns Landsting; 2015.

10. Sjolander P. What is known about the health and living conditions of the indigenous people of northern Scandinavia, the Sami? Global health action. 2011;4.

11. Swedish Council on Health Technology A. Metoder för behandling av långvarig smärta. En systematisk litteraturöversikt Stockholm; 2006. Report No.: SBU-rapport nr 177/1.

12. G. B. D. 2015 DALYs, Hale Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet (London, England). 2016;388(10053):1603-58.

13. Calvo-Munoz I, Gomez-Conesa A, Sanchez-Meca J. Prevalence of low back pain in children and adolescents: a meta-analysis. BMC pediatrics. 2013;13:14.

14. Lemeunier N, Leboeuf-Yde C, Gagey O. The natural course of low back pain: a systematic critical literature review. Chiropr Man Therap. 2012;20(1):33.

15. Hoy D, Bain C, Williams G, March L, Brooks P, Blyth F, et al. A systematic review of the global prevalence of low back pain. Arthritis and rheumatism. 2012;64(6):2028-37.

16. Walker BF. The prevalence of low back pain: a systematic review of the literature from 1966 to 1998. Journal of spinal disorders. 2000;13(3):205-17.

17. Andersson GBJ. Epidemiological features of chronic low-back pain. Lancet. 1999;354(9178):581-5.

18. Costa C, Maher CG, McAuley JH, Hancock MJ, Herbert RD, Refshauge KM, et al. Prognosis for patients with chronic low back pain: inception cohort study. BMJ. 2009;339:b3829.

19. Juniper M, Le TK, Mladsi D. The epidemiology, economic burden, and pharmacological treatment of chronic low back pain in France, Germany, Italy, Spain and the UK: a literature-based review. Expert Opin Pharmacother. 2009;10(16):2581-92.

20. Försäkringskassan. Vad kostar olika sjukdomar i sjukförsäkringen? Kostnader för sjukpenning i sjukskrivningar (över 14 dagar) samt sjukersättning och aktivitetsersättning år 2009 fördelat på diagnos. Stockholm: Försäkringskassan; 2011. Report No.: 1654-8574.

21. Hubertsson J, Englund M, Hallgarde U, Lidwall U, Lofvendahl S, Petersson IF. Sick leave patterns in common musculoskeletal disorders--a study of doctor prescribed sick leave. BMC Musculoskelet Disord. 2014;15:176.

22. Ekman M, Jonhagen S, Hunsche E, Jonsson L. Burden of illness of chronic low back pain in Sweden: a cross-sectional, retrospective study in primary care setting. Spine (Phila Pa 1976). 2005;30(15):1777-85.

23. Ekman M, Johnell O, Lidgren L. The economic cost of low back pain in Sweden in 2001. Acta orthopaedica. 2005;76(2):275-84.

24. Olafsson G, Jonsson E, Fritzell P, Hagg O, Borgstrom F. Cost of low back pain: results from a national register study in Sweden. Eur Spine J. 2018;27(11):2875-81.

25. Haldeman S, Dagenais S. A supermarket approach to the evidence-informed management of chronic low back pain. Spine J. 2008;8(1):1-7.

26. Swedish Council on Health Technology Assessment. Rehabilitering vid långvarig smärta. Stockholm: Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU); 2010. Report No.: 198.

27. Kamper SJ, Apeldoorn AT, Chiarotto A, Smeets RJ, Ostelo RW, Guzman J, et al. Multidisciplinary biopsychosocial rehabilitation for chronic low back pain: Cochrane systematic review and meta-analysis. BMJ. 2015;350:h444.

28. Swedish Council on Health Technology A. Acute neck and back pain: preventive interventions – Effects of physical training, manual treatment and cognitive behavioral interventions. Stockholm: Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU); 2016.

29. The National Board of Health and Welfare. Nationella riktlinjer för rörelseorganens sjukdomar 2012: Osteoporos, artros, inflammatoriskryggsjukdom och ankyloserande spondylit, psoriasisartrit och reumatoid artrit: Stöd för styrning och ledning. The National Board of Health and Welfare (SoS); 2012.

30. Chou R, Deyo R, Fu R, Dana T, Griffin J, Hashimoto R, et al. Noninvasive Treatments for Low Back Pain. 2016.

31. Chou R, Deyo R, Devine B, Hansen R, Sullivan S, Jarvik JG, et al. The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain. Evid Rep Technol Assess (Full Rep). 2014(218):1-219.

32. Saragiotto BT, Maher CG, Yamato TP, Costa LO, Menezes Costa LC, Ostelo RW, et al. Motor control exercise for chronic non-specific low-back pain. Cochrane Database Syst Rev. 2016;1:Cd012004.

33. Rubinstein SM, de Zoete A, van Middelkoop M, Assendelft WJJ, de Boer MR, van Tulder MW. Benefits and harms of spinal manipulative therapy for the treatment of chronic low back pain: systematic review and meta-analysis of randomised controlled trials. BMJ (Clinical research ed). 2019;364:l689.

34. Enthoven WT, Roelofs PD, Deyo RA, van Tulder MW, Koes BW. Non-steroidal anti-inflammatory drugs for chronic low back pain. Cochrane Database Syst Rev. 2016;2:Cd012087.

35. Swedish Council on Health Technology A. multimodal rehabilitering vid långvarig landryggssmärta. Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU); 2015.

36. Skargren EI, Carlsson PG, Oberg BE. One-year follow-up comparison of the cost and effectiveness of chiropractic and physiotherapy as primary management for back pain. Subgroup analysis, recurrence, and additional health care utilization. Spine (Phila Pa 1976). 1998;23(17):1875-83; discussion 84.

37. Saha S, Grahn B, Gerdtham UG, Stigmar K, Holmberg S, Jarl J. Structured physiotherapy including a work place intervention for patients with neck and/or back pain in primary care: an economic evaluation. The European journal of health economics : HEPAC : health economics in prevention and care. 2019;20(2):317-27.

38. Niemisto L, Lahtinen-Suopanki T, Rissanen P, Lindgren KA, Sarna S, Hurri H. A randomized trial of combined manipulation, stabilizing exercises, and physician consultation compared to physician consultation alone for chronic low back pain. Spine (Phila Pa 1976). 2003;28(19):2185-91.

39. Niemisto L, Rissanen P, Sarna S, Lahtinen-Suopanki T, Lindgren KA, Hurri H. Cost-effectiveness of combined manipulation, stabilizing exercises, and physician consultation compared to physician consultation alone for chronic low back pain: a prospective randomized trial with 2-year follow-up. Spine (Phila Pa 1976). 2005;30(10):1109-15.

40. UKBEAM. United Kingdom back pain exercise and manipulation (UK BEAM) randomised trial: effectiveness of physical treatments for back pain in primary care. BMJ. 2004;329(7479):1377.

41. UKBEAM. United Kingdom back pain exercise and manipulation (UK BEAM) randomised trial: cost effectiveness of physical treatments for back pain in primary care. BMJ. 2004;329(7479):1381.

42. Whitehurst DG, Lewis M, Yao GL, Bryan S, Raftery JP, Mullis R, et al. A brief pain management program compared with physical therapy for low back pain: results from an economic analysis alongside a randomized clinical trial. Arthritis and rheumatism. 2007;57(3):466-73.

43. Haas M, De Abreu Lourenco R. Pharmacological management of chronic lower back pain: a review of cost effectiveness. Pharmacoeconomics. 2015;33(6):561-9.

44. Fairbank J, Pynsent P. The Oswestry Disability Index. Spine (Phila Pa 1976). 2000(25(22)):2940-52.

45. Chapman JR, Norvell DC, Hermsmeyer JT, Bransford RJ, DeVine J, McGirt MJ, et al. Evaluating common outcomes for measuring treatment success for chronic low back pain. Spine (Phila Pa 1976). 2011;36(21 Suppl):S54-68.

46. Chiarotto A, Maxwell LJ, Terwee CB, Wells GA, Tugwell P, Ostelo RW. Roland-Morris Disability Questionnaire and Oswestry Disability Index: Which Has Better Measurement Properties for Measuring Physical Functioning in Nonspecific Low Back Pain? Systematic Review and Meta-Analysis. Phys Ther. 2016;96(10):1620-37.

47. Vianin M. Psychometric properties and clinical usefulness of the Oswestry Disability Index. J Chiropr Med. 2008;7(4):161-3.

48. Monticone M, Baiardi P, Vanti C, Ferrari S, Pillastrini P, Mugnai R, et al. Responsiveness of the Oswestry Disability Index and the Roland Morris Disability Questionnaire in Italian subjects with sub-acute and chronic low back pain. Eur Spine J. 2012;21(1):122-9.

49. Hjermstad MJ, Fayers PM, Haugen DF, Caraceni A, Hanks GW, Loge JH, et al. Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: a systematic literature review. J Pain Symptom Manage. 2011;41(6):1073-93.

50. Salaffi F, Sarzi-Puttini P, Atzeni F. How to measure chronic pain: New concepts. Best Pract Res Clin Rheumatol. 2015;29(1):164-86.

51. Salaffi F, Stancati A, Silvestri CA, Ciapetti A, Grassi W. Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. Eur J Pain. 2004;8(4):283-91.

52. Ferreira-Valente MA, Pais-Ribeiro JL, Jensen MP. Validity of four pain intensity rating scales. Pain. 2011;152(10):2399-404.

53. Alghadir AH, Anwer S, Iqbal A, Iqbal ZA. Test-retest reliability, validity, and minimum detectable change of visual analog, numerical rating, and verbal rating scales for measurement of osteoarthritic knee pain. J Pain Res. 2018;11:851-6.

54. Rabin R, Charro Fd. EQ-SD: a measure of health status from the EuroQol Group. Annals of Medicine. 2009;33(5):337-43.

55. Dolan P. Modeling valuations for EuroQol health states. Medical care. 1997;35(11):1095-108.

56. Burstrom K, Sun S, Gerdtham UG, Henriksson M, Johannesson M, Levin LA, et al. Swedish experience-based value sets for EQ-5D health states. Qual Life Res. 2014;23(2):431-42.

57. Solberg TK, Olsen JA, Ingebrigtsen T, Hofoss D, Nygaard OP. Health-related quality of life assessment by the EuroQol-5D can provide cost-utility data in the field of low-back surgery. Eur Spine J. 2005;14(10):1000-7.

58. Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G. Methods for the Economic Evaluation of Health Care Programmes. Oxford University Press; 2015.

59. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness--the curious resilience of the $50,000-per-QALY threshold. NEJM. 2014;371(9):796-7.

60. Hirth RA, Chernew ME, Miller E, Fendrick AM, Weissert WG. Willingness to pay for a quality-adjusted life year: in search of a standard. Medical decision making : an international journal of the Society for Medical Decision Making. 2000;20(3):332-42.

61. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. JAMA. 1996;276(15):1253-8.

62. Gold M, Siegel J, Russell L, Weinstein M. Cost-effectiveness in health and medicine. New York, USA: Oxford University Press; 1996.

63. Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. JAMA. 2016;316(10):1093-103.

64. Ramsey SD, Willke RJ, Glick H, Reed SD, Augustovski F, Jonsson B, et al. Cost-effectiveness analysis alongside clinical trials II-An ISPOR Good Research Practices Task Force report. Value Health. 2015;18(2):161-72.

65. Hughes D, Charles J, Dawoud D, Edwards RT, Holmes E, Jones C, et al. Conducting Economic Evaluations Alongside Randomised Trials: Current Methodological Issues and Novel Approaches. Pharmacoeconomics. 2016;34(5):447-61.

66. Johannesson M. Theory and methods of economic evaluation of health care. Developments in health economics and public policy. 1996;4:1-245.

67. The Swedish National Board of Health and Welfare. Nationella riktlinjer för rörelseorganens sjukdomar - Reumatoid artrit, axial spondylartrit, psoriasisartrit, artros och osteoporos The Swedish National Board of Health and Welfare (SoS); 2020.

68. Inspektionen för socialförsäkringen I. Rehabiliteringsgarantin. Inspektionen för socialförsäkringen, ISF.; 2012. Report No.: Rapport 2012:17

69. SALAR. Nationellt uppdrag: Smärta. Sveriges Kommuner och Landsting; 2016.

70. Hägglund P, Johansson P, Laun L. Rehabiliteringsgarantin. Institutet for marknads- och utbildningspolitisk utvärdering (IFAU); 2012. Report No.: 2012:26.

71. Riksrevisionen. Rehabiliteringsgarantin fungerar inte – tänk om eller lägg ner. Stockholm: Riksrevisionen; 2015 2015-10-13. Report No.: RiR 2015:19.

72. Jarl J, Nilsson P, Gerdtham U-G, Grahn B, Nyberg A. Hälsoekonomisk utvärdering av rehabiliteringsgarantin i Region Skåne – en retrospektiv registerstudie. Lund, Sverige: IHE 2017. Contract No.: IHE Rapport 2017:3.

73. Vårdguiden. Primärvårdsrehabilitering - godkända vårdgivare i SLL Stockholm: Stockholms Läns Landsting; 2020 [200909]. Available from: https://vardgivarguiden.se/avtal/vardavtal/avtal-vardval-lov/lov-vardval-stockholm/primarvardsrehabilitering/.

74. Vårdguiden. Primärvårdsrehabilitering: Stockholm Läns Landsting; 2020 [updated 20170914.

75. Mann CJ. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. Emergency medicine journal : EMJ. 2003;20(1):54-60.

76. Sharma M, Nazareth I, Petersen I. Observational studies of treatment effectiveness: worthwhile or worthless? Clinical epidemiology. 2019;11:35-42.

77. Boynton PM. Administering, analysing, and reporting your questionnaire. BMJ. 2004;328(7452):1372-5.

78. Van Tulder M, Becker A, Bekkering T, Breen A, del Real MT, Hutchinson A, et al. Chapter 3. European guidelines for the management of acute nonspecific low back pain in primary care. Eur Spine J. 2006;15 Suppl 2(Suppl 2):S169-91.

79. Kane RL, Radosevich DM. Conducting health outcomes research. Sudbury: Jones and Bartlett; 2011.

80. IBM. IBM SPSS Statistics for Windows. 21.0. ed: IBM Corp Armonk; 2012.

81. Gedin F, Skeppholm M, Burstrom K, Sparring V, Tessma M, Zethraeus N. Effectiveness, costs and cost-effectiveness of chiropractic care and physiotherapy compared with information and advice in the treatment of non-specific chronic low back pain: study protocol for a randomised controlled trial. Trials. 2017;18(1):613.

82. O'Sullivan AK, Thompson D, Drummond MF. Collection of health-economic data alongside clinical trials: is there a future for piggyback evaluations? Value Health. 2005;8(1):67-79.

83. Jensen I. Ryggboken : en bok till dig som har ont i ryggen: baserad på de senaste medicinska rönen om ryggbesvär. Stockholm: Libris; 2004.

84. Machin D, Campbell M, Walters S. Medical Statistics. England: John Wiley & sons Ltd; 2007.

85. Region Stockholm. Prislista vårdval primärvårdsrehabilitering inkl. patientavgift. Stockholms Läns Landsting; 2020 2017-01-01.

86. The Dental and Pharmaceutical Benefits Agency T. Läkemedel Stockholm: The Dental and Pharmaceutical Benefits Agency; 2020 [Available from: https://www.tlv.se/beslut/sok/lakemedel/.

87. Region Stockholm. Prisjustering inom vårdval ryggkirurgi 2020.

88. Region Skåne. Regionala priser och ersättningar för södra sjukvårdsregionen. Södra sjukvårdsregionen; 2020.

89. Grant MJ, Booth A. A typology of reviews: an analysis of 14 review types and associated methodologies. Health information and libraries journal. 2009;26(2):91-108.

90. Schünemann H, Brożek J, Guyatt GH, Oxman AD. GRADE Handbook 2013 [cited 2019 190603]. Available from: https://gdt.gradepro.org/app/handbook/handbook.html#h.wlsfq2lmj0gb.

91. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6.

92. Page MJ, Shamseer L, Altman DG, Tetzlaff J, Sampson M, Tricco AC, et al. Epidemiology and Reporting Characteristics of Systematic Reviews of Biomedical Research: A Cross-Sectional Study. PLoS Med. 2016;13(5):e1002028.

93. Mejare IA, Klingberg G, Mowafi FK, Stecksen-Blicks C, Twetman SH, Tranaeus SH. A systematic map of systematic reviews in pediatric dentistry--what do we really know? PLoS One. 2015;10(2):e0117537.

94. Osterberg M, Holmlund A, Sunzel B, Tranaeus S, Twetman S, Lund B. Knowledge Gaps in Oral and Maxillofacial Surgery: A Systematic Mapping. Int J Technol Assess Health Care. 2017;33(1):93-102.

95. Whitlock EP, Lin JS, Chou R, Shekelle P, Robinson KA. Using existing systematic reviews in complex systematic reviews. Annals of Internal Medicine. 2008;148(10):776-82.

96. Swedish Council on Health Technology A. Utvärdering av metoder i hälso- och sjukvården och insatser i socialtjänsten-En handbok. Stockholm: Statens beredning för medicinsk och social utvärdering; 2017 May 2017.

97. Shekelle PG, Ortiz E, Rhodes S, Morton SC, Eccles MP, Grimshaw JM, et al. Validity of the Agency for Healthcare Research and Quality clinical practice guidelines: how quickly do guidelines become outdated? JAMA. 2001;286(12):1461-7.

98. Moher D, Tsertsvadze A, Tricco AC, Eccles M, Grimshaw J, Sampson M, et al. A systematic review identified few methods and strategies describing when and how to update systematic reviews. Journal of clinical epidemiology. 2007;60(11):1095-104.

99. Shojania KG, Sampson M, Ansari MT, Ji J, Doucette S, Moher D. How quickly do systematic reviews go out of date? A survival analysis. Ann Intern Med. 2007;147(4):224-33.

100. West S, King V, Carey TS, Lohr KN, McKoy N, Sutton SF, et al. Systems to rate the strength of scientific evidence. Evidence report/technology assessment (Summary). 2002(47):1-11.

101. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Medical Research Methodology. 2007;7(1):1-7.

102. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210.

103. Rice DP. Cost of illness studies: what is good about them? Injury prevention: Journal of the International Society for Child and Adolescent Injury Prevention. 2000;6(3):177-9.

104. Swedish Council on Health Technology A. SBU Methods Resources. Assessment of Methods in Health Care: A Handbook. Stockholm: Swedish Council on Health Technology Assessment (SBU)

105. WHO. International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) Who.org: WHO; 2016 [Available from: https://icd.who.int/browse10/2016/en.

106. Swedish Social Insurance Agency [Försäkringskassan]. Social Insurance in Figures 2017. Stockholm: Swedish Social Insurance Agency 2017.

107. Tarricone R. Cost-of-illness analysis. What room in health economics? Health policy (Amsterdam, Netherlands). 2006;77(1):51-63.

108. Statistics Sweden. Average salary, by sector, occupation, age, sex and year Statistics Sweden; 2010 [Available from: http://www.statistikdatabasen.scb.se/pxweb/sv/ssd/START__AM__AM0110__AM0110A/LonYrkeAlder4/table/tableViewLayout1/?rxid=26290d43-4316-43a7-915e-ca6b2cdd0b80.

109. Hansson I. Tax statistical yearbook of Sweden 2010. Swedish Tax Agency; 2011. Report No.: SKV 104.

110. Eurostat. Annual exchange rates (ECU/EUR exchange rates versus national currencies [Available from: http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=prc_hicp_aind&lang=en.

111. Taylor JB, Goode AP, George SZ, Cook CE. Incidence and risk factors for first-time incident low back pain: a systematic review and meta-analysis. Spine J. 2014;14(10):2299-319.

112. Ferreira PH, Beckenkamp P, Maher CG, Hopper JL, Ferreira ML. Nature or nurture in low back pain? Results of a systematic review of studies based on twin samples. Eur J Pain. 2013;17(7):957-71.

113. Currie SR, Wang J. More data on major depression as an antecedent risk factor for first onset of chronic back pain. Psychological medicine. 2005;35(9):1275-82.

114. Lacey RJ, Belcher J, Croft PR. Does life course socio-economic position influence chronic disabling pain in older adults? A general population study. European journal of public health. 2013;23(4):534-40.

115. Shmagel A, Foley R, Ibrahim H. Epidemiology of Chronic Low Back Pain in US Adults: Data From the 2009-2010 National Health and Nutrition Examination Survey. Arthritis Care Res (Hoboken). 2016;68(11):1688-94.

116. Myers JL, Well AD, Lorch RF. Research Design and Statistical Analysis. Third Edition. Taylor & Francis; 2013.

117. Da C, Menezes CL, Maher CG, Hancock MJ, McAuley JH, Herbert RD, et al. The prognosis of acute and persistent low-back pain: a meta-analysis. CMAJ. 2012;184(11):E613-24.

118. Dionne CE, Von Korff M, Koepsell TD, Deyo RA, Barlow WE, Checkoway H. Formal education and back pain: a review. Journal of epidemiology and community health. 2001;55(7):455-68.

119. Foster NE, Anema JR, Cherkin D, Chou R, Cohen SP, Gross DP, et al. Prevention and treatment of low back pain: evidence, challenges, and promising directions. Lancet (London, England). 2018;391(10137):2368-83.

120. Moustgaard H, Clayton GL, Jones HE, Boutron I, Jorgensen L, Laursen DLT, et al. Impact of blinding on estimated treatment effects in randomised clinical trials: meta-epidemiological study. BMJ. 2020;368:l6802.

121. Statens offentliga utredningar. Effektiv vård Stockholm; 2016. Report No.: SOU 2016:2.

122. Statens offentliga utredningar. God och nära vård: En primärvårdsreform Stockholm; 2018. Report No.: SOU2018:39.

123. Fairbank JC, Pynsent PB. The Oswestry Disability Index. Spine (Phila Pa 1976). 2000;25(22):2940-52; discussion 52.

124. Zwarenstein M, Treweek S, Gagnier JJ, Altman DG, Tunis S, Haynes B, et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. BMJ. 2008;337:a2390.

125. Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. Lancet (London, England). 2009;374(9683):86-9.

126. Ho CM, Thorstensson CA, Nordeman L. Physiotherapist as primary assessor for patients with suspected knee osteoarthritis in primary care-a randomised controlled pragmatic study. BMC Musculoskelet Disord. 2019;20(1):329.

127. Bornhoft L, Larsson ME, Nordeman L, Eggertsen R, Thorn J. Health effects of direct triaging to physiotherapists in primary care for patients with musculoskeletal disorders: a pragmatic randomized controlled trial. Therapeutic advances in musculoskeletal disease. 2019;11:1759720x19827504.

128. Leppänen A. Tobacco cessation on prescription: a primary healthcare intervention targeting socioeconomically disadvantaged areas in Stockholm. Stockholm: Karolinska Institutet; 2019.

129. Uvhagen H. Make it happen and make it matter : implementation and impact of primary healthcare-academia partnerships. Stockholm: Karolinska Institutet; 2019.

130. Leppänen A, Ekblad S, Tomson T. Tobacco Cessation on Prescription as a primary health care intervention targeting a context with socioeconomically disadvantaged groups in Sweden: a qualitative study of perceived implementation barriers and facilitators among providers. PLoS One. 2019;14(2):e0212641.

131. Dedering A, Peolsson A, Cleland JA, Halvorsen M, Svensson MA, Kierkegaard M. The Effects of Neck-Specific Training Versus Prescribed Physical Activity on Pain and Disability in Patients With Cervical Radiculopathy: A Randomized Controlled Trial. Arch Phys Med Rehabil. 2018;99(12):2447-56.

132. Cummings P. Missing data and multiple imputation. JAMA Pediatr. 2013;167(7):656-61.

133. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008.

134. Swedish Agency for Health Technology Assessment and Assessment of Social Services. SBU:s metodbok 2020 [Updated 2020-10-15. Available from: https://www.sbu.se/metodbok.