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RECURRENT AND PERSISTENT LOW BACK PAIN - COURSE AND PREVENTION

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Recurrent and persistent low back pain - course and prevention

THESIS FOR DOCTORAL DEGREE (Ph.D.)

by

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"It is more important to know what sort of person has a disease than to know what sort of a disease a person has."

Hippocrates

ABSTRACT

Background: Non-specific low back pain (LBP) causes more disability than any other condition in the world. The need to understand the clinical course of LBP, develop effective strategies to manage and if possible prevent future episodes are greater than ever. A fundamental aspect of specifying an episode of pain is to define when it ends, however to date no evidence based definition of recovery from LBP exists.

Psychological factors have been shown to affect the prognosis and treatment response for patients with LBP. To what extent psychological and behavioral factors affect chiropractic patients and the outcome of treatment is unclear.

Although it seems logical to prevent a condition such as recurrent and persistent LBP few strategies have been shown to be effective. Many patients who seek treatment from chiropractors for recurrent and persistent LBP often get the recommendation to continue treatments after the pain has subsided with the intention to prevent future episodes. Whether this strategy is effective or cost-effective is unknown.

Aims: The overall aim of the thesis is to investigate the course of LBP from the perspective of episodes, psychological factors and prevention. The specific objectives were to investigate the:

I) Prevalence of four consecutive weeks free from pain and its applicability as a marker of episode.

II) Psychological and behavioral characteristics of chiropractic patients and compare them to three other back pain populations from primary and secondary care.

III) Short-term predictive properties of the West-Haven Yale Multidimensional Pain Inventory (MPI-S) among patients with recurrent and persistent LBP receiving chiropractic care.

IV) Effect and cost-effectiveness of Chiropractic Maintenance Care (MC) in a population with recurrent and persistent LBP.

Methods: Five different data materials were used in the four studies.

Study I	Study II	Study III	Study IV
Observational prospective cohort study	Cross-sectional study	Prospective multicenter outcome study	Investigator blinded randomized clinical trial
Subjects (Materials 1-5)			
Experiencing LBP with or without leg pain, **1** (**n** = 262).	Experiencing LBP with or without leg pain. Two samples from primary care **2** (n = 480; and **3** (n = 128). Two samples from secondary care, **4** (n = 273) and **5** (n = 235).	Experiencing recurrent and persistent LBP with or without leg pain. **2** (n = 329).	Experiencing Recurrent and persistent LBP with or without leg pain. Subjects with a favorable response to an initial course of treatments. **2** (n = 321)
Primary outcomes			
Prevalence of four consecutive weeks without bothersome LBP.	MPI-S dimensions and subgroups	Perceived improvement, pain intensity	Number of days with bothersome LBP.

Results: Four consecutive weeks without bothersome LBP may be applied as a marker for a LBP episode in a primary care population. Chiropractic patients are more affected by their pain compared to another primary care population, but less compared to two secondary care populations. Subgrouping patients according to MPI-S could not predict the short term treatment outcome in chiropractic patients. MC is more effective and costlier compared to symptom-guided treatment.

Conclusions: Absence of pain as a marker of LBP episodes is a novel and promising concept. Chiropractic patients are more affected by their pain than other patients from primary care. Psychological and behavioral factors could not predict a short-term differentiated treatment response in chiropractic patients. MC resulted in significantly fewer days with bothersome LBP compared to symptom-guided treatment. MC may be considered cost-effective, but further investigations are needed.

Keywords: low back pain, non-episodes, psychological factors, chiropractic, maintenance care, prevention

LIST OF SCIENTIFIC PAPERS

I. **Eklund A**, Jensen I, Lohela-Karlsson M, Leboeuf-yde C, Axen I
Absence of low back pain to demarcate an episode: a prospective multicentre study in primary care.
Chiropr Man Therap, 2016, Feb, 18;24:3

II. **Eklund A**, Bergström G, Bodin L, Axén I
Psychological and behavioral differences between low back pain populations: a comparative analysis of chiropractic, primary and secondary care patients.
BMC Musculoskelet Disord, 2015, Oct, 19;16:306

III. **Eklund A**, Bergström G, Bodin L, Axén I.
Do psychological and behavioral factors classified by the West Haven-Yale Multidimensional Pain Inventory (Swedish version) predict the early clinical course of low back pain in patients receiving chiropractic care?
BMC Musculoskelet Disord., 2016, Feb, 12;17(1):75

IV. **Eklund A**, Jensen I, Lohela-Karlsson M, Hagberg J, Bodin L, Lebouf-Yde C, Kongsted A, Axén I.
Prevention of low back pain: effect and cost-effectiveness of preventive manual treatment (Chiropractic Maintenance Care) – a randomized clinical trial
Manuscript

CONTENTS

LIST OF ABBREVIATIONS

LBP	Non-Specific Low Back Pain
NP	Neck Pain
SD	Standard Deviation
MSK	Musculoskeletal
HEE	Health Economic Evaluations
CLBP	Chronic Low Back Pain
IBS	Irritable Bowel Syndrome
RA	Rheumatoid Arthritis
SBU	The Swedish Council on Health Technology Assessment
NRS-11	Numerical Rating Scale (0-10)
RMDQ	Roland Morris Disability Questionnaire
MC	Maintenance Care
MPI	West Haven-Yale Multidimensional Pain Inventory

MPI-S	Swedish version of MPI
AC	Adaptive Copers
ID	Interpersonally Dysfunctional
DYS	Dysfunctional
EQ5D	European Quality of Life-5 Dimensions
ÖMPSQ	The Örebro Musculoskeletal Pain Screening Questionnaire
SBT	The STarT Back Tool
SMS	Short Message Service
HEE	Health-Economic evaluations

1 INTRODUCTION

Disease prevention is likely to become an area of great expansion in the future (1). With increasing costs for incurable chronic diseases effective health promotion and preventive healthcare will become the focus when considering allocation of resources (1).

Pain is a common cause or consequence of ill health in today's society and is associated with high disability and large health care expenditures (2-4). The ability to perceive pain is an important signal that warns the individual of injury or disease. In the acute stages of a pain experience this is especially important to react appropriately. However the individual experience of pain is highly subjective and is affected by neurophysiological, psychological, behavioral, social and environmental factors (5-8). The subjective experience of pain is complex and not fully understood. Recurrent or persistent pain in particular remains a puzzle for the scientific community, with many pieces of the jigsaw still missing (5-8).

Fundamental when designing effective interventions for the treatment or prevention of a condition is to understand the course. Knowing how and when a disease will occur or when to intervene is a crucial part of the decision making process for a clinician and a cornerstone of preventive interventions.

Non-specific low back pain (LBP) is a condition that is often recurrent and sometimes persistent. To study this condition, the definition of an episode is fundamental. It is required for the study of effectiveness, to be able to specify the pain period as well as the time to the next LBP event (recovery). What constitutes a period of recovery is an important aspect but still remains an equivocal question when it comes to LBP (9). Even though much effort has been spent on defining what constitutes an episode of LBP the task has been challenging and the conclusions are unsatisfactory (10-12).

To fully understand the course of a painful disease or condition we have to consider the patient's subjective experience and perspective. Today we live in the realm of the bio-psycho-social model where the patient's disease should be considered not only from a biological perspective but also from a psychological and social dimension (13). Not seeing the individual from this "holistic" perspective is outdated at best and ineffective or harmful at worst (14-22). Identifying psychological and behavioral factors that may

perpetuate the disease or reduce the effect of interventions is fundamental to a bio-psycho-social care model (23-25).

Prevention of disease has been the very heart of the Chiropractic health paradigm (26-39). As part of the undergraduate education Chiropractors are trained to deliver health promotion and preventive interventions for lifestyle related chronic diseases such as cardiovascular disease, cancer, diabetes etc. alongside musculoskeletal treatments (40). The chiropractor, with a specialization in musculoskeletal medicine, sees the patient in a primary care setting within the bio-psycho-social framework. Many chiropractors also include preventive manual treatments as part of a package of care with the aim of preventing future episodes of LBP.

The allocation of resources in the healthcare budget is becoming more and more strict and interventions are expected to not only to show they are effective but also cost-effective (41). Cost-effectiveness is becoming an integral part of the design of may clinical trials (42).

The main theme of this thesis is the study of *the clinical course of low back pain* from the perspective of episodes without pain, psychological factors and prevention.

2 BACKGROUND

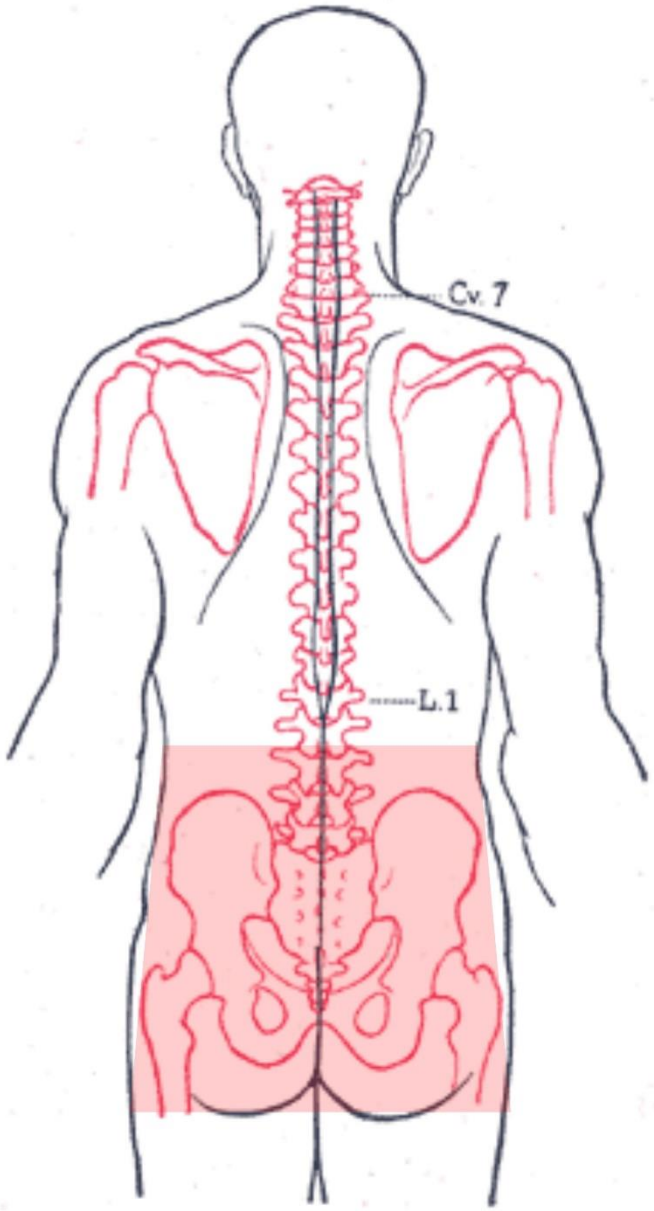
LBP is one of the greatest health challenges facing the majority of the world's countries and unfortunately, despite the number of available treatments being greater than ever, the problem seems to be increasing (4, 43). Given the vast choice of treatment options one would expect a promising chance of tailored treatments and effective interventions, however LBP still remains incurable for many and the etiology for the majority of patients is unknown, thus the pain is termed unspecific (44-47). The Global Burden of Disease study from 2010 (4) concluded that LBP causes more global disability than any other condition and that there is an urgent need to understand the phenomenon across different settings.

2.1 DEFINITION

The most common description of LBP, also used in Global Burden of Disease study (4) defined LBP as *"pain in the low back for at least one day (the area on the posterior aspect of the body between the lower margins of the twelfth ribs to the lower gluteal folds) with or without leg pain"*. See Figure 2.1 for a graphical representation.

This definition is similar to those used in national health surveys and clinical guidelines. Other studies also specify, additionally, that the pain has to be activity limiting (48).

Figure 2.1: Graphical representation of the defined area of low back pain (LBP). The Pink area represents the anatomical region of pain (modified from Wikimedia Commons).



2.2 PREVALENCE

A number of studies have investigated the prevalence of LBP resulting in varying estimates (48, 49). The variation is a consequence of methodological differences specifically in case definition, prevalence period and extent of measures to prevent bias. One of the most recent systematic reviews on the global prevalence of LBP from 2012 (48) included 165 studies and 966 age- or sex-specific estimates from 54 countries.

The point prevalence globally has been estimated at 18.3% and the one-month prevalence at 30.8%. Globally the one-year prevalence has been estimated at 38.0% and the lifetime prevalence at 38.9% (48). Mean overall prevalence regardless of period was 31% and higher in females across all age groups and the overall prevalence estimates have gradually increased over the past 3 decades (48). The prevalence of LBP gradually increases with age and is highest in the age range 40-69 with a peak around the retirement age and a small reduction thereafter (50-54). High income countries have higher prevalence compared to middle and low income countries, however no difference has been found between rural and urban areas (48).

2.3 COURSE

For many years LBP was assumed to have a self-limiting benign course where the pain spontaneously resolved itself for a majority of patients (55-57). This conclusion was primarily drawn from occupational studies where “recovery from disability” or “return to work” were studied (55-58). Most patients do however resume activities and return to work even though they still have pain (59) which has underestimated the actual pain duration. Recent studies have revealed a different picture of a condition that is highly recurrent were 42% to75% of individuals who experience an acute episode of LBP still have pain one year later (60). The course of the pain is highly individual where some patients have a very intermittent presentation and others experience a more stable pain (61, 62).

2.3.1 Episodes

Defining an episode of LBP is fundamental for the study of risk factors, resolution, persistence and recurrence (9). Early research has mostly focused on the length of an episode to characterize LBP by dividing it into either acute, sub-acute or chronic (63).

Resent research suggests that most patients will have either fluctuating or persistent pain rather than well-defined episodes (62). The notion of well-defined episodes of pain with periods without pain seem less common than previously thought. In fact, a number of pain trajectories have been identified across different settings and it seems more useful to define individuals according to these rather than duration of pain in well-defined episodes (64). Future research may be able to define these trajectories as prognostic phenotypes with clinical implications (64). A more careful understanding of the fluctuation of pain may clinically be more important than the classical definitions based on duration.

In order to define individuals with episodic patterns we need to be able to specify when one episode ends and a new one begins, and a period free from pain (in previous research described as a "non-episode") is required (65, 66). Recovery is a term that has previously been used to describe such a period with absence of pain following or preceding an episode of LBP. However, there is no evidence-based definition of recovery to date (9). A recent systematic review concluded that the suggested pain-free period to define recovery ranges between 1 and 6 months (67).

Based on an extensive literature search and group discussions with researchers and clinicians, de Vet et al (9) suggested a definition of an episode of LBP. They proposed that an episode of LBP be defined as: "*a period of pain in the lower back lasting for more than 24 hours preceded and followed by a period of at least 1 month without LBP*". Recently de Vet's definition was agreed to be incorporated into the consensus definition of recovery (68).

A specific definition of recovery would aid in the exploration of pain trajectories to subgroup individuals and possibly tailor interventions accordingly. Exploring and defining the concept of recovery may very well be the most important aspect of actually defining an episode.

2.4 ETIOLOGY

Identifying the cause of LBP has been one of the 20th century's largest medical challenges. LBP has been found to have a multifactorial etiology and cannot be attributed to one singe disease pathway or cause therefore the quest has been largely unsuccessful (43, 69, 70). The closest we have come to defining the causal mechanisms for LBP has been to identify specific risk factors for the development of the disease.

2.4.1 Risk factors

A large number of risk factors have been identified as important in the development of persistent pain. Overall these risk factors can be divided into sex differences, pain characteristics, comorbidity, psychological, sociodemographic and occupational factors. Their level of contribution and the degree to which they affect the course/prognosis is, however unclear (54).

2.4.1.1 Sex differences

A number of epidemiological studies have found sex differences regarding the prevalence and impact of LBP (71, 72). Musculoskeletal pain in general and comorbidity (depressive symptoms, anxiety, sleep disturbance) is more prevalent in women across all ages, whereas LBP have shown to be more prevalent up to the age of 35 (73). Among men, education and unemployment are associated with higher prevalence of musculoskeletal (MSK) pain. Only among women are economic difficulties, part time work and being married associated with higher prevalence of other MSK pain. Both women and men seem to have higher prevalence of pain conditions generally for those subjects with poorer socioeconomic status, early disability retirement, long-term sick leave and lifestyle factors (obesity, lack of exercise) (73).

2.4.1.2 Pain characteristics

Repeated stimuli of taste, sound, smell or physical touch normally results in gradually smaller responses in the central nervous system through adaption (74). The reaction to a painful stimulus is the exact opposite with a gradually increasing response in the so called "pain neuro-matrix" like a warning signal getting louder through the process of sensitization (75). In line with this, epidemiological research has shown that previous

episodes, long duration of pain and high pain intensity are factors associated with poor prognosis and the development of persistent LBP (43, 76). This may be partly explained by the process of sensitization. Research has shown that persistent LBP in adolescence is associated with a higher risk of developing LBP as an adult (77). A combination of persistent LBP, persistent headache and asthma in adolescence increases the risk even more for future LBP.

2.4.1.3 Comorbidity

A large body of evidence shows that LBP is associated with a number of comorbidities where other MSK conditions (rheumatoid arthritis (RA), osteoarthritis, osteoporosis) are the most common (78-80). For some patients LBP is associated with a cluster of other diseases. If LBP is part of a syndrome of ill health or a precursor for comorbidity is a question that has been debated in the literature and the direction and nature of this association is unclear as most studies haven't addressed causality (81-83). A positive association with LBP and a number of comorbidities (headache/migraine, respiratory disorders, cardiovascular disease, general health, gynecological disease, irritable bowel syndrome (IBS), allergy, constipation and neck pain (NP)) has been found (83).

Patients sick listed (8-12 weeks due to LBP) compared to a "normal" reference population have been shown to have more neck pain, upper back pain, pain in the feet during exercise, headache, migraine, sleep problems, hot flushes/heat sensations, anxiety and sadness/depression (81). It has been suggested that a syndrome exists with whole spine pain, leg and head pain, sleep problems, anxiety and sadness/depression (81).

Among patients 18 years of age or older, the pattern of comorbidity seem to exist in a dose-response like relationship where the prevalence of comorbidity and use of analgesics increase with increasing number of LBP episodes (84). Those with the highest number of LBP episodes were frequent users of primary care and most frequent users of all forms of specialty care (84). The dose-response like association with comorbidity has also been studied in the elderly population. In a cross-sectional population based survey of Danish twins (70-102 years old), an inverse dose relationship between LBP prevalence and self-rated health was found (82). Individuals with LBP had higher prevalence of bone & joint disorders, migraine headaches, cardiovascular disorders, gastric ulcer and lower physical functioning.

2.4.1.4 Psychological risk factors

The presence of psychological impairments has been known to be associated with the development and maintenance of persistent pain states. In particular anxiety, depression, catastrophizing, kinesiophobia (fear of movement) and somatization (distress expressed as physical symptoms) have been identified as risk factors for LBP (22, 85-93). Subjects with LBP and/or neck pain (NP) have more psychological distress and more risky health behaviors compared to subjects without either condition (94).

With regards to psychological factors subjects with LBP and/or NP were more likely to report depression, anxiety, sleep disturbance, nervousness, restlessness, fatigue, sadness, hopelessness/worthlessness and serious mental illness compared to a population reference (without LBP and NP) (94). Risky health behaviors were also higher among LBP and/or NP subjects who were more likely to smoke, be overweight/obese, drink heavily and be physically inactive (94).

2.4.1.5 Sociodemographic risk factors

The prevalence of pain in general and LBP specifically is closely related to socioeconomic factors where blue collar workers experience pain more prevalently, with higher severity and has higher functional impairment than white collar workers and senior managers (95). Individuals from a lower socioeconomic class are also more likely to take early retirement due to pain compared to individuals of higher socioeconomic class (69).

Ethnicity also seems to affect the prevalence of LBP with regards to differences in the expression of pain where language, coping mechanisms, perceptions and the view of the healthcare system can differ (96). Individuals living in Sweden with a non-Nordic heritage have a higher prevalence of LBP compared to individuals with a Nordic heritage (95).

2.4.1.6 Occupational risk factors

The Swedish Council on Health Technology Assessment (SBU) conducted a systematic literature review (2014) of occupational risk factors for back disorders (70). They concluded there were a number of specific occupational exposures associated with the

development of LBP. Individuals exposed to manual handling (e.g. lifting), prolonged postures with a bent back, work in a kneeling or squatting posture, physically heavy or demanding jobs and whole body vibration had a higher risk of developing LBP. Individuals who perceive their work as demanding but lack control over their own working situation or felt they had insufficient opportunities for personal development were more likely to experience LBP (70).

2.5 THE COGNITIVE BEHAVIORAL PERSPECTIVE

The cognitive behavioral model of pain stems from the early work on operant theory proposed by psychologist B.F. Skinner (97) and developed in a pain framework by W. Fordyce (98, 99). The early theories suggested a clear distinction between the original source of the pain and the behaviors associated with it (reports and display of pain). More recent research have suggested a number of limitations of the early behavioral model, some of these relate to the assumption that behaviors need to be interpreted (construct validity) as well as strictly questionable effectiveness of strictly behavioral interventions (only effective for some patients with high risk of relapse) (100, 101).

The cognitive-behavioral theories were partly developed as a response to this critique in order to also take into considerations the patient's beliefs about their pain to develop a shared conceptualization with patients to be able to address "mistaken beliefs" about their condition (100-103). Overall the aim of cognitive behavioral therapy is to help the patient "identify, reality test, and correct maladaptive, distorted conceptualizations and dysfunctional beliefs" in relation to their maladaptive behavior and condition (103). A body of evidence suggests that consideration of psycho-social and cognitive factors (catastrophizing, sense of control/self-efficacy) should be considered in the management and treatment of persistent pain and are included in current practice guidelines (104-106).

2.6 OUTCOME MEASURES

Experts have concluded that the impact of LBP should be conceptualized as the combination of three main constructs; pain intensity, pain interference with normal activities and functional status (10). A number of instruments have been designed to measure these aspects such as Numerical Rating Scale 0-10 (NRS-11) for pain intensity, Roland Morris Disability Questionnaire (RMDQ) for activity limitation and bothersomeness (pain interference).

Pain intensity (NRS-11) is one of the most common instruments used to measure LBP and has been included as a standard outcome measure by the NIH taskforce (10, 107).

RMDQ is a widely used instrument that has shown acceptable test-retest reliability and concurrent validity in patient with sub-acute and persistent LBP (108).

Expert panels have suggested that a 30% change can be considered a clinically important difference with regards to change in pain intensity (NRS-11) or function (RMDQ) and is therefore a recommended level to consider (10, 107, 109).

Another term that has been considered as a general measure of the impact "of clinically relevant pain" is bothersome LBP or bothersomeness (109-111). One previous study has shown that pain intensity correlates well with the number of days with bothersome LBP (112). Other outcome measures such as disability, psychological health (anxiety, depression), prediction of future work absence/ healthcare consultations and self-rated health, also correlate with bothersomeness (113, 114). Even though the measure has been suggested as a standard outcome in LBP research it has not been included in the recommendations by the NIH taskforce or the IMMPACT group as it needs further empirical evaluation (10, 109, 115, 116).

Health-Economic evaluations (HEE) has become an integral part of clinical trials and most trials collect data on direct and indirect costs alongside effect evaluations (41). In essence, an HEE focuses on comparing the tested interventions with regards to differences in cost and effect. The ratio between the difference in cost and effect is termed the incremental cost-effectiveness ratio (ICER) and describes the cost or cost reduction for one unit change in the effect measure. The ICER is often reported as a point estimate with cost-effectiveness planes and cost acceptability curves to illustrate

uncertainty of the estimate and probabilities of being cost-effective at different levels of cost (willingness to pay). HEE is often performed with the aim of describing different perspectives such as patient, healthcare or societal. Depending on the chosen perspective different costs will be included in the analysis (41). For example: in the patient perspective only costs such as patient fee, time lost for participation in the intervention, travel etc. would be included, whereas from a societal perspective all possible cost such as the use of other medical services, sick leave, production loss etc. would be included. Well-designed HEEs informs decision makers upon how to best distribute the health-care budget so the payers get best value for every EUR spent.

2.7 PREVENTION OF LOW BACK PAIN

Although important from both the patient and societal perspective little is known about the effectiveness of preventive strategies for LBP. In a recent systematic review it was concluded that the only evidence-based intervention that may reduce the number of recurrent episodes of LBP is exercise therapy or exercise therapy combined with patient education (117). The effect of these interventions only seems to be evident up to a year, after which there seem to be no difference compared to the natural course of the disease.

Most research within the field of preventive medicine is focused on identifying modifiable risk factors that when addressed would change the course of the disease or prevent it from occurring (118). Although a number of risk factors have been identified for LBP it is unclear to what extent a modification of these would reduce future episodes of pain (119, 120). Given the weak scientific body of evidence for prevention of LBP SBU conducted a systematic review with a slightly different aim, namely to investigate if interventions aimed at treating acute LBP can reduce the risk of persistence (43). They conclude there is not enough high quality evidence to draw any conclusions and that there is a need for more research in the field.

2.8 CHIROPRACTIC

Chiropractors are licensed healthcare professionals in Sweden regulated by the Swedish National Board of Health and Welfare (Socialstyrelsen). As a profession chiropractors are specialized in the diagnosis and management of disorders from the musculoskeletal system such as LBP (121, 122). Some of the most common components of chiropractic care are spinal manipulation and mobilization (manual therapy) in addition to this it is also common for chiropractors to use other methods such as exercise therapy, lifestyle advice and patient education (29, 37, 121, 123). Manual therapy have been shown to be effective for some patients, however the mechanism of action is poorly understood (76, 124). Research has identified biomechanical and neuromuscular mechanisms (sensorimotor integration, motor control, joint mobility, muscle tension) as well as reduction of psychosocial barriers (catastrophizing, fear avoidance beliefs and low self-efficacy) as possible factors responsible for reducing the risk of relapse into pain (125-130).

2.8.1 Maintenance Care

Chiropractors often recommend manual treatment as a form of prevention of LBP to patients with little or no pain. The approach is often performed over longer periods of time and has been termed "maintenance care (MC)" (27). Among Scandinavian chiropractors about 20% of all visits are MC visits and among Swedish chiropractors 98% of use the approach to some degree (27).

Traditionally MC has been described as: *"…a regimen designed to provide for the patient's continued well-being or for maintaining the optimum state of health while minimizing recurrences of the clinical status"* (34) and *"…treatment, either scheduled or elective, which occurred after optimum recorded benefit was reached, provided there was no evidence of relapse"* (131).

In an ambitious research effort, the indications, frequency and content of MC have been investigated in a number of studies and there seems to be a common management concept shared by most Scandinavian chiropractors (26-30, 32, 33, 35, 36, 38, 39). MC is also used in the rest of the world but only in the Scandinavian countries have efforts been made to investigate the concept in detail. MC can be defined as an intervention focused secondary or tertiary prevention and may include manual therapy, individual

exercise programs and lifestyle advice delivered over longer time periods in regular intervals. (27, 29, 32, 36, 37, 123).

The evidence for the effectiveness and cost-effectiveness of MC is lacking and a large evidence gap exists (132-134). Previous research has either been pilot studies on small samples or conducted without considering the current evidence regarding practice procedures.

3 AIM/PURPOSE

The overall aim of the thesis was to investigate the course of LBP from the perspective of episodes and psychological factors **(study I-III)** as well as to investigate an intervention aimed at preventing the reoccurrence of LBP **(study IV)**.

3.1 STUDY I

Investigated the applicability of the proposed definition (by de Vet et al) of four weeks of absence of LBP as a demarcation of an episode of LBP in a primary care population (9).

3.2 STUDY II

Compared the psychological and behavioral characteristics of chiropractic patients with LBP to three other back pain populations from primary and secondary care.

3.3 STUDY III

Investigated the probability of predicting the short-term clinical course after subgroup assignment in accordance with MPI-S among patients with recurrent and persistent LBP receiving chiropractic care.

3.4 STUDY IV

Investigated the effect and cost-effectiveness of Maintenance Care (MC) in a population with recurrent and persistent LBP.

4 METHODS

4.1 MATERIALS

The 4 studies in this thesis are based on 5 different data materials, 4 previously collected (materials 1, 3-5) and 1 collected during the course of the PhD education (material 2).

4.1.1 Material 1

Material 1 came from a prospective cohort study of 6 months duration between May-Dec 2008 with the primary aim of investigating the clinical course of LBP in a primary care population consulting Chiropractic clinics for LBP (61, 62, 135).

Chiropractors who were part of an established practice-based research network recruited consecutive patients with LBP (with or without leg pain) aged 18-65. Subjects were screened for specific spinal pain, other serious pathology and were excluded if pregnant, did not have a cell phone, could not respond using short message service (SMS) or had visited a chiropractor during the past 3 months. Weekly SMS were used to collect data on the number of days with bothersome LBP over the previous week. Data from material 1 was used in Study 1.

4.1.2 Material 2

Material 2 came from a recently conducted randomized controlled trial (136) investigating patients recruited from chiropractic primary care clinics (part of a practice based research network) in Sweden. The trial started in April 2012 and finished in January 2016. The primary aim of the RCT was to investigate the effect and cost-effectiveness of preventive manual care, MC for recurrent and persistent LBP. Patients seeking care for persistent and recurrent LBP were screened consecutively and included in a 3-stage process.

Subjects were randomized into groups of either MC (scheduled according to a clinician's recommendation) or control (treatment only when in pain, symptom guided). The follow up period was 12 months during which they responded to 52 weekly SMS messages reporting how many days with bothersome LBP they had experienced (primary outcome).

The RCT has been described in detail in a published study protocol (136). Data for study 2 were collected at the initial visit (baseline 1) of the inclusion procedure. Study 3 utilizes data from both the 1st (baseline 1) and 4th visit (baseline 2) of the RCT. The final analysis of the primary outcome of the RCT is reported in study 4.

4.1.3 Material 3

The third material came from a large intervention study entitled "Work and Health in the Processing and Engineering Industries" (abbreviated AHA in Swedish) conducted between 2000 and 2003, the study has been described in detail elsewhere (137, 138).

The primary aim of the AHA-study was to evaluate an extensive risk assessment tool and an evidence based work place intervention. Subjects considered at high risk of developing chronic disabling NP and/or LBP and long term sick leave were selected based on the responses on the risk assessment tool, and were included in this study. Data from material 3 was used in study 2.

4.1.4 Materials 4 and 5

The fourth and fifth materials came from the HUR project (Health-Economic Evaluation of Rehabilitation) which was conducted in 1994 with the primary aim of evaluating multidisciplinary rehabilitation interventions with regards to effect on sick leave and health-related quality of life as well as cost-effectiveness.

The part of the HUR study that focused on NP/LBP was designed as two separate prospective trials with patients from specialized secondary care units. The first trial was a matched controlled observational outcome study with a selection of subjects with intermittent sickness absence (cumulative of 1-6 months in total) (139-141).
The second trial was a randomized clinical trial investigating the effect of components of cognitive behavioral interventions on subjects with continuous sickness absence (1-3 months) (142, 143). Data from materials 4 and 5 were used in study 2.

4.2 ABSENCE OF PAIN

In recent research from Denmark absence of pain (non-episodes) have been investigated with regards to prevalence of pain-free episodes (65, 66) .

The part of de Vet et al´s proposed definition of LBP episodes, that an episode should be surrounded by "at least 1 month without LBP" was investigated by Leboeuf-Yde et al (65) in terms of its applicability in two populations of LBP patients from secondary care. Using weekly SMS data, the prevalence of periods of at least four consecutive weeks free from bothersome LBP was estimated. They found that only 18% and 20% of the patients reported at least one period of a minimum of four consecutive weeks free from bothersome LBP during the one-year study period.

It was proposed that a relationship should exist between duration of pain and the absence of pain. Thus, one would expect that patients with LBP of shorter duration to have longer consecutive pain-free periods compared to patients with LBP of longer duration. The above described method was therefore repeated in another study with a different sample from the general population and the prevalence of at least four consecutive weeks free from bothersome LBP was, as expected, found to be much higher, 83%, during the one-year study period (66).

Based on the prevalence data that showed a large proportion of the subjects had experienced four consecutive weeks without pain, it was now suggested that the concept of non-episodes hold the potential of being a useful outcome measure in the study of LBP episodes. Similar studies in samples from primary care had not been performed and doing so could reveal if a relationship between pain-free periods and previous duration of pain exists across populations.

4.3 THE WEST HAVEN-YALE MULTIDIMENSIONAL PAIN INVENTORY (MPI)

The West Haven-Yale Multidimensional Pain Inventory (MPI) is a psychometric instrument based on the cognitive-behavioral conceptualization of pain. Patients with a wide variety of chronic pain conditions have been assessed with the MPI instrument.

The instrument has been used to investigate the psychometric properties of the chronic pain experience for conditions such as neck NP and LBP (138, 140, 144, 145), tempero-mandibular disorders (146), headaches (147), fibromyalgia (148) and cancer pain (149)and has been tested cross- culturally with translations into several languages (150-152).

Studies II and III used the Swedish version of the MPI (MPI-S) to categorize and subgroup individuals according to psychological and behavioral variables. The MPI-S has been shown to have acceptable reliability and validity (14, 153, 154). which has been reported in earlier trials. Material 4 (142, 143) was previously used in the validation process of the Swedish version of MPI. To arrive at reliable estimates Material 4 was used as a reference sample in this thesis.

4.3.1 MPI Dimensions

In the publication by Kerns, Turk and Rudy (1985) the MPI instrument was initially presented with 52 items (0-6 scale) divided into 3 parts (155).

The first part is the most comprehensive and designed to measure the extent and impact of pain on different aspects of the patient's life. The second part appraises social relations and behaviors of significant others in response to the patient's displays of pain. Lastly, the third part records the activity level by accessing daily living activities such as household chores, outdoor activities, activities away from home and social activities.

When the instrument was translated into Swedish, a number of adjustments were made to achieve satisfactory levels of factor structure, reliability and generalizability (156). This was done by removing items 13 and 16 in the first part, items 1 and 3 in the second part and items 2, 3, 6, 7 and 16 from the third part (156).

In the validated Swedish version, the first part has 22 remaining items generating five dimensions (pain severity, interference, life control, affective distress and support). The second part has 12 items generating 3 dimensions (punishing responses, solicitous responses and distracting responses). In the studies in this thesis, the third part with the remaining general activity dimension was not used as the factor structure has not been replicated in the Swedish version following removal of the above mentioned items (156).

See Table 4.1 for a detailed description of the dimensions (modified from the original article by Kerns et al.) (155).

Table 4.1: Description of the MPI-dimensions (155)

	MPI-dimension	Description
Psychological	**Pain severity (PS)**	Perceived pain severity and suffering
	Interference (I)	Perceived pain related life interference, including interference with family and marital functioning, work and work-related activities, and social-recreational activities.
	Life control (LC)	Perceived life control, incorporating the perceived ability to solve problems and feelings of personal mastery and competence.
	Affective distress (AD)	Ratings of depressed mood, irritability and tension.
	Support (S)	Appraisal of support received from spouse, family and significant others - such as worrying, being supportive and attentive.
Behavioral	**Punishing responses (PR)**	Perceived range and frequency of responses (behaviors) by significant others to displays of pain and suffering by showing frustration, irritation, anger and ignorance.

Solicitous responses (SR)	Perceived range and frequency of responses (behaviors) by significant others to displays of pain and suffering by helping with medication, food, chores and rest.
Distracting responses (DR)	Perceived range and frequency of responses (behaviors) by significant others to displays of pain and suffering by such things as involving them in activities, taking their mind off their pain and encouraging them to focus on things other than their pain experience.

MPI, The West Haven-Yale Multidimensional Pain Inventory

4.3.2 MPI Clusters/Subgroups

Turk and Rudy (1988) further developed the inventory by demonstrating that three different subgroups can be identified from the data generated from the instrument. A cluster analytical strategy was used to form the subgroups named adaptive copers (AC), interpersonally distressed (ID) and dysfunctional (DYS) (144, 154, 157).

These subgroups have been replicated in several studies and in different populations and are described in table 4.2 (158). Some authors have added hybrid clusters to adjust for subjects that do not fit perfectly into any of the three suggested subgroups. In Study II and III it was decided not to include these hybrids to allow for better comparison with the reference population (154). The hybrid subjects were therefore categorized into the closest and most representative cluster (my means of the predefined centroid vectors).

Both the scales and the subgroups have been used to quantify aspects of the chronic pain experience resulting in clinically meaningful applications. In LBP patients the subgroups

have been found to have predictive value and clinical relevance with regards to treatment outcome and sick leave (138, 140, 159-161).

See Table 4.2 for a description of the subgroups.

Table 4.2: Description of MPI-subgroups

MPI-subgroups (abbreviations)	**Patient characteristics**
Adaptive Copers (AC)	Low pain severity. Low interference with everyday life due to pain. Low life distress. High activity level. High perception of life control.
Interpersonally Distressed (ID)	Low levels of social support. Low levels of solicitous and distracting responses from significant others. High scores on punishing responses compared to the DYS and AC patients.
Dysfunctional (DYS)	High pain severity. Marked interference with everyday life due to pain. High affective distress. Low perception of life control. Low activity level.

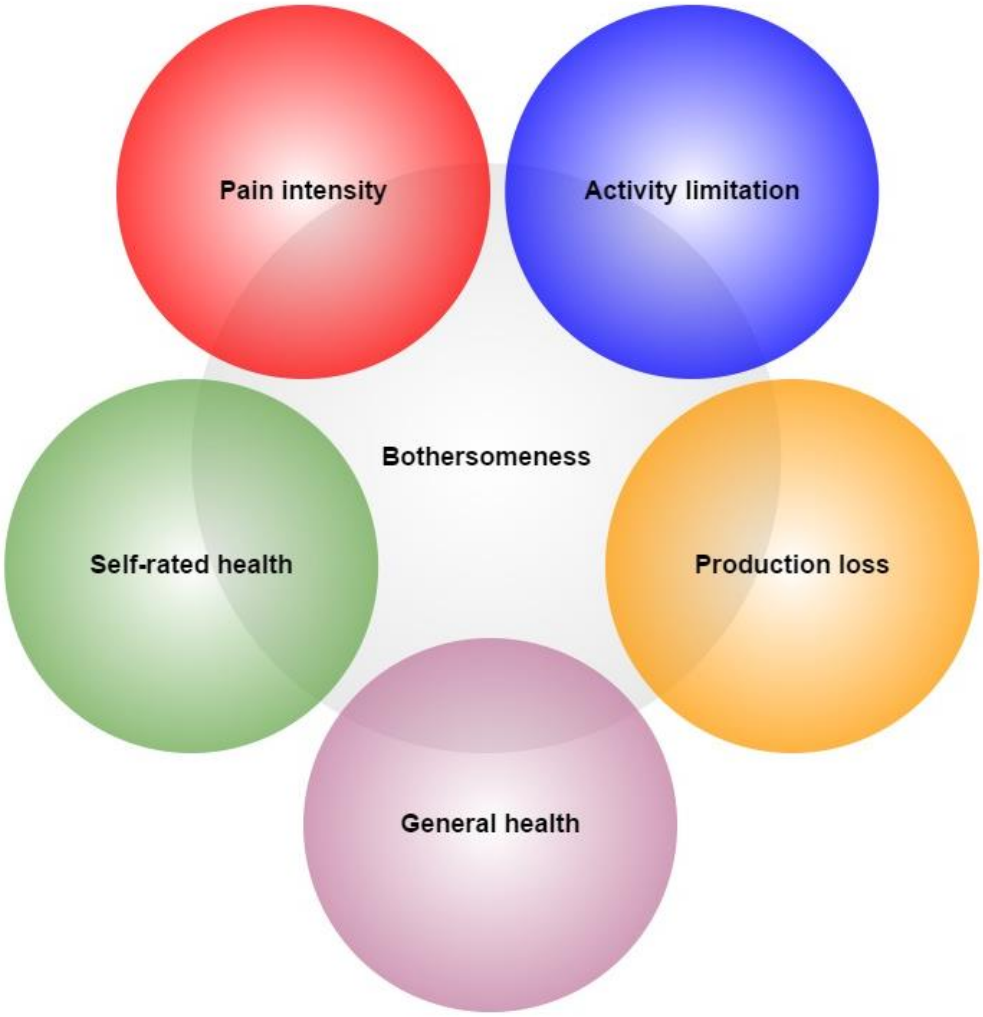
4.4 BOTHERSOMENESS

In this thesis pain intensity, activity limitation, production loss, general health, self-rated health and bothersomeness are thought of (in the proposed model) as six distinctly different constructs each describing different aspects of the pain experience. Although different, these constructs are also thought to overlap somewhat resulting in a certain degree of correlation and agreement (figure 4.1).

Most patients who experience pain and activity limitation would also be bothered by it to some degree, however this relationship is likely to be highly individual as some individuals may tolerate fairly high levels of pain and activity limitation before rating it as bothersome whereas others may not.

It was hypothesized that pain intensity, activity limitation and production loss would show the highest correlations with number of days with bothersome LBP whereas self-rated health and general health would have lower estimates.

Figure 4.1: Proposed model



4.4.1 Validity

As part of this thesis summary the construct validity of the measure “days with bothersome LBP” was investigated by estimating the correlation with pain intensity, activity limitation, production loss, general health and self-rated health.

Data from material 2 was used in the analysis. All subjects who completed the trial with complete data on either of the two variables to be correlated were used in the analysis. Descriptive data on the study sample can be found in table 4.1.

The total number of days with bothersome LBP the last 4 weeks and for the last week of the study period were correlated against measures of pain intensity, activity limitation, production loss, general health and self-rated health collected with the follow-up questionnaire received approximately 4-7 after concluding the trial.

Pain intensity was recorded using an NRS-11 item (0-10, no pain – worst possible pain) during the past 24 hours (162, 163).

Activity limitation was recorded using the Swedish version of the Roland Morris Disability Questionnaire (RMDQ), a 24 item instrument with yes-no response resulting in a 0-24 score where a higher score indicates higher activity limitation (108). The instrument asks the subject to reflect on their current activity limitation.

Production loss was measured with a single item question, a modified WPAI instrument (NRS-11 scale, 0-10, no loss of productivity – complete loss of productivity) asking about how the pain had affected their productivity during the last month (164).

General health was recorded using a single item with a 5 step ordinal scale asking the subject to rate their current general health (ranging from worst possible health – perfect health) (165).

Self-rated health was recorded using the Swedish version of the EQ5D instrument (5 items each with 3 levels each resulting in 243 different combinations) (166, 167). Each of the possible answer combinations from the instrument have been assigned a specific weight from a population average using a time trade off method (TTO). In this thesis the Danish TTO weights have been used to allow for better comparisons with older data as it is population based and more widely used contrary to the Swedish weights which are experience based, newer and less widely used. After the weights have been applied to the answer combination a score between 0 (dead) and 1 (perfect health) is obtained (168).

Pearson product-moment correlation coefficient was used and Cohen's conventions utilized to interpret the effect sizes (of the correlations) according to the following; small <0.30; moderate 0.30-0.50, large >0.50 (169, 170).

Although the instruments are essentially categorical in nature, they are often analyzed as continuous variables in research practice (except the variable general health). General health was therefore also analyzed with the Spearman Rank Coefficient due to the strict ordinal nature of the measure. Scatterplots were used to graphically illustrate the relationship in the bivariate analysis. The categorical nature of the instruments results in less than optimal graphical representation of the relationship between the variables as many of the data points have identical values. Still the scatter plots reveal some information regarding the variance and distribution of the sample and have been included, see appendix 11.2-11.11.

Given the different time points for the measurements, bothersomeness (last week and moth of the study period) and the other measurements (approximately 1 week after the study period has ended), estimates will likely have a smaller effect size and larger variation than if the measurements would have occurred at the same time.

Days with bothersome LBP the week before the follow-up measurement was thought to reflect the closest measurement to the follow-up measurement whereas the last month was thought to capture the pain profile of the individual. Although there were individual fluctuations of pain during the last month the mean number of days with bothersome LBP was quite stable. Therefore, it is likely that the correlation will capture the individual's pain experience although the measurements did not occur at the same point in time. The results are presented in the result section of this thesis summary.

4.5 PRACTICE-BASED RESEARCH NETWORKS

To collect the data for material 1 and 2 an established practice based research network of clinically active chiropractors was employed. This network of clinicians has been used successfully in a number of studies with high compliance rates (171).

A project officer at Karolinska Institutet managed 5 project group members who each had contact with 7-8 clinicians and were responsible for assuring that the data collection proceeded according to protocol. Although completely different study protocols, the data for materials 1 and 2 were collected in the same organizational structure. Clinicians who are part of the research network are representative of the members of the SCA in terms of age, sex, years in practice and level of education (27, 28).

4.6 REPEATED MESURES USING SMS

The use of text messages (SMS) is an efficient and cost-effective method to collect data in clinical trials where frequent repeated measures are of interest. The method is particularly suitable when the response options are a single number or word and the researcher wants real time access to the incoming responses.

SMS-Track® is a web-based system designed specifically for research to enable frequent data collection using text messages (172). Previous studies have shown this to be an inexpensive method (173) that yields high response rates (112, 135), and good compliance. Compliance is not affected by age, sex or season (135). The system uses a web-based interface, which can be accessed in real time to monitor compliance. The SMS-track system has been used to collect data in materials I and II.

4.7 STATISTICAL METHODS

In study I prevalence (proportions with 95% confidence intervals) was used to describe and evaluate the outcome.

In study II a non-hierarchical cluster procedure was used to classify individuals according to MPI subgroups and a discriminant analysis was used to evaluate the clustering procedure. Hypotheses were analyzed with ANOVA and chi-square tests.

In study III a non-hierarchical cluster procedure was again used to classify individuals according to MPI subgroups. Further, a parametric robust regression (Poisson) approach was used to estimate relative risk.

In study IV a UNIANOVA regression approach (ANCOVA) was used to estimate the primary outcome. To analyze repeated measures a parametric regression approach (generalized estimating equations) was used to estimate the outcome over time.

In the health economic evaluation in study IV the analysis was performed from a patient perspective. Means and 95% CIs for cost data were estimated with a Bootstrap method based on percentiles. The ICER was estimated using a Bootstrap method based on regression, 95% CIs were estimated using a bias corrected accelerated Bootstrap method (BC_a) and presented in a cost- effectiveness plane and a cost- effectiveness acceptability curve.

4.8 ETHICS

Ethical approvals were obtained by the local ethics committee for all the studies. All studies were conducted according to the Helsinki declaration and good clinical research practice.

Table 4.4: Summary of methods

Study	I	II	III	IV
Title	Absence of low back pain to demarcate an episode: an observational study in primary care	Psychological and behavioral differences between low back pain populations. A comparative analysis of chiropractic, primary and secondary care patients	Do psychological and behavioral factors classified by the West Haven-Yale Multidimensional Pain Inventory (Swedish version) predict the early clinical course of low back pain in patients receiving chiropractic care?	Prevention of low back pain: effect, cost-effectiveness of chiropractic maintenance care - a randomized clinical trial
Aim	To investigate the applicability of de Vet et al´s definition (of non-episodes)	To investigate and compare different patient samples with LBP with regards to psychosocial and behavioral characteristics.	To investigate if MPI-S subgroup assignment at the 1st visit could predict the short-term clinical course.	To investigate the effect and cost-effectiveness of preventive manual care as compared to manual care given only when there is a subject perceived need.
Design	An observational prospective cohort study with a 6 month follow up period	A cross-sectional study	A prospective multicenter outcome study	A randomized clinical trial
Materials	Material 1	Material 2, 3, 4 and 5	Material 2	Material 2

Subjects	n = 262, non-specific LBP with or without leg pain.	Non-specific LBP with or without leg pain **2:** n = 480, primary care, chiropractic. **3:** n = 128, primary care, short term sickness absence with high risk of chronicity. **4:** n = 273 secondary care, intermittent sickness absence. **5:** n = 235, secondary care, ongoing sickness absence.	n = 329, recurrent and persistent non-specific LBP with or without leg pain.	n = 321, recurrent and persistent non-specific LBP with or without leg pain. Subjects must have had responded favorably to an initial course of treatments.
Primary outcomes	Non-episodes	MPI-S scales, MPI-S clusters	Perceived improvement, pain intensity	Number of days with bothersome LBP.
Statistical analysis	Prevalence	Non-hierarchical cluster procedure, ANOVA, discriminant analysis, chi-square.	Non-hierarchical cluster procedure, (robust) modified Poisson regression, relative risk	ANCOVA (UNIANOVA), generalized estimating equations (GEE), Incremental cost-effectiveness ratio (ICER)

Ethical approvals	2007/ 1458-31/4	2015/1483-32, 2007/1458-31/4, 00-012, 94:340	2007/1458-31/4	2007/1458-31/4

5 RESULTS

The studies in this thesis have explored recurrent and persistent LBP from the perspective of clinical course. The focus has been three main areas; pain-free episodes, psychological and behavioral factors and preventive manual care.

5.1 BOTHERSOMENESS

As part of this thesis summary the construct validity of number of days with bothersome LBP has been explored. In table 5.1 the descriptive data of the study subjects for the validation sample have been presented.

Table 5.1: Descriptive statistics of validation sample.

		Statistic
Age at study start n=286, mean (SD)		43.2 (12.4)
Female n=291, %		62.2
Type of work n=321, % (some subjects selected more than 1 answer)	Heavy	10.9
	Intermittent heavy and light	31.5
	Walking and standing	31.8
	Sitting	46.1

Sick leave the past year n=277, %	None	84.1
	1-7 days	10.5
	8-14 days	2.9
	>15 days	2.5
Total number of days with bothersome LBP the last 4 weeks of the study period n=305, mean (SD)		6.5 (7.7)
Total number of days with bothersome LBP the last week of the study period n=302, mean (SD)		1.6 (2.0)
Pain intensity at follow-up n=276, mean (SD)		2.0 (2.1)
Activity limitation at follow-up n=266, mean (SD)		3.52 (3.93)
Production loss at follow-up n=276, mean (SD)		1.81(2.12)
General health at follow-up n=277, %	Excellent	13.4
	Very good	44.0
	Good	33.2
	Somewhat	9.0
	Poor	0.4
Self-rated health at follow-up n=274, mean (SD)		0.85 (0.13)

SD, Standard Deviation

5.1.1.1 Pain intensity

The correlations (Pearson's) for pain intensity and bothersomeness were large with estimates of 0.70 (week) and 0.75 (month). The scatterplots reveal a dispersed pattern for the week measure (R^2=0.48, Appendix 11.1), and a more focused graph for the month measure (R^2=0.56, Appendix 11.2). Pain intensity had the highest correlation of the 5 different measures used and the results are congruent with the previous research by Kongsted et.al. (112).

5.1.1.2 Activity limitation

The correlations (Pearson's) for Activity Limitation and bothersomeness were large with estimates of 0.51 (week) and 0.63 (month). Similar to Pain Intensity the scatterplots reveal a dispersed pattern for the week measure (R^2=0.26, Appendix 11.3), and a more focused graph for the month measure (R^2=0.39, Appendix 11.4). Activity limitation had the second highest estimates of correlation of the 5 measure.

5.1.1.3 Production loss

The correlations (Pearson's) with production loss and bothersomeness were moderate for week 0.45 and large for month 0.51. The scatterplots reveal a dispersed pattern for both week (R^2=0.20, Appendix 11.5), and month (R^2=0.26, Appendix 11.6).

5.1.1.4 General health

The parametric correlations (Pearson's) with General health and bothersomeness were moderate for both week (0.33) and month (0.40). The non-parametric correlations (Spearman) were moderate for both week (0.41) and month (0.36). Given the ordinal nature of the measure the scatterplots show a dispersed pattern for both week (R^2=0.20, Appendix 11.7), and month (R^2=0.26, Appendix 11.8).

5.1.1.5 Self-rated health

The correlations (Pearson's) with Self-rated health and bothersomeness were moderate for week -0,45 and large for month -0.53. The scatterplots reveal a pattern of clustered

values in the range 0,7-0,9 for Self-rated health for both week (R^2=0.20, Appendix 11.9), and month (R^2=0.28, Figure 11.10).

5.1.1.6 Summary

Days with bothersome LBP showed large significant correlations with pain intensity, activity limitation and production loss. The correlations with general health and self-rated health were moderate and significant. These findings support the proposed model in this thesis and add additional evidence for a simplified construct validity of the outcome measure "number of days with bothersome LBP". As hypothesized the outcome measure "number of days with bothersome LBP" seem to capture a number of factors/constructs associated with the pain experience.

Table 5.2: Summary of parametric correlations (Pearson product-moment correlation coefficients)

Variables collected at follow-up		Days with bothersome LBP (last week)	Days with bothersome LBP (last month)
Pain intensity	Correlation	0.695	0.747
	Sig. (2-tailed)	<0.01	<0.01
	n	276	276
Activity limitation (RMDQ)	Correlation	0.506	0.625
	Sig. (2-tailed)	<0.01	<0.01
	n	266	266
Production loss	Correlation	0.446	0.506
	Sig. (2-tailed)	<0.01	<0.01
	n	276	276
General health	Correlation	0.330	0.395
	Sig. (2-tailed)	<0.01	<0.01
	n	277	277

Self-rated health (EQ-5D)	Correlation	-0.450	-0.527
	Sig. (2-tailed)	<0.01	<0.01
	n	274	274

RMDQ, Roland Morris Disability Questionnaire; EQ-5D, European Quality of Life-5 Dimensions

5.2 PAIN-FREE EPISODES (STUDY I)

The data in study I show that de Vets definition of recovery (four consecutive pain-free weeks) is applicable in a primary care population and exerts a dose-response relationship in terms of severity of pain status (comparing our results to those from other populations) and previous duration of pain (within our sample).

A total of 59% of patients reported at least one period of four consecutive pain-free weeks during the study period. When considering the total number of consecutive weeks free from pain, 82 % had at least one and 31% had 9 or more during the six months of the study.

When taking into account previous duration of pain, 75% of the subjects with a shorter previous duration of pain (≤ 30 days with pain the previous year) reported at least one period of four consecutive pain-free weeks during the study period, whereas only 48% of subjects with a longer previous duration of pain (>30 days with pain the previous year) had such periods.

Figure 5.1 describes the prevalence of consecutive pain-free weeks reported in study I.

Figure 5.2 illustrate how the data from Study I fit in with previous research (65, 66).

Figure 5.1: Prevalence of maximum number of consecutive weeks free from bothersome Low Back Pain (LBP).

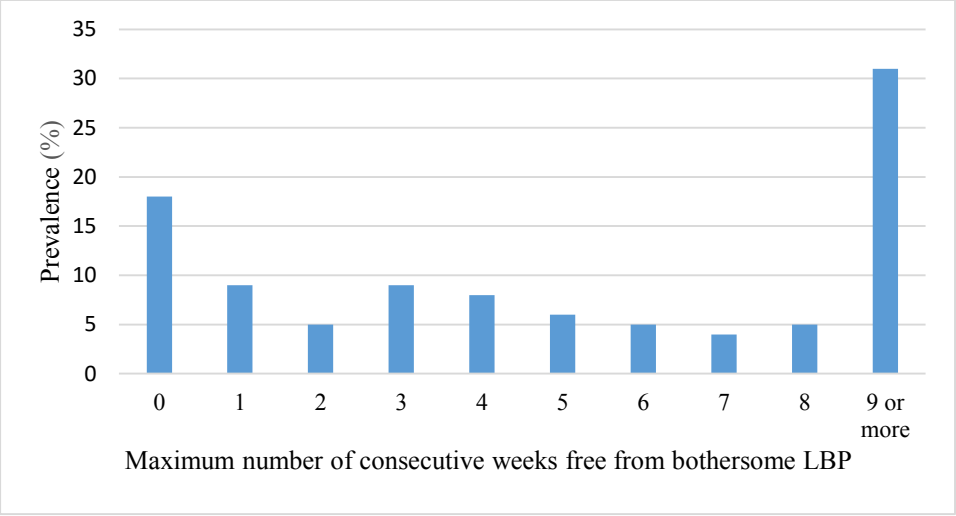
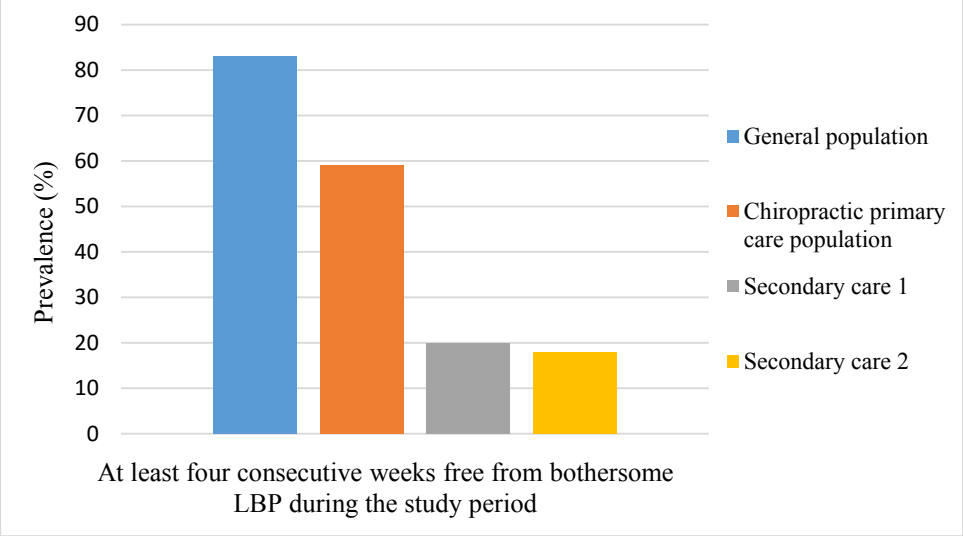


Figure 5.2: Prevalence of at least four consecutive weeks free from LBP.



The figure illustrate how the data from Study I compare to the previous research by Lebouf-Yde et al. (65, 66).

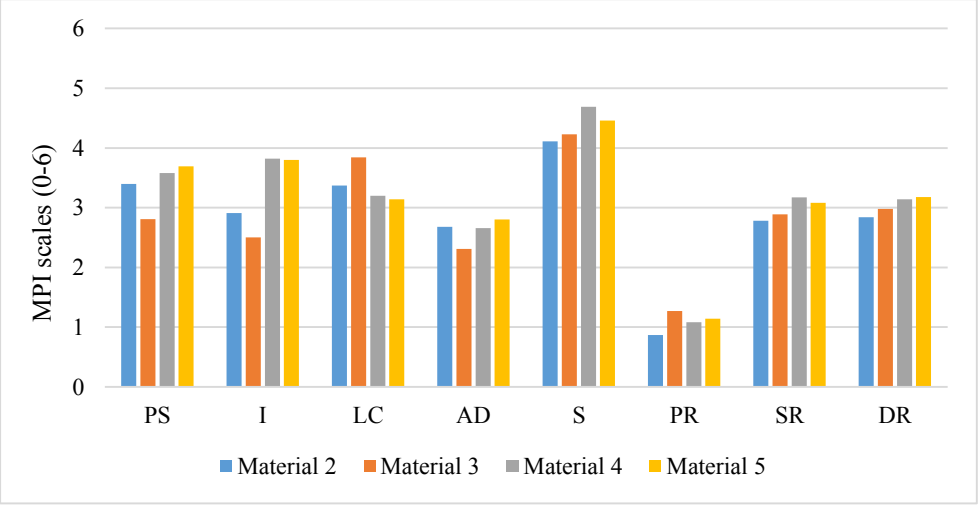
5.3 PSYCHOLOGICAL AND BEHAVIORAL FACTORS (STUDY II AND III)

In this thesis psychological and behavioral aspects of the chronic pain experience for chiropractic patients was explored and evaluated against other samples (study II) and as predictors of the early clinical course (study III).

5.3.1 Comparison of populations

The MPI-S instrument could classify the different study samples based on psychological and behavioral characteristics and successfully subgroup/cluster the subjects accordingly (figure 5.3).

Figure 5.3: MPI-S Scales across the four study samples/materials, mean scores

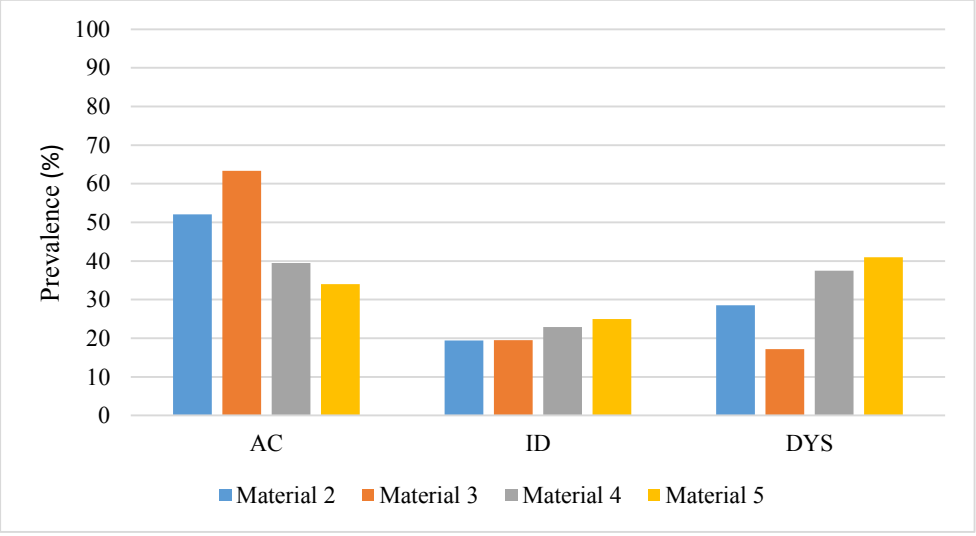


PS= Pain Severity; **I**=Interference; **LC**= Life Control; **AD**=Affective Distress; **S**= Support; **PR**= Punishing Responses; **SR**= Solicitous Responses; **DR**= Distracting Responses, **Material 2**= Chiropractic primary care patients, **Material 3**= Primary care patients with high risk of developing chronic disabling LBP and long term sick leave, **Material 4**= Secondary care patients with intermittent sickness absence, **Material 5**= Secondary care patients with continuous sickness absence.

The data showed statistically significant overall differences across samples for the MPI scales and subgroups, suggesting 4 distinctly different samples. The primary care chiropractic population (material 2, study II) could be placed (in terms of the proportions of the adaptive copers and dysfunctional subgroups) between the other sample from primary care and the two secondary care samples (figure 5.4).

The chiropractic patients are affected by LBP to a greater extent from a psychological and behavioral perspective (with a higher proportion of individuals classified into the DYS subgroup) than the other sample from a primary care setting.

Figure 5.4: MPI-S Cluster proportions across different samples of patients with LBP/NP



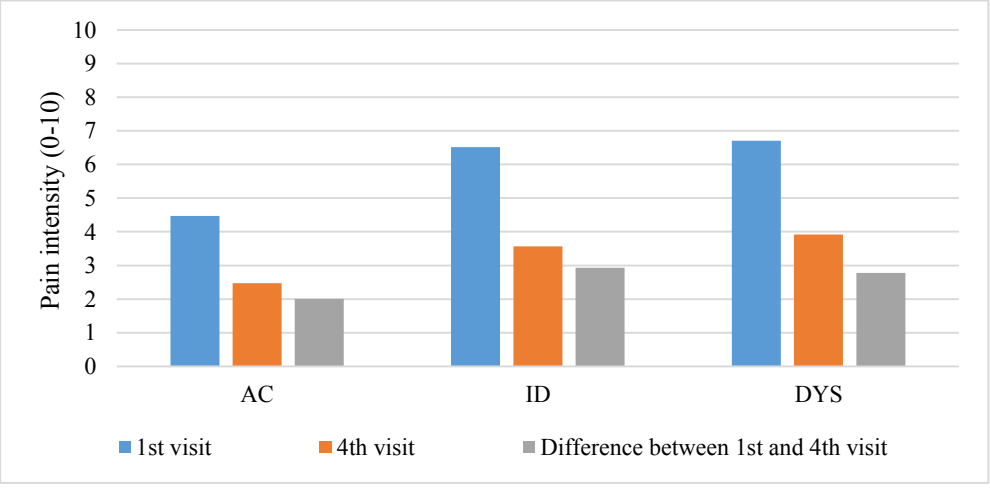
AC= Adaptive Copers; **ID**= Interpersonally Distressed; **DYS**= Dysfunctional, **Material 2**= Chiropractic primary care patients, **Material 3**= Primary care patients with high risk of developing chronic disabling LBP and long term sick leave, **Material 4**= Secondary care patients with intermittent sickness absence, **Material 5**= Secondary care patients with continuous sickness absence.

5.3.2 Prognostic properties of the MPI-S instrument in a chiropractic population

The MPI-S instrument successfully classified subjects within the sample from chiropractic care according to the predefined subgroups. Absolute values for pain intensity both at baseline and short term follow-up were different across the three subgroups (figure 5.5).

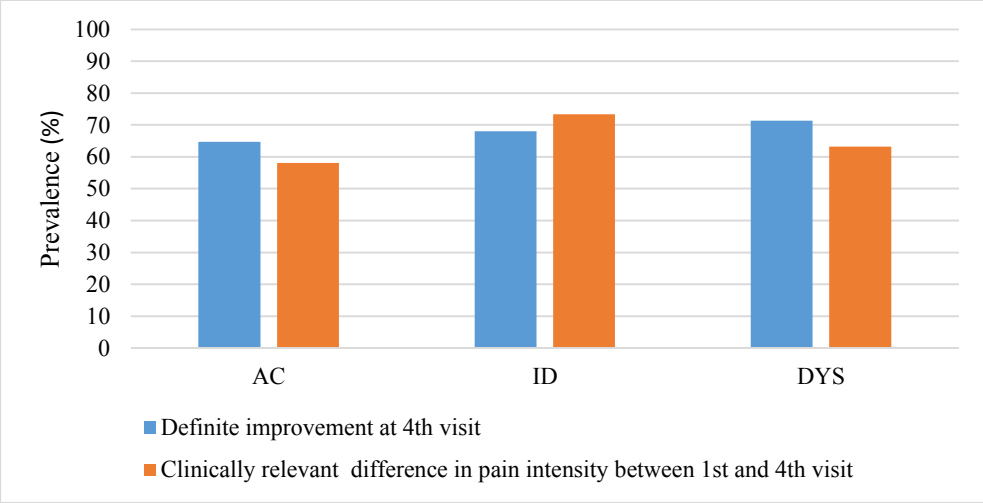
However, the relative risk of having either a clinically relevant change in pain intensity (AC group as reference, 1.26 (.91-1.76) for the ID and 1.09 (.78-1.51) for the DYS groups) or to experience a "definite" subjective improvement by the fourth visit (AC group as reference, 1.05 (.87-1.27) for the ID and 1.10 (.93-1.31) for the DYS groups) was not different across subgroups (figure 5.6). The MPI-S instrument could not predict which patients would experience a significant clinical improvement during the early clinical course of chiropractic care.

Figure 5.5: Absolute values of pain intensity (mean)



AC= Adaptive Copers; **ID**= Interpersonally Distressed; **DYS**= Dysfunctional

Figure 5.6: Proportions of individuals who reported a definite improvement at the 4th visit and clinically relevant reduction of pain (%).



AC= Adaptive Copers; **ID**= Interpersonally Distressed; **DYS**= Dysfunctional

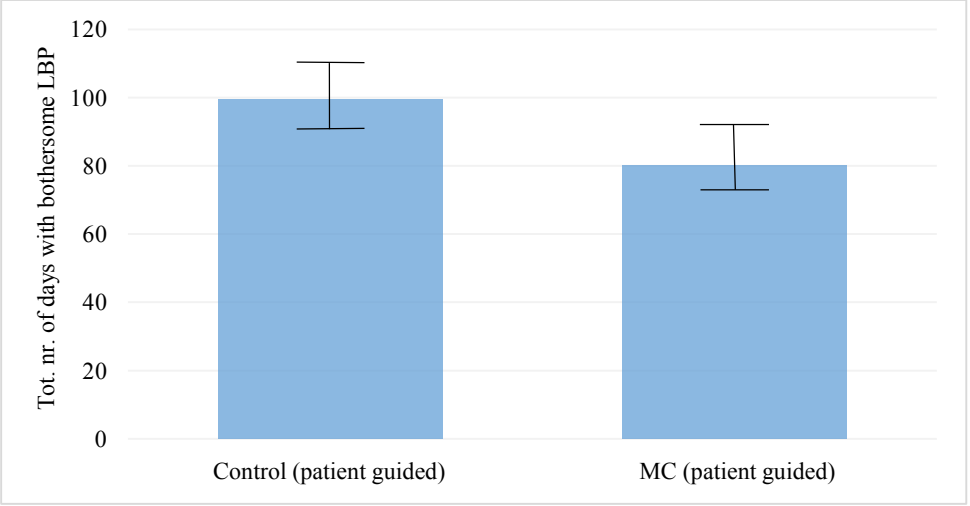
5.4 CHIROPRACTIC MAINTENANCE CARE (STUDY IV)

In study IV the effect and cost-effectiveness of preventive manual care, MC was evaluated.

5.4.1 Effect

At the 12 month follow up the MC group reported a significant difference ($p<0.01$) of 19.3 (19.4%) (CI 95: 5.0, 33.5) days less of bothersome LBP during the study period compared to the control group (symptom guided), see Figure 5.7.

Figure 5.7: Total number of days with bothersome LBP during the full study period, reported with 95% confidence intervals.



The difference between groups (number of days with bothersome LBP) per week is apparent from week 13 to 50. This suggest that MC needs to be in place for more than 13 weeks to be more effective than the control and has no added value after 50 weeks.

5.4.2 Cost-effectiveness

From a patient perspective, when considering costs directly associated with the treatment (fee, time during visit and for travel), it was found that MC was more expensive with a difference in total costs of 164 € (CI 95%: 70, 255) for the entire study period. The ICER was estimated at 8.50 € (95% CI 2.90, 31.61) per reduced day/year of bothersome LBP. If the willingness to pay is 8.50 € to prevent a day with bothersome LBP (over a 12-month period), MC may be considered cost-effective from a patient perspective (in 51.3 % of the cases).

6 DISCUSSION

Understanding the course of a disease to be able to predict the future is fundamental to be able to deliver cost-effective interventions. For instance, a self-limiting short lasting disease such as a common cold which may greatly affect an individual's health state may be less important from a health-economic perspective compared to chronic long lasting conditions resulting in a substantial economic burden. For many years LBP was seen as a self-limiting condition that needed little attention. Research on the course and consequences of the condition, particularly for individuals with persistent and recurrent pain, has revealed an altogether different picture where the condition is now considered the most activity limiting the world (48). From clinical experience working with LBP the most common questions from patients concerns the prognosis and how to relate to the future. Therefore, the results from studies I-IV could be of importance both for clinical researchers and clinicians.

6.1 PAIN-FREE EPISODES

An episode of "four consecutive weeks free from pain" as an outcome measure or a prognostic factor is promising concept but it needs further enquiry. Although it has now been 14 years since the publication of deVet's et al's article there is still a great need for uniform definitions regarding recovery and terminology to describe the course of LBP (9).

Study 1 adds to the knowledge base in this area and provides a piece of the jigsaw by showing a dose-response-like-relationship between duration of pain and prevalence of consecutive pain-free weeks. It also clearly shows a similar dose-response relationship when comparing the data to a general population and a secondary care population, Figure 5.2. There is now some evidence that support that a period four consecutive weeks without pain is sensitive to change (in association to previous duration of pain) within and across populations.

6.2 PSYCHOLOGICAL AND BEHAVIORAL FACTORS

Psychological factors are seen as important when considering treatment outcomes and persistent pain in particular. However, there is still uncertainty with regards to what it means for chiropractic patients. Stratification has improved the effectiveness of physiotherapy interventions yet a similar stratification has not improved outcomes for chiropractic patients.

Study 2 compares chiropractic patients to other samples from primary care and secondary care with regards to psychological and behavioral factors and clearly shows that chiropractic patients are indeed affected by psychological distress, in fact data indicate they are worse off compared to the other sample form primary care.

Study 3 expands on this theme by investigating the early clinical course of these patients and concludes that these factors do not seem to affect the reduction of pain or the patient's experience of subjective improvement. This is in line with the previous studies performed on chiropractic patients but still does not explain why there is a discrepancy when comparing with other patient groups (e.g. physiotherapy).

One possible explanation may be that physiotherapy interventions are predominantly based on active interventions (activities where the patient actively participates, performs the therapy) whereas chiropractic interventions are predominantly based on passive interventions (activities where the therapist performs the therapy "on the patient"). Perhaps active interventions require more from the patient in terms of self-efficacy, physical performance, attitude etc. and are therefore more sensitive to psychological and behavioral characteristics. If this is the case, then stratified care should also consider psychological and behavioral aspects as well as patient preference as regards how demanding the intervention is to improve effectiveness and compliance.

Another perspective may be that the consultation with a chiropractor already contains a stratified care model naturally at the initial visit. There could be inherent cognitive behavioral aspects addressing dysfunctional beliefs, behaviors, challenging the patient to make lifestyle changes and offer challenging activities to overcome catastrophizing, fear avoidance and low self-efficacy.

Study III takes a short term perspective on the predictive properties of the MPI-S instrument. A possibility, is that the long term predictive properties are very different and that at a 12-month perspective a differentiated treatment response may be evident.

Even though the chiropractic group appears to have similar psychological characteristics to other primary care samples there may of course be other unknown factors that explain the discrepancy with regards to outcomes such as expectations and socioeconomic background or other psychological variables not captured by the current body of knowledge. This is certainly an interesting and intriguing area that needs more research to be fully understood.

6.2.1 Measuring psychological characteristics

MPI was designed to be a comprehensive screening instrument capturing the entire range of psychosocial effects in chronic pain patients based on the current state of evidence in the field at the time (1985). Since then a number of other instruments have been developed to identify subgroups of patients with prognostic indicators aimed at improving treatment outcome and identifying individuals at risk of a poor prognosis.

The Örebro Musculoskeletal Pain Screening Questionnaire (ÖMPSQ) was developed in 1998 (Linton and Hallden) to identify high risk individuals requiring targeted treatment (174). Since the instrument was presented it has been extensively evaluated and come to be one of the most widely used instruments to identify high risk subgroups of patients and is considered a reference standard (175). The ÖMPSQ is a 24 item instrument that explores a patient's background, physical functioning, fear-avoidance beliefs, the experience of pain, work, and reactions to the pain. The items were chosen based on variables suggested as risk factors in the literature and many had been used in other valid and reliable instruments. The instrument was further developed 2006 (Nordeman et.al.) by adding thresholds to the scale that divided individuals into three subgroups (Low, Medium, High).

The STarT Back Tool (SBT) was developed 2008 and is another instrument that is similar to the ÖMPSQ but in a much shorter format (6 items) with the primary aim of subgrouping patients into one of three a priori treatment categories (Low, Medium, High) depending on prognostic indicators (18). These subgroups have very similar psychometric properties as the ones derived from the ÖMPSQ and allow for a more

effective and easier scoring procedure aimed at the busy primary care sector (175, 176). The SBT has been widely used and is considered a useful tool when tailoring stratified care strategies and has been shown to improve effectiveness and cost-effectiveness of physiotherapy interventions for patients with low back pain (177).

It is likely, to some degree, that the MPI subgroups and STB/ÖMPSQ subgroups capture similar constructs. However, the older MPI instrument was designed with a different aim given the current state of knowledge at the time and did not capture the concepts of fear-avoidance, disability, kinesiophobia, catastrophizing, anxiety and depression as specifically as the STB/ÖMPSQ do. The MPI on the other hand is a more comprehensive instrument and captures a wider range of the pain experience which to some degree is likely to include these concepts too.

6.3 CHIROPRACTIC MAINTENANCE CARE

The use of MC has been an extensively debated subject within the Chiropractic profession. Due to the lack of scientific evidence the debate has been largely focused on personal experience and opinion. This is the first large randomized clinical trial with a pragmatic design that mimics the clinical reality in order to investigate the procedure.

The data are of high quality and the recruitment process of subjects suggest the sample is generalizable to patients seen by chiropractors in Sweden. Geographically individuals have been recruited across Sweden in a distribution that resembles that of the Swedish population in general, see figure 6.2.

By utilizing repeated data (of high frequency) during the entire study period a detailed description of the individual pain patterns (in total 15 910 data points on 321 individuals) has been obtained.

The results from the trial are thought provoking for clinicians, third party payers and researchers. MC can effectively reduce the number of days with bothersome LBP in subjects with recurrent and persistent LBP. What can be considered a clinically significant difference when it comes to number of days with bothersome LBP in not known and needs to be evaluated further. Therefore, although statistically significant the

results may not be clinically relevant. Initially during the planning stages of the trial a 30% difference was suggested to be considered a clinically significant change. The estimate was based on group discussions and clinical experience as there were no empirical data to base this estimate on. The arbitrary nature of the clinically relevant threshold may or may not be correct. Our data suggest approximately a 20% difference between the groups and according to the initial assumption not clinically relevant. As reported in study IV there were small non-significant differences between the groups with regards to self-rated health (EQ5D), activity limitation (RMDQ) and pain intensity. This data supports the assumption that the finding is not clinically relevant. However, considering that the effect of MC is only statistically significant between week 13 and 50 and the baseline and follow-up data was recorded outside of this period, it may explain why the other health outcomes showed no difference. Also there is a large variation within the sample and for some patients the intervention may have yielded clinically relevant effects.

At this point clinical relevance of the intervention should be questioned based on previous assumptions and other health outcomes.

From a patient perspective the intervention is also more expensive and needs to be viewed with regards to willingness to pay. Our data suggest there are large variations within the sample and for some subjects the intervention seems more cost-effective. Therefore, the evidence must be seen in the light of patient preferences and the individual responsiveness to the treatment.

6.4 GENERALIZABILITY

The results from studies (I-IV) are directly transferrable to the clinical practice of the chiropractors in the northern European countries (Sweden, Denmark, Finland and Norway) as studies have shown the practice behaviors of clinicians and patient characteristics are similar. As to practice outside of this region it becomes more difficult. More research is needed to test the generalizability outside of the Scandinavian countries. The results from study I and II may be generalizable to any population that resembles any of the materials 1-5 used in the studies.

6.4.1 Subjects

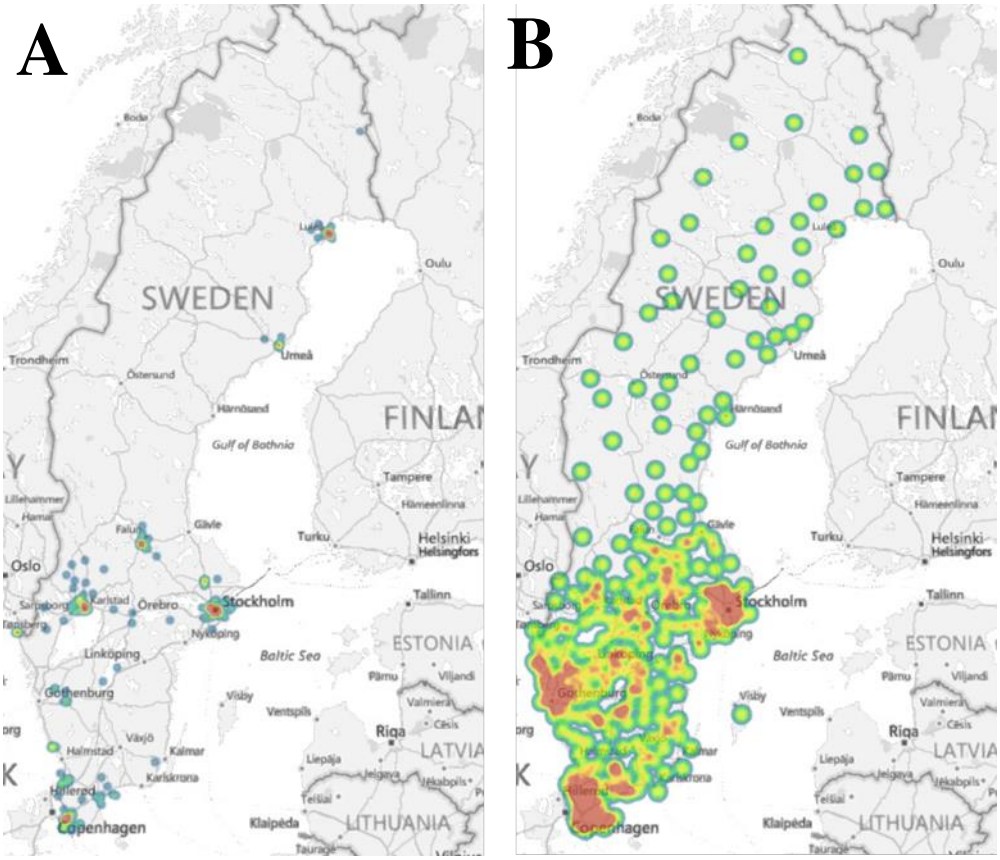
In all studies the recruitments base of patients comes from chiropractic clinics across Sweden which are part of a practice-based research network with mostly self-funded and self-referred patients with low back pain as the primary complaint. In figure 6.2 the distribution (across Sweden) of the included subjects from study IV is illustrated and suggests patients are well represented from a geographical perspective.

To what extent these patients resemble patients within the state-funded healthcare system as seen by chiropractors, physiotherapists and general practitioners is unclear.

A major contribution from this thesis is the comparative analysis of these patients in study II with other patient groups. The findings from the MPI-S instrument indicate that the chiropractic patients are worse off (with regards to psychological and behavioral characteristics) compared to the other primary care population.

Whether we see a distinctly different group of patients here is not possible to say from our investigations but certainly warrants further investigations.

Figure 6.2: Distribution of study subjects compared to the general population of Sweden



Heat maps showing geographical distribution and density of individuals (study subjects). Map A = included subjects in Study IV, Map B = Swedish population (2015) by state/province.3

6.5 STRENGTHS AND WEAKNESSES

Five large independent datasets are a major strength of this thesis. The data of all five datasets are of high quality with longitudinal designs.

A weakness of this investigation is the difference in time period that is obvious in study II. Data materials 4 and 5 were collected 1994, material 3 2000, material 1 2008, and material 2 2012. There may have been differences in practice procedures, treatment alternatives, societal trends, healthcare systems and treatment paradigms that may have biased the results in study II.

The thesis has utilized a wide variety of study designs. Studies I, III and IV are all longitudinal studies with different follow-up periods appropriate for answering the objectives of the individual projects. Study II has a cross-sectional design performing an in-depth psychological and behavioral assessment of large data-samples. Pre-defined centroid vectors based on the sample from the initial validation of the MPI-S were used to classify subjects in to the subgroups. This is a major strength of the trial as it ensures an appropriate comparison of samples.

Study III uses a stratification strategy based on the MPI-S subgroups and investigates the predictive properties with regards to improvement and pain intensity. This approach has not been used in a chiropractic population before and is a unique contribution to the field of stratified medicine and chiropractic clinical practice. A weakness of this study was the large amount of missing data at the 4th visit. However, based on the baseline data and psychological characteristics the data seem to be missing at random rather than as a result of systematic bias. One of the reasons for the missing data was the complicated inclusion procedure for the clinicians with a high administrative load where many forms where misplaced in the office and returned later. During the analysis phase of Study IV, a number of 4th visit forms (used in the analysis of study III) where found in the returned material from the clinicians at the end of the trial.

Study IV has a pragmatic investigator blinded randomized design with detailed longitudinal data over 12 months. A major strength of the project is the robust study design and large longitudinal data set obtained in this project. This is also the first trial to investigate MC in a controlled experiment where both effect and cost-effectiveness are analyzed.

In study IV a cost-effectiveness analysis is performed and based on detailed data on both effect and costs (direct and indirect) associated with the visit (fee and time consumption). Data were adjusted for inflation and given the follow up time of 12 months no discounting was necessary. A weakness of the economic analysis is the

limitations of only taking the patient perspective. An economic evaluation from a societal perspective where production loss, sick leave and healthcare utilization would have been included could reveal an altogether different conclusion and a more complete analysis.

The data collection methods used in this thesis have been both traditional questionnaires and the novel approach of SMS. Both methods have yielded response rates ranging from adequate to excellent.

Most of the instruments and individual items have been chosen because of the valid and reliable properties (MPI-S, RMDQ, EQ5D, NRS-11 for Pain Intensity etc.). However, the primary outcome in study IV number of days with bothersome LBP may be considered a "wildcard" given the novel and somewhat untested properties. However, the measure was used due to its appropriateness as a single item question capturing multiple dimensions of the pain experience which no other pain measure does. Also, findings from previous research have indicated a moderate to high correlation with other health dimensions. This was supported in the evaluation part of this thesis summary and in hindsight it was a good choice although not without risk.

7 CONCLUSION

The main findings from this thesis can be concluded as following:

- Four consecutive weeks free from pain is a promising concept as a marker of recovery and may be an important characteristic of the pain trajectory. There is now evidence to support its usefulness and sensitivity (dose-response) with previous duration of pain within and across populations. More research is needed to explore the clinical characteristics and thresholds of pain-free periods.

- Chiropractic patients with LBP from clinics in Sweden seem to have specific psychological and behavioral characteristics different from other primary care and secondary care populations with LBP. The sample of chiropractic patients is more psychologically affected by their pain compared to another primary care sample with recurrent LBP (at risk of developing chronic LBP and long-term sick leave).

- The MPI-S instrument could not predict differentiated short-term treatment response with regards to pain intensity and subjective improvement in chiropractic patients with LBP.

- MC (preventive manual care) is more effective compared to a control (treatment when in pain only) in reducing the total number of days with bothersome LBP. The clinical relevance of the effect is however debatable.

- From a patient perspective, the cost is higher for MC compared to a control (treatment when in pain only) and willingness to pay will decide the probability of the intervention being cost-effective.

8 FUTURE PERSPECTIVES

The work presented in this thesis has not only contributed to the knowledge base in the field of LBP but also found new perspectives worth investigating.

The measure "four consecutive weeks free from pain" has been found to be useful in describing patients with different LBP severity. A future perspective may be to use the measure as a means to stratify patients when deciding on different care models. A disease or syndrome with a recurrent pattern where the episodes consist of densely accumulated days with pain clearly separated by longer periods of absence of pain may be suited for an intervention targeted at preventing these episodes.

For instance, the use of preventive manual care may be most effectively administered when the course has a clear episodic pattern. If the intervention is targeted in time before a relapse into pain, hypothetically the impact may be reduced or the episode prevented entirely.

More research is needed to further identify if the measure "four consecutive weeks free from pain" is associated with clinically relevant properties. Studies investigating the correlation between prevalence of "four consecutive weeks free from pain" and other clinical measures such as bothersomeness, activity limitation, pain intensity, psychological characteristics and self-rated health would inform on this matter.

Stratified medicine is an important field for the healthcare sector in general, including chiropractic practice. To determine at an early stage which patient benefits the most from which treatment is an important perspective, which may improve the effect and cost-effectiveness of interventions.

The MPI-S instrument has predictive properties in some patient groups. In this thesis, the predictive ability of the instrument on the short-term clinical course was investigated in patients seeking chiropractic care. The MPI-S profiles were not found to be predictive of short term outcome, but it is however possible that the instrument has different predictive properties when considering a long term perspective.

The results regarding MC are interesting and suggest preventive treatment is more effective compared to a control, however MC needs further enquiry as the clinical

relevance of the results is debatable. In addition to the patient perspective the analysis should be repeated from a societal perspective taking into consideration the costs from production loss, sick leave, use of medication and other medical services. A cost-utility analysis would investigate additional dimensions of the treatment response such as the in-depth effects on self-rated health and activity limitation. This would also offer the chance to compare this intervention to other interventions using the concept of quality-adjusted life years (QALY). This way different interventions can be valued according to the same outcome measure and willingness to pay thresholds which allows for comparisons in a much broader sense.

Further, a psychological subgroup analysis of the patients in the MC trial may be used to investigate the presence of a differentiated treatment response. If so, such a subgroup analysis may be used to conduct a differentiated effect and cost-effectiveness analysis. Hypothetically it is possible that different psychological profiles benefit more or less from MC. If this is the case the MPI instrument could be used as part of a management strategy to identify suitable patients for MC.

Another aspect may be to investigate how and where the intervention (MC) affects the pain trajectory to improve dose and timing of treatments. Study IV has provided evidence about effect and cost-effectiveness of MC. It has been hypothesized that the preventive treatments minimize the reoccurrence of pain by intervening before the new episode and the difference is a result of less severe episodes. However, the intervention was on average more treatment intensive and the difference could be due to the difference in number of treatments rather than the actual timing of the treatments. A time-series analysis investigating the pain trajectory just before and after the treatment could answer such a question.

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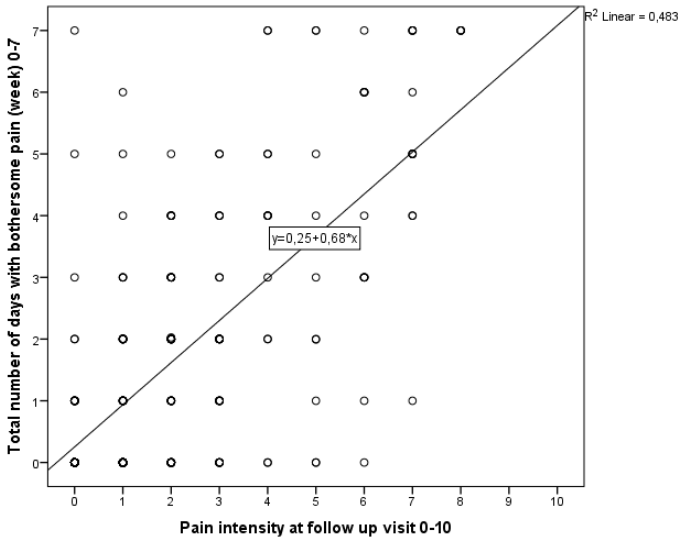
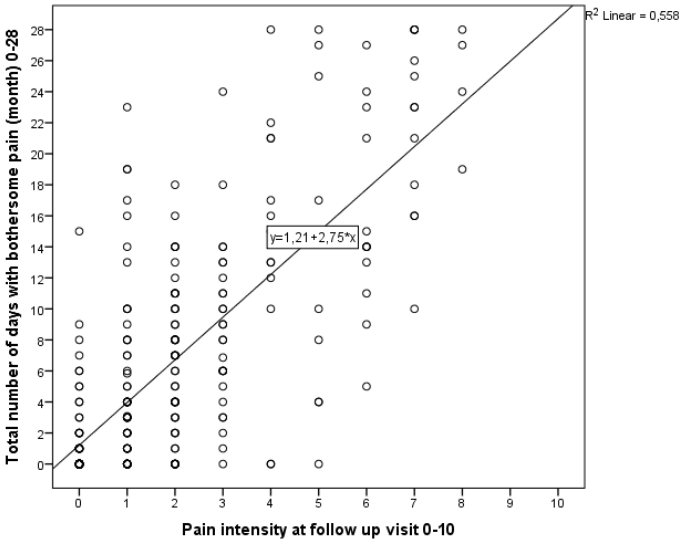
11 APPENDIX

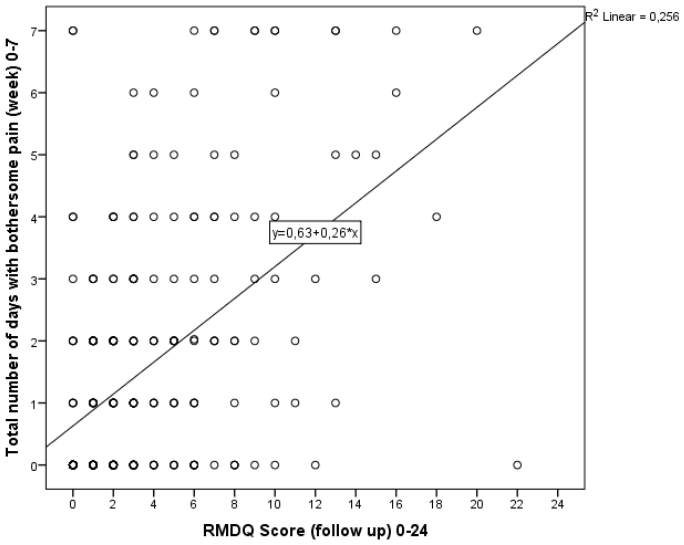
Appendix 11.1: Bothersomeness (week) vs Pain Intensity



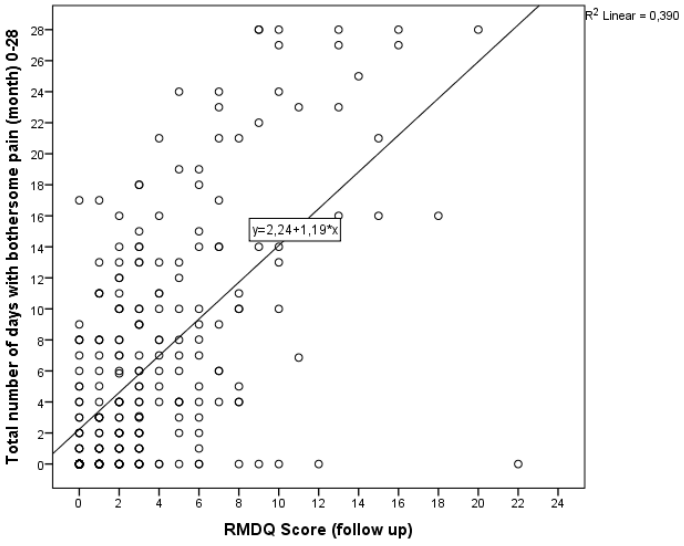
Appendix 11.2: Bothersomeness (month) vs Pain Intensity



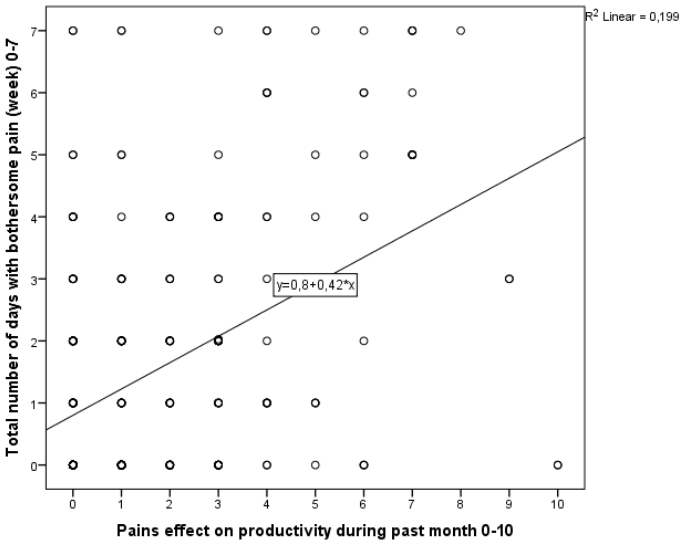
Appendix 11.3: Bothersomeness (week) vs Activity Limitation



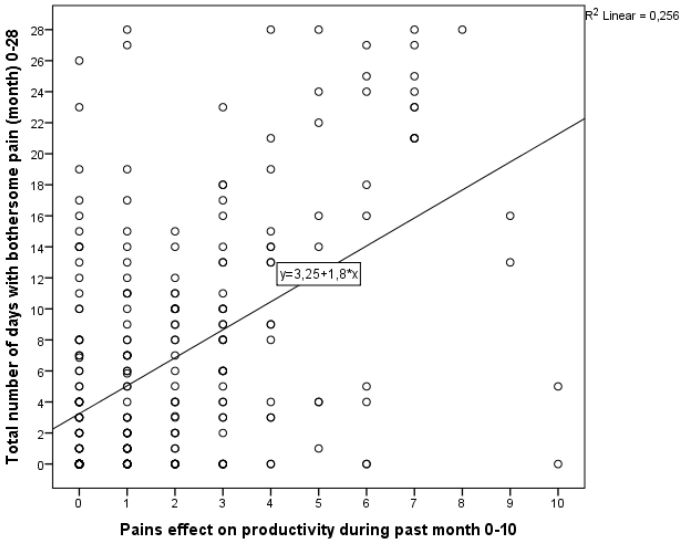
Appendix 11.4: Bothersomeness (month) vs Activity Limitation



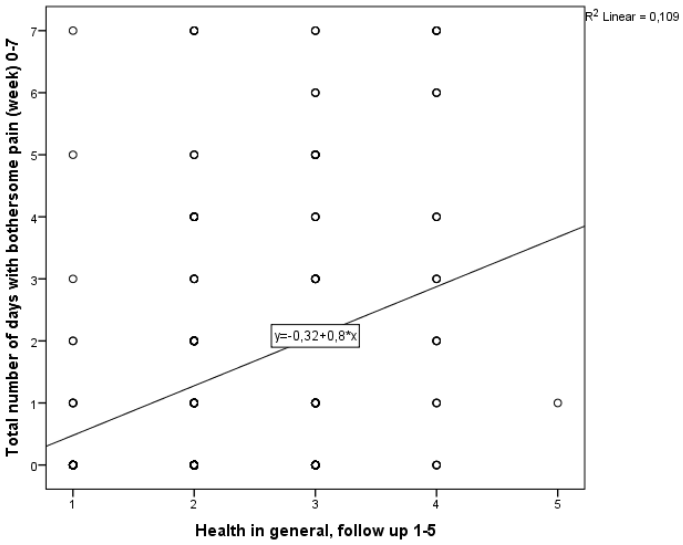
Appendix 11.5: Bothersomeness (week) vs Production Loss



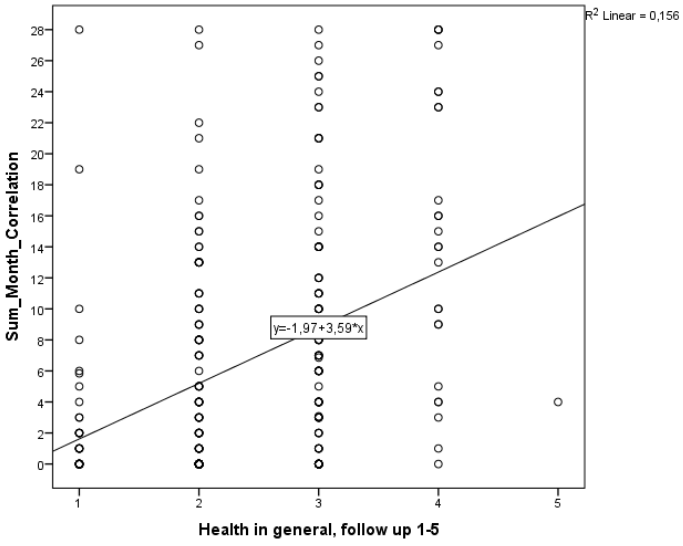
Appendix 11.6: Bothersomeness (month) vs Production Loss



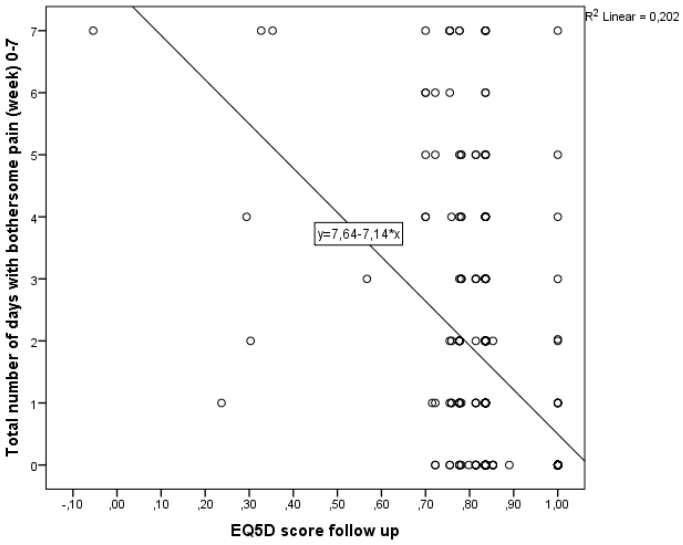
Appendix 11.7: Bothersomeness (week) vs General Health



Appendix 11.8: Bothersomeness (month) vs General Health



Appendix 11.9: Bothersomeness (week) vs EQ5D



Appendix 11.10: Bothersomeness (week) vs EQ5D