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Trondheim, April 2020

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Norsk sammendrag

Korsryggsmerter: Prognostiske og assosierte faktorer innenfor et biopsykososialt rammeverk

Korsryggsmerter er en av de ledende årsakene til nedsatt funksjon og arbeidsevne både i Norge og globalt, og fører til utstrakt bruk av helsetjenester og trygdeytelser. Personer med korsryggsmerter har ofte tilleggsplager innenfor de biopsykososiale områdene, som utbredt smerte, depresjon, angst og dårlig generell helse. Under bevegelse kan man ofte identifisere et avvikende bevegelsesmønster og mange har nedsatt arbeidsevne på grunn av ryggsmertene. Personer med slike tilleggsplager responderer dårligere på behandling og har økt forbruk av helsetjenester. For å bedre forståelsen om hvordan korsryggsmerter forløper, forbedre tilpasning av behandling, og å forebygge forverring, tilbakefall og funksjonstap hos personer med korsryggsmerter, er det derfor viktig å øke kunnskapen om i hvilken grad biopsykososiale faktorer påvirker både prognose og smerte- og funksjonsnivå hos personer med korsryggsmerter.

Det overordnede formålet med doktorgradsarbeidet var å undersøke hvordan biopsykososiale faktorer som antall smertepunkt, psykologiske symptomer, funksjons-nivå, arbeidsevne og bevegelsesmønster påvirker prognosen og de funksjonelle følgene av korsryggplager. I tillegg ønsket vi å se om bevegelsesmønsteret hos pasienter med korsryggsmerter samvarierte med 'fear-avoidance beliefs'. Første artikkel er en populasjonsbasert prognostisk studie med 10-11 års oppfølging. Artikkel 2 og 3 er observasjonsstudier av korsryggpasienter som fikk fysioterapibehandling, med tre og ni måneders oppfølging.

Hovedfunnene i doktorgradsarbeidet var at tilleggsplager som utbredt smerte, psykologiske symptomer, nedsatt funksjon og dårlig generell helse reduserte sannsynligheten for å bli kvitt langvarige korsryggsmerter etter 10-11 år. Hos pasienter som oppsøkte fysioterapibehandling fant vi at flere smertepunkter, mer psykologiske symptomer og dårligere arbeidsevne var assosiert med dårligere funksjon, mer intense smerter og lavere livskvalitet over en tre måneders periode. Videre fant vi at bedring i arbeidsevne ved tre måneder var eneste faktor assosiert med klinisk betydningsfull bedring i både funksjon, smerte og livskvalitet ved tre måneder. Vi fant ingen klare sammenhenger mellom bevegelsesmønster og selvrapportert smerte- og funksjonsnivå.

Redusert bevegelsesutslag ved ryggfleksjon/-ekstensjon hadde svak sammenheng med redusert funksjon, og lavere bevegelseshastighet i startfasen av en ryggfleksjon hadde svak sammenheng med økt 'fear-avoidance beliefs' for fysisk aktivitet.

Studiene bidrar til økt forståelse om hvordan antall smertepunkt, psykologiske symptomer, funksjonsnivå, arbeidsevne og bevegelsesmønster påvirker prognosen hos personer med korsryggsmerter. Resultatene kan ha en betydning for klinisk resonnering og planlegging av behandlingsforløp hos personer med korsryggsmerter.

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for graden Ph.D. i samfunnsmedisin, Doctor Philosophiae.

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List of content

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Anne Lovise, November 2019

Illustrations by Jan-André Granheim

List of papers

1. Nordstoga AL, Nilsen TIL, Vasseljen O, Unsgaard-Tøndel M, Mork PJ. The influence of multisite pain and psychological comorbidity on prognosis of chronic low back pain: Longitudinal data from the Norwegian HUNT Study. *BMJ Open* 2017. **7**(5)

2. Nordstoga AL, Vasseljen O, Meisingset I, Nilsen, TI, Unsgaard-Tøndel M. Improvement in work ability, psychological distress and pain sites in relation to low back pain prognosis: A longitudinal observational study in primary care. *Spine (Phila Pa 1976)* 2019. **44**(7)

3. Nordstoga AL, Meisingset I, Vasseljen O, Nilsen, TI, Unsgaard-Tøndel M. Longitudinal associations of kinematics and fear-avoidance beliefs with disability, work ability and pain intensity in persons with low back pain. *Musculoskeletal Science and Practice* 2019. **41**

Abbreviations and acronyms

BMI	Body mass index
CI	Confidence intervals
EQ-5D	Standardized health related quality of life instrument (EuroQoL 5L)
FABQ	Fear-Avoidance Beliefs Questionnaire
FABQ-PA	Fear-Avoidance Beliefs Questionnaire for physical activity
FABQ-W	Fear-Avoidance Beliefs Questionnaire for work
HADS	Hospital Anxiety and Depression Scale
HUNT	The Nord-Trøndelag Health Study
LBP	Low back pain
ODI	Oswestry Disability Index
OR	Odds ratios
RR	Risk ratio

English Summary

Low back pain (LBP) is one of the leading causes of reduced function and work ability in Norway and globally, and it is a large contributor to health care utilization, sick leave and disability pensions. Co-complaints within the domains of the biopsychosocial framework, such as multisite pain, depression, and anxiety are common in persons with LBP, and the presence of co-complaints is often followed by poor treatment response and high health care utilization. Furthermore, persons with LBP have shown divergent spinal movement compared to persons without LBP and the ability to work is commonly affected. To improve our knowledge on the course of LBP, improve treatment effects, and prevent worsening and reduced function in persons with LBP, investigating how biopsychosocial factors influence the LBP prognosis and functional- and pain-related outcomes is of importance.

The overall aim of this thesis was to explore the influence of biopsychosocial factors, such as multisite pain, psychological distress, work- and functional ability, fear-avoidance beliefs, and spinal kinematics on LBP prognosis and functional consequences of LBP. Additionally, to investigate the association between spinal kinematics and fear-avoidance beliefs. The first paper was a population-based prospective study with ~10-11 years follow-up. The second and third papers were observational studies of LBP patients attending physiotherapy, with three and nine months follow-up.

The main results were that co-complaints, such as multisite pain, psychological distress, reduced functional ability, and poor overall health reduced the probability of recovery from LBP after ~10-11 years. In patients receiving physiotherapy, we found that more pain sites, more psychological distress, and reduced work ability were associated with higher disability, more pain, and reduced quality of life over 3 months follow-up. Furthermore, we found that improvement in work ability was the only variable that was associated with clinically important improvement in disability, pain intensity, and quality of life at three months. No clear associations were found between the kinematic measures and self-reported outcomes. Reduced lumbar range-of-motion during a spinal flexion/extension movement was weakly associated with higher self-reported disability, and lower peak velocity was weakly associated with increased fear-avoidance beliefs at the initial phase of a spinal flexion.

This thesis contributes with increased knowledge of how multisite pain, psychological distress, work- and functional ability, fear-avoidance beliefs, and spinal kinematics influence the prognosis of LBP. The results may be useful for clinical decision making for LBP management.

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Financial support: The Norwegian Fund for Post-Graduate Training in Physiotherapy and by grants from the Liaison Committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology

1 Introduction

Among persons with low back pain (LBP), there is often a high prevalence of co-complaints, such as multisite pain [1], psychological symptoms [2, 3], general poor health [2, 3], and dysfunctional movement [4], which, in turn, may influence an individual's ability to work and engage in social activities. Persons with co-complaints in addition to LBP often present with worse physical and psychosocial functioning, have a less favourable response to treatment and have higher rate of health care utilisation than persons with only LBP [5-8]. However, it is still unclear how multisite pain, psychological distress, general poor health, work ability, and impaired movement function influence the prognosis and functional consequences of LBP.

Assessing chronic pain as a complex interaction between biological, psychological, and social factors was proposed in the 1970s by George L. Engel [9] by the biopsychosocial model of pain. Although there has been a shift toward a more holistic approach in understanding and managing LBP, the biological, psychological, and social dimensions are rarely fully and concurrently addressed in the scientific literature or clinical practice [10, 11]. LBP is one of the most frequent complaints among patients seeking physiotherapy [12], and the biological domain is still the most central part in LBP management among physiotherapists [13]. The social domain is frequently absent or only vaguely incorporated in the psychological domain in screening and management (e.g., in the Startback screening tool [14]), despite the current knowledge of a high prevalence of LBP among individuals in working age and the great importance of social- and work-related factors for an individual's well-being [10, 15]. Exploring common co-complaints and characteristics related to LBP within all domains of the biopsychosocial framework would improve the understanding of factors that may influence the course of LBP and may, in turn, improve secondary prevention and treatment.

The focus of this thesis was to investigate possible prognostic factors of recovery from LBP, and to explore how characteristics in persons with LBP relate to disability- and pain-related outcomes over time, from a biopsychosocial perspective. We wanted to investigate associations of multisite pain, disability, psychological distress, and general health with long-term prognosis of LBP in a general LBP population. Furthermore, we wanted to investigate whether multisite pain, psychological distress, and work ability

were associated with prognosis and severity of LBP in patients receiving physiotherapy. Additionally, we wanted to explore the biological domain in closer detail by performing kinematic measures of a spinal flexion/extension, since biomechanical factors are central to physiotherapists' clinical examination and treatment decision making [13] and to investigate whether the spinal kinematics may be associated with psychological factors such as fear-avoidance beliefs.

2 Background

2.1 Prevalence and burden of LBP

LBP is a common cause of reduced quality of life, sick-leave, and disability [16]. In the general population, the 1-month prevalence of LBP is estimated to be up to 37% and the lifetime prevalence is 51-84% [17]. In The Global Burden of Disease Study, LBP was identified as the most significant non-mortal contributor to years lived with disability, and it was estimated that LBP caused 83 million disability-adjusted life years in 2010 [17, 18]. In Norway, approximately 7.5% of men and 8% of women reported chronic low back or neck pain in 2012, which was the most common chronic musculoskeletal complaint in men and the second most common in women [19]. Musculoskeletal pain contributes substantially to primary health care utilisation: 30-37% of the population in Norway made at least one visit to a primary health care provider (i.e., a physiotherapist, chiropractor, or general practitioner) due to musculoskeletal complaints in 2012, and LBP is, by far, the most common musculoskeletal complaint in primary care, accounting for more than half of all consultations [19]. Furthermore, musculoskeletal pain is an important cause of sick leave and disability pensions in Norway. In 2015, 39% of the reported sick leave days were due to musculoskeletal disorders, while in 2014, 29% of all disability pensions were due to musculoskeletal disorders [20]. Consequently, musculoskeletal pain is a significant burden on affected individuals, the health care, and the society, largely contributed by LBP.

2.2 Classification of LBP

2.2.1 Non-specific LBP

LBP and subsequent disability may be defined as symptoms rather than as a disease. In most cases of LBP (80-90%), it is not possible to determine the pathoanatomical cause of the symptoms [21] and the exclusion of specific pathology is, therefore, used as a diagnostic criterion for patients with non-specific LBP. Due to the lack of a valid classification systems for these non-pathoanatomical symptoms, they are all defined as non-specific [21, 22], which results in a heterogenous patient group. In the remainder of this thesis, LBP refers to non-specific LBP.

2.2.2 Acute, subacute or chronic LBP

Duration of pain episodes is commonly used as selection criteria in epidemiological and clinical studies. Traditionally, LBP has been categorised as acute, subacute, or chronic based on the duration of the current pain episode; however, these terms do not describe the LBP trajectories or variation of symptoms over time. Recent studies suggest that LBP should be viewed as episodic symptoms of recurrent pain instead of a series of unrelated episodes, due to the fluctuating nature of LBP [23, 24]. Recurrent pain symptoms are often observed in persons with LBP, and therefore differentiating acute/subacute pain from chronic or persistent pain may be challenging and sometimes misleading [25, 26]. Risk factors for developing LBP is different from prognostic factors for persistence of LBP (Cohen 2008), but the episodic and recurrent nature of LBP limit the ability to distinguish risk factors of new episodes of LBP from prognostic factors for recurrence of LBP. In prognostic research, the duration of LBP episodes seem to be of less importance [27, 28]. Persons with acute and chronic LBP share similar prognostic indicators of 12-month disability [27] and persons with different durations of LBP (e.g., less than 3 months, 3-6 months or 7-12 months) have a similar prognosis of disability after one year [28]. We included persons with chronic LBP (i.e., a pain duration of at least 3 consecutive months) in Paper 1. In Papers 2 and 3, pain duration was not an inclusion criterion, so the clinical population included LBP patients within all pain duration categories.

2.3 Course of LBP

2.3.1 Natural course

The natural course of LBP is difficult to describe as most studies include patients from primary- and secondary care settings. In a population-based study of persons with new episodes of LBP in Norway, the natural course of LBP was characterised by pain relief in the majority of persons within the first month after onset [29]. However, most experience little change after the initial improvement, few are pain free one year after pain onset [29, 30], and recurrence of pain episodes are common [25, 26]. The long-term natural course of LBP was investigated in a systematic review [31], and the authors found that becoming pain-free was uncommon and that most of the participants had persistent LBP symptoms.

2.3.2 Clinical course

Patients with LBP who seek primary health care (e.g., by a physiotherapist, chiropractor, or general practitioner) generally report a decline in symptoms during the first 5-10 weeks [32, 33], and some studies have reported 66-77% recovery rates after one year [33, 34]. Thus, the clinical course of LBP is strikingly similar to the natural course of LBP; however, it is important to recognise that clinical populations included in studies of clinical course may differ from general populations included in studies of natural course. Furthermore, the clinical course of LBP has been compared in studies of patients enrolled in randomised controlled trials receiving specific treatments for LBP and of patients in observational studies who were not receiving specific treatments [35]. No notable differences in change in pain intensity were found, and similar symptom patterns were observed in both study designs; typically, an initial period of rapid improvement was followed by a period of slower improvement during mid- and long-term follow-up. These findings may indicate that the health care provided for LBP is inadequate, possible due to insufficient knowledge of factors that influence LBP. Better knowledge of possible modifiable factors that influence LBP prognosis may improve LBP management by facilitating targeted treatment.

2.4 Theoretical models of chronic pain

Different theories of pain have influenced the management of LBP. Historically, pain has been regarded as primarily a biological phenomenon, in which nociceptive stimuli caused by tissue damage are the main pain driver [36, 37]. In the nineteenth and early twentieth century, the understanding of back pain as the result of a spinal injury was established. 'Spinal irritation' was proposed as a link between the spine and the nervous system, and the discovery of 'a ruptured disc' supported the idea that pain evolves from the spine itself and from tissue damage [38]. These theories suggest that the source of spinal pain can be objectively identified. However, modern research has repeatedly shown that this is not the case [21, 39], and thus, factors unrelated to tissue damage seem to play a role in spinal pain.

Gradually, the spinal injury theories were replaced by or supplemented with more integrated, multidimensional theories. As the effects of psychological factors on pain perceptions were gradually acknowledged and observed, the gate control theory of pain, first proposed in 1965, was developed in an attempt to provide a physiological explanation of how cognitive processes may influence the experience of pain [40]. Central to the gate control theory is that nociceptive and non-nociceptive signals might prohibit or inhibit the transmission of noxious signals to the brain. Although the gate control theory does not fully describe the complexity of pain perception, it is still being used as a theoretical framework [41].

The theory of central sensitisation further explains the interaction between biological, psychological, and social factors in chronic pain [42-44]. Central sensitisation can be described as an over-reaction of the nervous system, resulting in a lower threshold for what is perceived as painful, which, for example, can result in hyperalgesia and allodynia [44, 45]. Adverse psychosocial factors can facilitate central sensitisation, which, in turn, can influence pain perception. This idea is supported by the results from experimental studies. For example, a study of healthy students showed that higher levels of fear of pain were associated with shorter pain threshold times and higher pain ratings [46]. Other factors, such as stress, anxiety, and depression, have also been associated with an exacerbated pain response [47, 48]. However, the exact causes of why central sensitization develop in patients with musculoskeletal pain remain uncertain, but behavioural and emotional factors have been suggested as contributing factors [49].

Thus, we need to increase our knowledge on factors that potentially influence pain perception.

Approximately two decades ago, the fear-avoidance model of chronic pain (Figure 1) was developed by Vlaeyen and colleagues [50]. The fear-avoidance model sought to explain and describe the development and maintenance of chronic musculoskeletal pain in the absence of pathology [50]. The main components of the model are two separate pathways of response to a painful experience that could lead to either chronicity or recovery from pain. A negative, catastrophising interpretation of pain could lead to pain-related fear and avoidance behaviour, which, in turn, may lead to long-term disability and a lower threshold for new pain experiences [51, 52].

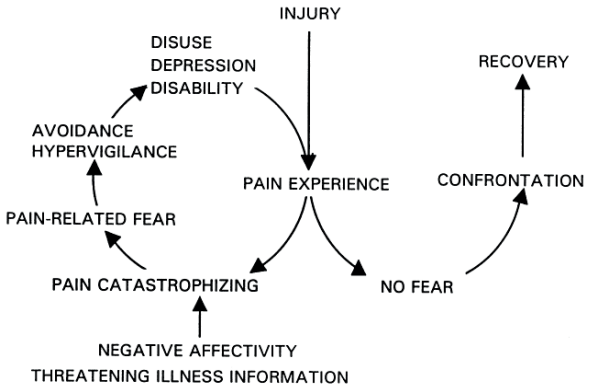

Figure 1: The fear-avoidance model. From Vlaeyen and colleagues [50], with permission from PAIN/Wolters Kluwer.

The impact of psychological and social factors in addition to biological factors on chronic pain conditions were gradually recognised with the development of the biopsychosocial model of chronic pain in the 1970s [9]. This model was further refined to a biopsychosocial model of LBP [38, 53] and has been widely used in LBP research (Figure 2). The model highlights the aetiology of chronic pain as multi-dimensional with complex interactions between biological, psychological, and social factors [38]. Moreover, the model also acknowledges that the contribution of each factor may differ between persons.

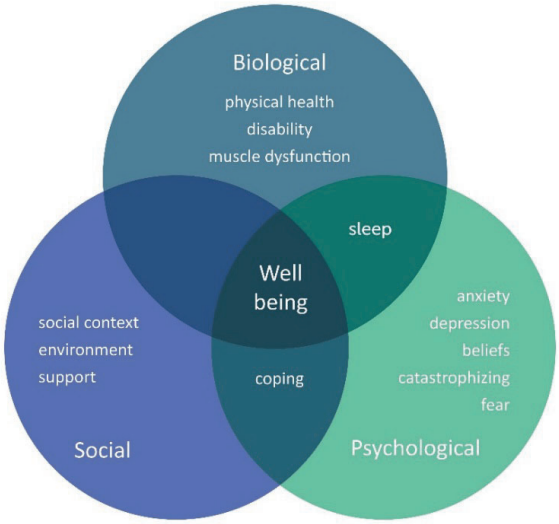

Figure 2: The Biopsychosocial model of pain, including the biological, psychological and social domain.

The view of pain as multidimensional and the acknowledgment of a complex interaction between the dimensions has led to an improved understanding of pain. However, the pain theories mentioned above still have shortcomings regarding incorporating all three dimensions, in particular the social dimension. The theories commonly have an individual focus, which are separate from the social context. To further investigate the LBP prognosis, integrated models within the whole aspect of the biopsychosocial framework are necessary [9, 54].

2.5 Description of the biopsychosocial domains represented by possible prognostic variables

A brief overview of the biopsychosocial domains is provided below. However, it is important to acknowledge that the domains should be seen as an integrated entity rather than evaluating them as separate or mutually exclusive factors.

2.5.1 Biological factors

The biological domain includes various factors, such as physical health, functional limitations, and nociceptive pain (Figure 2). Biological factors are central to

physiotherapists to determine clinical diagnosis and treatment decisions for patients with LBP [13, 55]. Traditionally, the management of musculoskeletal pain has primarily been based on a diagnosis limited to the pain *per se,* and the interventions have mainly targeted the primary pain location. However, most persons with musculoskeletal pain suffer from pain in multiple locations [1, 56]. The risk factors for developing musculoskeletal pain in different body locations are similar, for example, lifestyle factors [57, 58], age [57, 58], psychological distress [57-60], and work-related psychosocial factors [57, 59, 61, 62], and therefore, it is unsurprising that persons exposed to these risk factors may be affected by pain in different body locations.

Current evidence suggests that individual characteristics are different in persons with localised LBP compared to persons with multisite pain [7, 63, 64]. Experiencing multisite pain is more common among women than men [7, 64] and an increased number of pain sites has been associated with poorer physical and mental health [1, 63], as well as lower well-being and quality of life [65, 66], more sleep problems [63, 64], higher health care utilisation, increased sickness absences [6, 7], and decreased ability to work [67]. Although current evidence indicates that there is a higher prevalence of co-complaints in persons with multisite pain, longitudinal studies of the number of pain sites and how it influences the prognosis of LBP are scarce. It is unclear whether number of pain sites interacts with other common co-complaints such as pain-related disability and psychological distress on the prognosis of LBP.

Biological factors can also be viewed as a change in physiological functioning related to impaired or unfavourable spinal movement or muscle dysfunction [38]. Instability of the spine and insufficient muscle stabilisation were proposed as causes of LBP in the 1990s [68, 69]. However, these one-dimensional biomechanical theories have not provided sufficient evidence to fully explain LBP or for a gold standard for LBP management, and the recognition of individual differences has gradually been growing [70, 71]. Along with technological development and the increased accessibility of advanced equipment, the ability to measure the detailed biomechanics of movement has improved [72]. Measures of spinal kinematics have been used to differentiate patients with LBP from healthy controls, indicating that persons with LBP have reduced range-of-motion and reduced angular velocity in lumbopelvic movement compared to persons without LBP [4, 72, 73]. However, conflicting results have also been reported [74, 75]. A recent study of lumbar range-of-motion and velocity during lifting tasks in persons

with and without chronic LBP, found no differences between persons with chronic LBP and a low level of disability, persons with chronic LBP and a high level of disability, and healthy controls [74].

Spinal movement examination is frequently used in clinical practice and is likely driven by the belief that identifying and correcting this impairment will result in reduced pain and disability [76, 77]. However, whether impaired movement influences functional- and pain-related outcomes is not fully understood. Only a few studies have investigated if changes in kinematic measures influence outcomes in persons with LBP and the results are inconsistent [78, 79]. Thus, the influence of kinematic measures of spinal movement on self-reported outcomes in persons with LBP needs to be further investigated to determine whether it should be recommended as a tool for clinicians to classify patients, guide the management of LBP, and/or evaluate the effectiveness of treatment.

2.5.2 Psychological factors

A variety of terms and measures are used to define psychological symptoms [80], but the term psychological distress has commonly been used to represent an overall mental status, which includes a composite of symptoms of depression and anxiety. Thus, in the present thesis, the term psychological distress is used to indicate symptoms of depression and anxiety. Psychological distress is commonly reported by persons with both chronic and acute LBP [2, 80, 81], and clinical guidelines for LBP management recommend evaluating and addressing psychological obstacles to recovery [82]. Symptoms of anxiety and depression are associated with the persistence of LBP across studies [5, 57] and increased health care utilisation [83]. However, the prognostic value of psychological symptoms as a single factor has been questioned. In a literature review, the results of the studies that investigated psychological symptoms as predictors of LBP outcomes were inconsistent and showed only a modest ability to predict LBP outcomes [8]. The authors explained the inconsistency and the modest predictive ability by large methodological heterogeneity in the included studies.

Pain-related fear and catastrophising are other psychological factors that have been widely implemented in LBP research [84-86]. Catastrophising is defined as an exaggerated cognitive response to pain or expected pain, and previous studies have

shown that catastrophising thoughts can contribute to the intensification of pain and higher emotional distress [87, 88] and may be a predictor of pain intensity and disability in patients with LBP [84]. Fear-avoidance beliefs are explained as the avoidance of movements or activities due to fear or the expectation of painful experiences [89]. Fear-avoidance beliefs may amplify the experience of pain by increasing one's attention to pain stimuli [90]. In addition to their influence on the persistence of LBP [27, 50, 57, 87, 91, 92], fear-avoidance beliefs have been associated with altered movement behaviour and performance in persons with chronic LBP [50, 93]. It is therefore conceivable that fear of movement may influence spinal kinematics in persons with recent or present LBP. However, only a few studies have investigated this association, and the results are inconsistent [94-96].

Overall, the current evidence suggest associations between psychological distress and clinical and work-related outcomes in LBP [26], but there is also inconsistent findings on the influence of psychological factors on LBP prognosis [97]. Thus, the influence of psychological factors needs further exploration, and studies on how fear-avoidance beliefs in patients with LBP relates to outcome measures and spinal movement over time are needed.

2.5.3 Social factors

The social domain includes factors related to a persons' environment, for example, family relations and support, the ability to participate in social context, and work. Social factors are emphasised as important contributors to the prognosis of LBP and should therefore be addressed in LBP management [98]. The reduced work ability and sick leave that often accompanies prolonged LBP can influence a person's social interactions and belonging, which is a central aspect of a person's well-being [10, 15, 99]. Work is important for our identity, social roles, and status, and it provides financial resources, which are essential for participating in today's society [15]. The broad consensus is that persons with health problems should be encouraged to continue at work or to return to work as soon as possible, due to the positive effects of work: better health outcomes, improved quality of life and well-being, improved recovery, and participation in society [15]. Prolonged work absences progressively reduce the probability of returning to work

[53], which emphasises the importance of the early detection of factors associated with work participation.

Work ability is a multi-dimensional concept that includes physiological, psychological, and social factors, such as physical work demands, beliefs regarding harmful work or fear of re-injury, and support in the workplace [100]. Poor work ability has been associated with musculoskeletal pain in cross-sectional studies [101-103] and it has been identified as a predictor of long-term sick leave and disability pensions in general populations of workers [104, 105]. Furthermore, a prospective study of women on long-term sick leave showed that work ability was predictive of pain, self-rated general health, and quality of life [106]. However, there is lack of longitudinal studies that specifically investigated work ability and its association with pain intensity, disability, and quality of life in patients with LBP.

Although cross-national clinical guidelines recommend that LBP management should include aspects of biological, psychological, and social factors, the emphasis and specific details of psychological and social factors are not consistent or clearly described [107]. Studies have shown that physiotherapists have limited recognition of psychological and social factors in LBP management and underestimate the influence of these factors on prognosis of LBP [13, 54]. Thus, it is important to gain further insight into the importance of all domains of the biopsychosocial model in patients with LBP to develop and improve recommendations for LBP management.

2.6 Outcome measures for patients with LBP

'...a difference is a difference only if it makes a difference.'

-Darrell Huff [108]

Similar to many other health conditions, there is a lack of standardisation of measurement of improvement or recovery from LBP [109]. The lack of standardisation limits the interpretation and comparison of studies of patients with LBP. The results of studies on recovery may depend on how recovery is defined and operationalised, the methods, the study setting, and the length of follow-up [110]. Pain intensity and disability are commonly used as outcome measures in LBP research. However, they may provide only partial insight into the success of treatment [111], since the degree of

success may also be determined by the impact on daily activities, quality of life, pain symptoms, biomechanical performance, and self-efficacy [112, 113]. To reflect the biopsychosocial framework in the outcome measures, we included pain intensity, disability, quality of life, and work ability as outcome measures whenever such data were available. This decision is in line with the recommended core outcomes in LBP research, developed by an international committee of researchers, care providers, and patients' representatives [114]. Inclusion of outcome assessments from different domains of the biopsychosocial framework provides a more holistic assessment of the influence and importance of the independent variables on LBP.

2.7 Integrated biopsychosocial management of LBP

Since most cases of LBP are not explained by pathoanatomical findings, LBP management is mostly focused on pain relief, the reduction or prevention of disability, and the improvement of patients functioning in daily life. Despite the extensive research on LBP, we have yet to discover a treatment that is superior to others. The heterogeneity of the LBP population may contribute to the large variation in treatment responses. Studies on treatment effects may be confounded by heterogeneous pooling of participants, resulting in averaged treatment effects. Persons with LBP may be similar on one domain but differ on the other domains [115]. Thus, increased knowledge on biopsychosocial prognostic factors for recovery from LBP and integrating them in LBP management to encompass all aspects of a person's well-being may be necessary for successful treatment. Recent reviews of single non-pharmacological therapies for LBP have shown small to moderate short-term effects on pain and functioning, and the long-term effects are correspondingly small [22, 116]. More promising results have been found for LBP treatments that incorporate multiple disciplines to encompass the whole biopsychosocial framework [98]. In a systematic review, the authors found that multidisciplinary rehabilitation was more effective than usual care (e.g., provided by a general practitioner or a medical specialist) on long-term pain and disability among persons with chronic LBP, although the quality of the studies was rated as moderate. Additionally, they found that multidisciplinary rehabilitation had a favourable effect on long-term pain and disability compared to physical treatment; however, these studies were rated as low quality [98]. The findings from these studies indicate that there may

be potential for improvement in addressing all components of the biopsychosocial model in LBP management.

2.8 Summary of background

In the absence of clear underlying structural causes of LBP and the presence of a need to develop more effective treatment approaches for patients with LBP, a better and broader understanding of characteristics and possible prognostic factors in LBP is required. Models explaining LBP within a single domain have shown to be insufficient; therefore, investigating factors across the domains of the biopsychosocial model and the interaction between these domains may provide an increased understanding. Although previous studies indicate that the presence of co-complaints, reduced work ability, and dysfunctional movement in persons with LBP negatively influence the severity of the condition, their influence on the prognosis for recovery from LBP is poorly understood. More knowledge is needed on the prospective and longitudinal associations with functional, psychological, and social consequences of LBP in the general population and in patients attending physiotherapy.

New knowledge can be achieved by using broad methodological approaches. The results of studies investigating the same underlying research question using different approaches may be less prone to spurious findings [117]. While large cohort studies with long-term follow-up may provide improved knowledge of prognostic factors, clinical longitudinal data with repeated measurements can provide valuable information regarding how and whether individual characteristics are related to intrapersonal changes over time (e.g., whether patients report more psychological distress at time points when they experience more disability or pain and vice versa).

3 Aims

3.1 Overall aim

The overall aim of this thesis is to explore possible prognostic factors within a biopsychosocial framework, such as multisite pain, psychological distress, work- and functional ability, and spinal kinematics and their associations with self-reported outcomes in LBP. We examined the long-term prognosis of recovery from LBP in persons with LBP from a general population and we investigated biopsychosocial factors in persons with LBP seeking physiotherapy.

3.2 Specific aims of the papers

Paper 1 examined prognostic factors that could affect the long-term probability of recovery from chronic LBP. Specifically, we investigated the independent association of multisite pain, pain-related disability, psychological distress, and self-rated general health with the probability of recovery from chronic LBP after ~10-11 years. To assess possible synergistic effects, we estimated the joint association of multiple pain sites and co-complaints with the probability of recovery from LBP.

Paper 2 investigated longitudinal associations of multisite pain, psychological distress, and work ability with self-reported disability, pain intensity, and quality of life in patients with LBP attending physiotherapy. We also investigated whether changes in multisite pain, psychological distress, and work ability were associated with improvement in disability, pain intensity, and quality of life three months after initiation of the physiotherapy treatment.

Paper 3 investigated longitudinal associations of spinal kinematics and fear-avoidance beliefs with disability, work ability, and pain intensity in patients with LBP attending physiotherapy with three- and nine-months follow-up, as well as associations between fear-avoidance beliefs and spinal kinematics.

4 Method

4.1 Study design

This thesis includes three separate cohorts of varying size and characteristics to cover different aspects of prognostics in LBP. The first is a cohort of persons with chronic LBP retrieved from the Nord-Trøndelag Health Study (The HUNT Study), which is a large population-based study. The second is a clinical cohort of LBP patients who received physiotherapy, and the third is a smaller cohort of LBP patients who received physiotherapy and underwent kinematic measurements in a laboratory. In this thesis, the three cohorts are named 'the HUNT LBP cohort', 'the FYSIOPRIM cohort', and 'the Lab cohort', respectively. In Paper 1, we conducted a long-term prospective study of a chronic LBP population to investigate the prognosis of chronic LBP after ~10-11 years. In Papers 2 and 3, we performed observational studies of patients receiving physiotherapy with three (Paper 2 and 3) and nine (Paper 3) months follow-up to investigate longitudinal associations between biological, psychological, and social factors with functional and pain-related outcomes. An overview of the aims, variables, and the associated domains included in this thesis is provided in Table 1.

Table 1: Overview of biopsychosocial variables, aims, follow-up time and inclusion criteria in the three papers included in this thesis.

			General LBP population	Clinical LBP population	
	Domain	Variable	**Paper 1**	**Paper 2**	**Paper 3**
Independent variables	Biological	Number of pain sites	x	x	
		Leisure-time disability	x		
		Kinematic measures			x
	Psychological	Psychological distress	x	x	
		Self-rated general health	x		
		Fear-avoidance beliefs			x
	Social	Work ability[a]	x	x	
Outcome variables	Pain recovery/intensity		x	x	x
	Disability			x	x
	Quality of life			x	
	Work ability				x
Aim			Investigate the influence of multisite pain, pain-related disability, psychological distress, and self-rated general health on long-term probability of recovery from LBP in a general LBP population.	Investigate if multisite pain, psychological distress, and work ability, and change in these variables, are associated with disability, pain intensity, and quality of life in patients with LBP	Investigate spinal kinematics and associations with disability, work ability and pain intensity over time, and associations between fear-avoidance beliefs and spinal kinematics
Follow -up			10-11 years	3 months	3 and 9 months
Participants	Inclusion criteria		- Participation in both the second and third wave of the HUNT study - Reporting chronic LBP (pain for ≥3 consecutive months)	- Attending physiotherapy for ongoing LBP	- Attending physiotherapy for ongoing LBP

Abbreviations: LBP = low back pain; HUNT = The Nord-Trøndelag Health Study.
[a] Work ability was assessed by different questions in Paper 1 and Paper 2. In Paper 1, work disability was dichotomised into 'no disability' and 'disability'. In Paper 2, work ability was reported on an 11-point scale (0-10)

4.2 Participants and settings

A summary of baseline characteristics of the participants in the three cohorts is presented in Table 2.

4.2.1 Paper 1

In Nord-Trøndelag County, Norway, all inhabitants aged 20 years or older were invited to participate in three health surveys: the HUNT Study, which was first conducted in 1984-86 (HUNT1), and repeated in 1995-97 (HUNT2) and 2006-08 (HUNT3). Information regarding lifestyle and health-related factors were collected via questionnaires and clinical examinations were performed by certified personnel [118]. More detailed information about the selection procedures, participation, and questionnaires used in the HUNT Study can be found at *http://www.ntnu.edu/hunt*. Paper 1 was based on data from the HUNT2 and HUNT3 studies. Of the 93,898 eligible participants, 65,237 (65.5%) accepted the invitation to participate in HUNT2. In HUNT3, 93,860 were invited to participate, of which 50,807 (54.1%) accepted the invitation. For the study presented in Paper 1, the inclusion criteria were participation in both HUNT2 and HUNT3 and reporting chronic LBP for at least three consecutive months within the last year at HUNT2. Among the 37,070 people who participated in both HUNT2 and HUNT3, 9,147 persons with chronic LBP were eligible for the present study. However, we excluded participants with missing information on musculoskeletal pain at HUNT3 (1,557 persons) and 23 persons with missing information on body mass index (BMI). We also excluded participants with a BMI <18.5 kg/m^2 (44 persons) to reduce the possibility of reverse causation due to undetected disease. Thus, the final statistical analyses performed in Paper 1 were based on 7,523 persons (4,484 women and 3,039 men).

4.2.2 Paper 2

The patients in Paper 2 were recruited from Trondheim municipality between May 2014 and November 2017. The study sample consisted of pooled data from the two clinical cohorts, which included a total of 165 patients (121 participants from The FYSIOPRIM cohort and 44 participants from the Lab cohort). Patients in the FYSIOPRIM cohort

were recruited through a large ongoing study of primary care physiotherapy [12]. The physiotherapists recruited the patients for this study during their first appointment. The patients completed electronic baseline questionnaires immediately after the first consultation and were followed over time; detailed information of the FYSIOPRIM cohort has been published elsewhere [12]. Patients in the Lab cohort underwent a more comprehensive laboratory data collection procedure, which is described in detail in paragraph 4.2.3. The inclusion criterion in Papers 2 and 3 was seeking physiotherapy for ongoing LBP of any duration. The exclusion criteria were insufficient language capabilities, severe neurologic signs, pregnancy or pregnancy-related pelvic pain, and having received back surgery within the previous six months.

4.2.3 Paper 3

The 44 patients (the Lab cohort) included in Paper 3 were recruited from primary care physiotherapy clinics in Trondheim municipality between May 2014 and March 2017. Patients who contacted the clinics due to LBP were eligible for this study and were invited to participate. The exclusion criteria were insufficient language capabilities, severe neurologic signs, pregnancy, and back surgery within the previous six months. Baseline data collection was performed by the researchers prior to the first consultation with the physiotherapist and included comprehensive kinematic measurements of spinal movements and questionnaires. Identical measurements were performed by the researchers at the three- and nine-month follow-ups.

Table 2: Baseline characteristics of the persons included in the three cohorts.

Variables	HUNT LBP Cohort	FYSIOPRIM cohort	Lab cohort
Number of persons	7523	121	44
Female, n (%)	4484 (60%)	80 (66%)	28 (64%)
Age, mean (SD)	50.3 (12.0)	44.9 (18.1)	42.8 (14.8)
BMI, mean (SD)	26.7 (4.0)	26.8 (3.4)	25.4 (4.9)
Education ≤13 years, n (%)	6076 (81%)	44 (43%)	24 (55%)
Number of pain sites, mean (SD)	4.4 (2.4)	2.8 (2.1)	2.9 (1.6)
1 pain site, n (%)	780 (10%)	21 (25%)	9 (21%)
2-3 pain sites, n (%)	2331 (31%)	34 (41%)	23 (52%)
≥4 pain sites, n (%)	4412 (59%)	28 (34%)	12 (27%)
Average pain (0-10), mean (SD)	NA	4.6 (2.3)	5.4 (2.2)
Pain duration >9 months, n (%)	NA	47 (59%)	23 (62%)
On sick leave or disability leave, n (%)	NA	12 (11%)	6 (14%)
Psychological distress[a] (0-4), mean (SD)	NA	1.7 (0.5)	1.6 (0.5)
HADS depression (0-21), mean (SD)	4.0 (3.2)	NA	NA
HADS anxiety (0-21), mean (SD)	5.0 (3.6)	NA	NA
FABQ-PA (0-24), mean (SD)	NA	NA	8.8 (5.3)
FABQ-W (0-42), mean (SD)	NA	NA	11.3 (10.4)
Work ability[b] (0-10), mean (SD)	NA	5.9 (2.8)	6.1 (2.4)
Work disability[c], n (%)	1021 (14%)	NA	NA
Leisure disability[c], n (%)	507 (7%)	NA	NA
Work and leisure disability[c], n (%)	4514 (63%)	NA	NA
Disability[d] (0-100), mean (SD)	NA	23.3 (14.6)	23.6 (12.4)

Abbreviations: LBP = low back pain; SD = standard deviation; BMI = body mass index; HADS = Hospital Anxiety and Depression Scale; FABQ-PA = fear-avoidance beliefs of physical activity; FABQ-W = fear-avoidance beliefs of work; NA = not applicable.
The number of responders for the characteristic variables differs slightly due to missing values.
[a]Measured by the Hopkins symptom checklist.
[b]Work ability range 0 (completely unable to work) to 10 (work ability at its best).
[c]Questions of work and leisure disability dichotomised into 'no disability' and 'disability'.
[d]Measured by the Oswestry Disability Index, range 0 (not disabled at all) to 100 (completely disabled).

4.3 Questionnaires

All participants in the three studies completed a set of questionnaires. We selected specific variables shown in Table 1 to represent each domain of the biopsychosocial model to be included in this thesis. This selection was based on *a priori* knowledge of possible factors associated with musculoskeletal pain or LBP and patient's well-being, and factors that are often included in clinical assessments of patients with LBP. It should be noted that these variables only represent a limited part of each domain and that they cannot completely capture the complexity of the biopsychosocial model.

4.3.1 Descriptive variables and possible confounders

Body height and weight measurements were obtained during a clinical examination in the HUNT study, and BMI was calculated as weight divided by the square of height (kg/m^2). In the clinical cohorts, body height and weight were self-reported. In all papers, we classified BMI into groups according to the cut-off points suggested by the World Health Organization: normal weight (18.5-24.9 kg/m^2), overweight (25.0 – 29.9 kg/m^2), obese (≥30.0 kg/m^2) [119]. Physical work demands were assessed in Paper 1 by asking the participants, "If you have paid or unpaid work, how would you describe your work?" which had four possible responses: 'mostly sedentary', 'much walking', 'much walking and lifting' or 'heavy physical work'. Leisure time physical activity was assessed in Paper 1 by asking the participants, "How much of your leisure time have you been physically active during the last year? (Think of a weekly average for the year. Your commute to work count as leisure time)". The participants reported the number of hours of light and/or hard activity. Based on this information, we constructed four categories: 'inactive' (no light or hard activity), 'low activity' (<3 hours of light and no hard activity), 'moderate activity' (≥3 hours light and/or <1 hours of hard activity) and 'high activity' (any light and ≥1 hour of hard activity). The participants' education level was assessed by them "What is your highest level of education?", and their responses were divided into four categories: 'primary school', 'high school', 'college ≤4 years' and 'college >4 years'. In Paper 1, the smoking status was assessed by asking questions about past or present tobacco use, and the responses were divided into three categories: 'never-smoker', 'previous smoker', and 'current smoker'.

In the FYSIOPRIM cohort, pain duration at baseline was reported as the number of months with back pain. In the Lab cohort, data on pain duration was collected only at the three-month follow-up and the patients could report pain duration in four categories: 'less than one month', 1-3 months', 4-12 months', and 'more than 12 months'. For the purpose of Paper 2, we could only collapse this variable from the two clinical cohorts' by dichotomised pain duration as greater or less than nine months duration. The participants' current work status was categorised as 'paid work', 'unpaid work', 'retired', 'unemployed', 'student', 'sick leave', or 'disability pension' in Papers 2 and 3.

4.3.2 Variables representing the biopsychosocial domains

Biological variables

In all three papers, data on the number of pain sites was collected by asking the participants to indicate their pain-affected areas on either a pain diagram (HUNT2) or a body map (FYSIOPRIM cohort, LAB cohort, HUNT3) adopted from the Standardised Nordic Questionnaire [120], with the option to mark up to twelve body areas. We estimated the number of musculoskeletal pain sites by adding nine possible pain-afflicted body areas: neck, shoulders/upper arms, elbows, wrists/hands, upper back, lower back, hips, knees, and ankles/feet. The additional response options, which were 'head', 'chest', and 'abdomen', were not included in the total number of musculoskeletal pain sites.

In Paper 1, pain-related disability was measured by two separate questions regarding reduced work ability and reduced leisure time activity. Work-related disability is described later under 'social variables'. The question used to assess leisure time activity was, 'Has the pain and/or stiffness reduced your leisure activity?' with 'yes' and 'no' as the possible responses. The answers to the questions on leisure-time disability and work-related disability were categorised into four groups: 'no disability', 'work disability', 'leisure disability', and 'work and leisure disability'. Kinematic measures are described in paragraph 4.4.

Psychological variables

In Paper 1, psychological distress was measured by the Hospital Anxiety and Depression Scale (HADS). HADS includes a total of 14 questions; seven of which address anxiety and seven depression. It is a widely used and validated questionnaire, which has demonstrated the ability to detect depression and anxiety in patients seeking primary care [121]. We used the recommended cut-off score value for the presence of symptoms of anxiety or depression: ≥ 8 points for each dimension [121]. In Paper 2, psychological distress was measured using the 10-item Hopkins Symptom Checklist, mainly the items measuring symptoms of depression and anxiety [122, 123]. The total score ranges from one (not bothered) to four (extremely bothered). The more comprehensive 25-item version has shown good psychometric properties [124], and the shorter 10-item version have similarly shown to be a valid and reliable measure of psychological distress [123]. Both questionnaires identify symptoms of anxiety and

depression but were not used to indicate clinical disorders in the present study. The correlation between HADS and Hopkins Symptom Checklist has been investigated in a few studies, which found moderate correlations in the range of 0.49 - 0.73 [121].

Fear-avoidance beliefs were measured by the Fear-Avoidance Beliefs Questionnaire (FABQ) [52], which consists of 16 items. The questionnaire can be divided into fear-avoidance beliefs about physical activity (FABQ-PA) and fear-avoidance beliefs about work (FABQ-W). The total score for FABQ-PA is 24 points, which are based on four questions. The total score of FABQ-W is 42 points based on seven questions. In the present study we assessed the two subscales separately. The Norwegian version of the questionnaire has shown moderate to high reliability and acceptable construct validity [125].

In Paper 1, we assessed self-rated general health by asking the question, "How is your health at the moment?". The participants were given four response options: 'very good', 'good', 'not so good', and 'poor'. The nature of the question may include both the biological and the psychosocial dimension [126].

Social variables

Work-related variables were included to represent the social domain in our thesis. The ability to work is considered essential for social belonging and for societal involvement [15]. We included two variables to assess the participants' self-perceived ability to work. In Paper 1, work-related disability due to musculoskeletal pain was assessed by the single question: "Have the pain and/or stiffness reduced your ability to work during the last year?" with the response options: 'no/not significantly', 'to some degree', 'significantly' and 'don't know'. The response options 'no/not significantly' and 'don't know' were categorised as 'no disability', and the two remaining response options were categorised as 'work disability'. In Papers 2 and 3, work ability was assessed by a single item question obtained from the Work Ability Index [106, 127]. The patients were asked to 'Describe your current work ability compared with the lifetime best' on an 11-point numeric rating scale (0-10). Zero represents 'completely unable to work', and 10 represents 'work ability at its best'. Scores on this single item question have been shown to have a strong correlation with the complete Work Ability Index, and they both have shown a strong ability to predict future sick leave [106].

4.4 Kinematic measures

4.4.1 Data acquisition

Kinematic measures of spinal flexion/extension movement were recorded by a body-worn motion sensor attached to the body over the T6 spinous process (figure 3), using a Liberty motion tracker system (Polhemus, Inc, Colchester, Vermont, USA). An electromagnetic field is created by the system's source, which is placed above the patients' head and captures the position and orientation of the sensor, in relation to other sensors or to the source, with a sampling rate of 240 Hz. Detailed information on the Liberty motion tracker system can be found on the manufacturers' website (https://polhemus.com/motion-tracking/all-trackers/liberty). Raw data were low-pass filtered at 20 Hz using a second-order Butterworth filter. A software tool was custom-built in Matlab to record and analyse the kinematic data.

4.4.2 Test procedures

The kinematic measures used in this thesis included range-of-motion measured as degrees from the beginning to the end of spinal flexion/extension movement. Peak angular velocity was measured as degrees per second. The patients were asked to perform a sagittal spinal flexion as far as possible with the knee extended and return to an upright position (i.e.: extension; see figure 3). The instructor demonstrated the spinal flexion movement to ensure that the patients understood it. The patients were placed in a start position with a shoulder width distance between the feet and arms along their sides. We did not give the patients any instructions on how quickly to perform the movement.

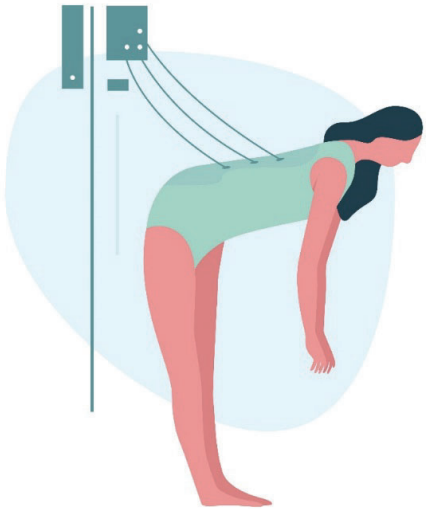

Figure 3: An illustration of the kinematic data collection method used in the laboratory. Sensors were placed on the patients' back and they were asked to perform a sagittal spinal flexion and return to an upright position.

4.4.3 Kinematic data analysis

Spinal movement was defined as movement of the sensor on T6 relative to the source. We defined the beginning and the end of the spinal flexion and the extension as the points when the velocity exceeded or fell below 5% of the maximum velocity. The beginning and end of the flexion were named T1 and T2, and the start and end of the extension were named T3 and T4. We obtained separate measures of peak angular velocity in the flexion and extension phase of the spinal movement. Range-of-motion was calculated as degrees of movement between T1 and T4. Further, we divided the flexion and extension movement into three equal segments based on range-of-motion, resulting in six segments that were analysed separately: the start-, middle-, and end phase (figure 4).

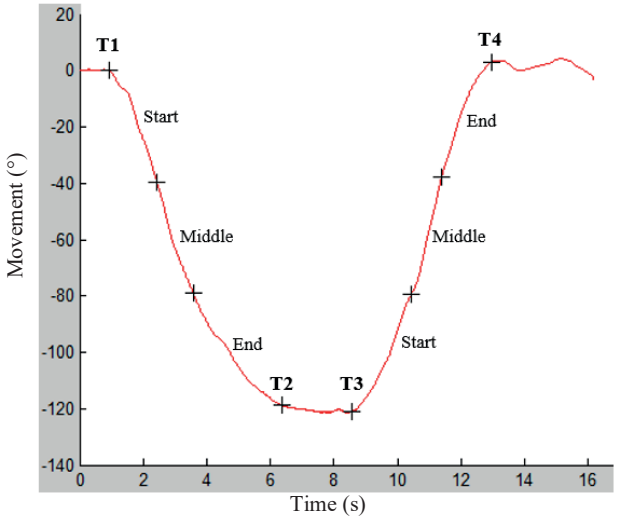

Figure 4: An example of a curve of range-of-motion during standing flexion and extension (from Nordstoga et al. 2019 [128]). Zero on the y-axis represents the marker position at the point where recording began. The start and end of trunk flexion (T1 and T2) and the start and end of extension (T3 and T4) were defined as the points the velocity exceeded or fell below 5% of maximum speed, respectively. The flexion and extension phases were divided into three equal range segments, the start-, middle-, and end phase, based on range-of-motion between T1 and T2, and between T3 and T4.

4.5 Outcome variables

The main outcome in Paper 1 was recovery from chronic LBP reported in HUNT3 at ~10-11 years follow-up, and it was measured using the same questions as the inclusion criterion in HUNT2. The question is adopted from the Standard Nordic Questionnaire [120] and the participants were asked, "During the last year, have you had pain and/or stiffness in your muscles and joints that lasted for at least three consecutive months?", with two response options: 'yes' and 'no'. Persons who responded "no" were defined as recovered from LBP, together with persons who responded 'yes' but did not indicate 'low back' as an affected body area.

Disability was the main outcome in Paper 2. It was measured at three months using the Oswestry Disability Index (ODI) [129], where the patients were asked to indicate their physical disability in activities of daily living. ODI scores ranges from 0 (not disabled at all) to 100 (completely disabled). Secondary outcomes were pain intensity and quality of life measured at three months. Pain intensity was reported on an 11-point Numeric pain rating scale [130] where 0 represent no pain, and 10 represents the worst possible

pain. Quality of life was measured by EQ-5D, which comprises a 5-dimensional self-reported health status based on mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Thus, EQ-5D reflects the diversity of the biopsychosocial framework and overlap with the other outcomes. Each of the dimensions has a five-level response option, and the answers were transformed into an index score using the Danish population value set (in lack of a Norwegian value set) [131]. The index score ranges from 0.0 (death) to 1.0 (perfect health). For the purpose of the secondary aim, we dichotomised ODI, pain intensity, and EQ-5D to define clinically meaningful improvement [132, 133] at three months. For ODI (0-100), we defined it as ≥10 points improvement [134], while for pain (0-10), we defined it as ≥ 2 points [134], and for EQ5D (0-1), we defined it as ≥0.08 points improvement [135].

In Paper 3, we included ODI, work ability, and pain intensity as the outcome measures (described in detail above), and due to the longitudinal design of this paper, all variables were collected at baseline, three and nine months.

4.6 Treatment during the follow-up period

We did not aim to investigate treatment effects or types of treatment in this thesis; however, for descriptive purposes, a brief overview of the treatment in the clinical cohorts are presented in the following paragraph. The treatment data are based on the physiotherapists' own description in the FYSIOPRIM cohort, and the treatment data in the Lab cohort is based on the patients' descriptions.

The most frequent treatment approach in the FYSIOPRIM cohort was exercise (95% of the patients), and about 31% of the patients received passive treatments. They received an average of 12 treatment sessions (median = 8, range = 2-30) during the three months of follow-up; however, it is important to mention that information regarding the number of treatment sessions was missing for most of the patients. The patients in the Lab cohort received an average of 5.4 treatment sessions (median = 3.5, range = 1-20) from physiotherapists during the first three months. Most of the patients received information (75%) and exercises (68%), but passive treatments were also performed (39% of the patients).

4.7 Statistical analyses

In Paper 1, we used a modified Poisson regression to estimate the relative probability of recovery from chronic LBP as risk ratios (RR). The precision was assessed by 95% confidence intervals (CI) using robust variance estimation. A RR above 1.0 indicates a higher probability of recovery compared to the reference category, while a RR less than 1.0 indicates a reduced probability of recovery. We conducted all the main analyses separately by gender. Additionally, we conducted analyses that combined the number of pain sites (<4 vs. 4 - 9 sites) and comorbid conditions in relation to the probability of recovery from chronic LBP. To evaluate statistical interactions, we performed a likelihood ratio test of the product term of the number of pain sites and each of the comorbid factors (i.e., self-reported health, pain-related disability, and HADS). The analyses were adjusted for possible confounders (i.e., age, BMI, physical activity, level of education, smoking, and physical work demands) based on *a priori* knowledge of possible association with both the exposure and the outcome. We performed sensitivity analyses where we adjusted for other physical health conditions in the associations between number of pain sites, HADS, pain-related disability, and general health with probability of recovery from LBP.

In Paper 2, the repeated measurements were analysed using linear mixed-effects models with a random intercept to estimate changes in each of the exposures and outcome variables from the baseline to three months. Linear mixed-effects models were also used to estimate the longitudinal associations of multisite pain, psychological symptoms, and work ability with concurrent measures of disability, pain intensity, and quality of life over a three-month period (baseline and three-month follow-up). The normality assumptions for random intercepts and residuals were assessed using histograms and QQ plots. To study the associations between baseline levels and change in the exposure variables and minimal important difference in disability, pain, and quality of life, odds ratios (OR) were estimated using logistic regression. In the analyses of change in the exposure variables, we adjusted for the respective baseline value of the exposure variable. Based on *a priori* knowledge of possible associations with the independent and dependent variables, all of the above-mentioned associations were adjusted for possible confounders that were available: Age, gender, level of education, and study population (the FYSIOPRIM cohort and the Lab cohort). We performed two sensitivity analyses where we (i) performed the analyses of change in the exposure variables without

adjusting for baseline values and (ii) excluded patients for whom follow-up information was missing. The precision of the estimated associations was assessed using a 95% CI.

In Paper 3, we performed fixed-effect models to analyse the within-person effects by using the 'xtreg' command with the 'fe' option in Stata. The analysis estimated change within persons, in contrast to estimating the patients at group-level, which may be closer to a clinical setting where the clinician typically performs individual assessments and evaluates treatment progress. In within-person models, each person serves as his or her own control, and the person's time-invariant characteristics (e.g., age, gender, and socioeconomic status) are accounted for. The within-person effect can be interpreted as differences in the mean values of the outcome variable (e.g., disability) for the individual who changes one unit on the exposure variable (e.g., fear-avoidance beliefs) between the time points [136, 137]. We adjusted for range-of-motion when peak velocity was the variable of interest due to a potential dependency with movement velocity. To further evaluate the robustness of our results, we performed various sensitivity analyses. We (i) included pain intensity as a covariate except when pain was the variable of interest, (ii) excluded persons without complete follow-up information, (iii) included only the persons who reported a pain duration longer than nine months, and (iv) excluded persons with values <8 points on FABQ-PA and <10 points on FABQ-W at the baseline. The statistical analyses were performed using Stata version 13.1 for Paper 1 and version 15.1 for Papers 2 and 3.

4.8 Ethical considerations

The studies were approved by the Regional Committee for Ethics in Medical Research (project no. 2014/2044 [the HUNT LBP cohort], 2013/2030 [the FYSIOPRIM cohort] and 2013/2244 [the Lab cohort] REK Mid-Norway), and all participants gave written informed consent. The study was conducted in compliance with the Declaration of Helsinki.

5 Results

A summary of the results included in the three papers is presented here. Detailed results and tables can be found in the respective papers.

5.1 Paper 1

The influence of multisite pain and psychological comorbidity on prognosis of chronic low back pain: Longitudinal data from the Norwegian HUNT Study.

We included 4,484 women and 3,039 men with chronic LBP at baseline in the analyses. Of these participants, 40.6% women and 51.9% men reported recovery from chronic LBP at the 11-year follow-up. Only 7% of the women and 15% of the men reported only LBP at baseline, whereas 66% of the women and 47% of the men reported pain in ≥4 sites.

Increasing number of pain sites was inversely associated with the probability of recovery. Reporting only one pain site was associated with a slightly higher probability of recovery from LBP (Women: RR 1.10, 95% CI 0.98 to 1.22. Men: RR 1.10, 95% CI 1.01 to 1.21) compared to reporting 2-3 pain sites. Women and men who reported 4-5 pain sites had slightly lower probability of recovery (RR 0.83, 95% CI 0.76 to 0.90 and RR 0.86, 95% CI 0.79 to 0.94, respectively), and reporting 6–9 pain sites had a substantially lower probability of recovery (Women: RR 0.58, 95% CI 0.52 to 0.63. Men: RR 0.70, 95% CI 0.63 to 0.79), compared with women and men who reported 2–3 pain sites. The presence of both work-related and leisure disability was associated with a reduced probability of recovery in both women (RR 0.68, 95% CI 0.62 to 0.74) and men (RR 0.76, 95% CI 0.70 to 0.83). HADS score of ≥8 on both depression and anxiety subscales was associated with reduced probability of recovery in both women (RR 0.77, 95% CI 0.66 to 0.91) and men (RR 0.79, 95% CI 0.67 to 0.94). Persons reporting their general health as poor or 'not so good' had a reduced probability of recovery, both in women (RR 0.66, 95% CI 0.61 to 0.71) and men (RR 0.72, 95% CI 0.67 to 0.78), when compared to persons reporting good or very good general health. Including other physical health diseases as a covariate in sensitivity analyses marginally influenced the results.

We did not find any synergistic effects of ≥4 pain sites and pain-related disability, psychological stress, or self-rated general health. However, we found that persons with

≥4 pain sites had a lower probability within all strata of pain-related disability and psychological distress.

5.2 Paper 2

Improvement in work ability, psychological distress and pain sites in relation to low back pain prognosis: A longitudinal observational study in primary care.

A total of 165 patients, pooled from two clinical cohorts, were included in the analyses in this paper. Of the included patients, 65% attended the three-months follow-up. At baseline, the patients had on average 2.9 (SD = 2.0) pain sites, 4% of the participants scored above the cut-of (≥8 points) on psychological distress, and the average work ability were 6.0 (SD = 2.7). At 3 months follow-up, 28% of the patients achieved clinically meaningful improvement in disability, 44% in pain intensity, and 43% in quality of life. Change in the number of pain sites, psychological distress, and work ability from the baseline to three months were -0.4 points (95% CI: -0.6 to -0.1), -0.1 points (95% CI: -0.1 to 0.0), and 0.9 points (95% CI: 0.5 to 1.2), respectively.

The longitudinal analyses showed that a one-point increase in the number of pain sites was associated with higher disability (1.9 points, 95% CI: 0.9 to 2.8), more pain (0.4 points, 95% CI: 0.2 to 0.5), and lower quality of life (0.02 points, 95% CI: 0.03 to 0.01). One-point increase in psychological distress was associated with higher disability (10.9 points, 95% CI: 7.7 to 14.1), more pain (1.9 points, 95% CI: 1.3 to 2.5), and a lower quality of life (0.1 points, 95% CI: 0.2 to 0.1). One-point increase in work ability was associated with less disability (2.6 points, 95% CI: 3.3 to 2.0), less pain (0.4 points, 95% CI: 0.5 to 0.3), and a higher quality of life (0.03 points, 95% CI: 0.02 to 0.04). In summary, change in the number of pain sites, the level of psychological distress, and work ability were longitudinally associated with all the outcome measures over a three-month period.

Compared to persons with an impaired or stable work ability from baseline to three months, improvement in work ability from the baseline to three months was the only variable associated with improvements in both disability, pain intensity, and quality of life. The odds ratios were for disability: 4.8 (95% CI: 1.3 to 18.1), for pain intensity: 3.6 (95% CI: 1.1 to 12.2), and for quality of life: 4.5 (95% CI: 1.4 to 15.1). In the sensitivity analyses without baseline adjustment, the associations between work ability and the

outcomes were marginally attenuated: OR 3.5 (95% CI: 1.1 to 11.5), OR 3.1 (95% CI: 1.0 to 10.0), and OR 4.5 (95% CI: 1.3 to 12.3) in disability, pain intensity, and quality of life, respectively. Improvement in psychological distress was only positively associated with improvement in average pain intensity (OR 4.0, 95% CI: 1.3 to 12.3), whereas no significant associations were found for changes in pain sites.

5.3 Paper 3

Longitudinal associations of kinematics and fear-avoidance beliefs with disability, work ability and pain intensity in persons with low back pain.

The analyses were based on repeated measurements obtained from 44 patients. Four patients did not attend the three-month follow-up, and 14 patients did not attend the nine-month follow-up, resulting in a total of 114 observations during the follow-up period. Range-of-motion increased at three- and nine-months follow-up by 10.3° (95% CI 1.4 to 19.2) and 8.0° (95% CI -1.6 to 17.6), respectively, and peak velocity increased in all phases of the movement from baseline to three- and nine-months. FABQ-PA decreased 2.7 points (95% CI -4.5 to -1.3) and 3.4 points (95%CI -5.2 to -1.6) at three- and nine-months, respectively. FABQ-W decreased 2.1 points (95% CI -4.0 to -0.2) at three months and 3.6 points (95% CI -5.8 to -1.5) at nine months.

The longitudinal analyses showed that within persons, a one-degree increase in range-of-motion was accompanied by lower disability (-0.14 points, 95% CI -0.22 to -0.06), indicating that persons had slightly larger range-of-motion at times they reported less disability. We did not find any within-person associations between peak velocity and disability, work ability, or pain intensity. A 10% increase in FABQ-PA were accompanied by somewhat higher disability (1.50 points, 95% CI 0.51 to 2.49) and more pain (0.37 points, 95% CI 0.11 to 0.62), whereas a 10% increase in FABQ-W were accompanied by lower work ability (-0.37 points, 95% CI -0.68 to -0.05).

The within-person analyses of associations between fear-avoidance beliefs and kinematic measures showed that a 10% increase in FABQ-PA were weakly associated with lower peak velocity at the start phase of the flexion movement only (-3.3°/s, 95% CI -6.1 to -0.5). When we included pain intensity as a covariate in the analyses of fear-avoidance beliefs, all of the associations were slightly weaker. The results remained

largely similar when we performed sensitivity analyses that excluded persons without complete follow-up information, excluded persons who reported a pain duration of fewer than nine months, and excluded persons with low fear-avoidance beliefs, although with lower precision.

6 Discussion

6.1 Summary of main findings

Overall, the results from this thesis identified that factors within all domains of the biopsychosocial framework, that is, multisite pain, psychological distress, work- and functional ability, and spinal kinematics were associated with LBP outcomes. The presence of multisite pain, psychological distress, and poor general health among persons with chronic LBP in the general population reduced the probability of recovery from LBP after ~10-11 years follow-up, but no statistical interaction was found between multisite pain and the other co-complaints. Similarly, in persons attending physiotherapy, we found that the presence of multisite pain, psychological distress, and lower work ability was accompanied by more severe disability, higher pain intensity, and lower quality of life during three months follow-up. When we investigated change over time in the independent variables, improvement in work ability was the only variable associated with clinically meaningful improvement on all the outcome variables. No clear associations were found between the kinematic measures and self-reported outcomes. Increased range-of-motion was associated with less disability, and lower peak velocity at the initial phase of a spinal flexion were associated with increased FABQ-PA; however, the associations were weak, and the clinical importance of spinal kinematics remains uncertain.

6.2 Methodological considerations

6.2.1 The strengths of the studies

A strength of Paper 1 was the prospective design with the ability to select persons with LBP from a general population without specific interest in LBP. It is therefore likely that this study was less prone to bias due to selection of participants with LBP incentives. Furthermore, another strength is the broad collection of health-related

variables, which allowed us to adjust for several potential confounders. Collection of multiple health-related variables was also performed in the FYSIOPRIM study, which provides a large spectrum of baseline prognostic factors and outcome measures. FYSIOPRIM is currently the only study with systematically collection of longitudinal data from patients receiving physiotherapy in Norway. A strength of Paper 3 was the repeated-measure design and the comprehensive data collection of spinal kinematics, which provided detailed movement data during a spinal flexion/extension.

6.2.2 Biases that may influence the results

We can distinguish between two main types of errors that typically may occur in observational studies: systematic errors and random errors [138]. Systematic errors can arise from different sources, and these errors may affect the validity of the results. Systematic error can be classified into three broad categories: confounding, selection bias, and information bias. The following sections discusses systematic errors that should be considered when interpreting the results of this thesis.

Confounding variables

We cannot rule out that the results in our studies are influenced by confounding, i.e., that the effect of the exposure on the outcome is mixed with the effect of another variable. Criteria for confounding to occur, is that the confounding variable is associated with both the exposure and the outcome and that the variable is unequally distributed among the exposure groups [139]. In both the HUNT study and the FYSIOPRIM cohort, we had the possibility to control for several potential confounders. We selected confounders based on prior knowledge about factors that can be related to both the exposures and the outcomes. For example, in Paper 3, pain intensity could represent a confounder in the association between fear-avoidance beliefs and disability and work ability. Due to the possible bidirectional relationship between pain intensity and fear [51, 140], we cannot determine whether pain intensity is a true confounder or if it is on the casual pathway between the exposure variable and the outcome and, therefore, part of the effect we are studying. Due to the uncertainty, we included pain intensity as a confounder in sensitivity analyses of fear-avoidance beliefs and disability and work ability. The sensitivity analyses did not change the conclusion of the study, but the associations became somewhat weaker. Furthermore, since some evidence indicates that

women have a higher risk of chronic pain than men [141, 142], gender may be a confounder when studying persons with LBP. Due to the large study sample in Paper 1, we were able to take gender differences into account by performing stratified analyses instead of adjusting for gender. It is also likely that there exists effect heterogeneity in our studies that cannot be handled by adjusted analyses, i.e., that subgroups in the study population have different associations between the exposure and the outcome [14, 143]. Stratified analyses were not possible in Papers 2 and 3 due to the small sample sizes.

We cannot rule out that our results are influenced by residual confounding. For instance, we had no information about genetics or environmental factors (i.e., familial or social factors). Genetic variation may represent a confounder in the relation between psychological distress and LBP, as genetic factors are associated with both risk of developing LBP and developing symptoms of anxiety and depression [144]. Due to the observational design of Papers 2 and 3, we did not interfere with the treatment provided by the physiotherapists, and we have no information regarding whether other pain afflicted areas, psychological distress, or work ability were specifically addressed. It is also important to mention that since we only had two time-point measurements in Paper 2, changes in the independent variables were calculated from the same time point as the outcome measures and the temporal relation between the variables was not investigated. We attempted to disentangle this temporality by investigating the baseline value of psychological distress and its associations with disability, pain, and quality of life after three months. In contrast to the longitudinal associations, the baseline values were not associated with any of the outcomes after three months. A bidirectional relation between pain and depression has previously been supported [145, 146], and it is well documented that pain and depression often coexist [2, 145]. A strength in Paper 3 was the ability to control for unmeasured time-invariant confounders by performing fixed-effects models to analyse the within-person associations.

Selection bias

Selection bias is a systematic error that stems from the procedures used to select subjects and from factors that influence study participation [138]. Different characteristics between participants and non-participants may introduce selection bias if these characteristics influence the association between exposure and outcome. In Paper 1, we selected persons with LBP from a general population invited to participate in the

HUNT Study. All persons that reported chronic LBP in HUNT2 and participated in both HUNT2 and HUNT3 were eligible to enrol in the study. On the contrary, in Papers 2 and 3, we included only patients that contacted a physiotherapist due to LBP. It is likely that the persons that seek health care for LBP included in Papers 2 and 3 represents a different population than the persons selected for Paper 1, and thus, the results are not directly comparable. Unfortunately, we had some loss to follow-up in our studies. Withdrawals and loss to follow-up may introduce selection bias if the probability of recovery in our exposure groups are different at follow-up compared to the original cohort that was enrolled. For instance, if pain intensity at baseline affect loss to follow-up and loss to follow-up influences the risk of the outcome, selection bias may occur because remaining in the study is related to both exposure and the outcome. Unfortunately, we have no information regarding why some persons dropped out of the study, and we cannot disregard that they experienced for example, increased pain or other diseases. In Papers 2 and 3, we tried to investigate if the drop-out influenced the results by comparing baseline characteristics of the patients that dropped out and those that completed the studies. In Paper 2, the completers did not differ from the non-completers in any of the baseline characteristics. In Paper 3, the non-completers were more often women (78% vs. 64%), they were slightly younger (38.0 years vs. 42.8 years), and more on sick leave or disability leave (29% vs. 14%) compared to the completers. They did not differ in any of the outcome measures (i.e., disability, pain intensity, work ability). In both studies, we used mixed-model analyses, and multiple imputations of missing values were therefore not considered necessary [147].

Information bias

The cause of information bias can lie either within the observer or the participant and may lead to misclassification. In Paper 1, the outcome variable was based on the question, “During the last year, have you had pain and/or stiffness in your muscles and joints that lasted for at least three consecutive months?”. We cannot rule out that some participants may report ‘yes’ on this question based on specific diagnoses, such as osteoporosis or inflammatory diseases, rather than non-specific LBP. It is conceivable that persons with specific diagnoses reported more severe symptoms in the exposure variables (e.g., more psychological distress or more pain sites). This can cause imbalances between the exposure groups and, in turn, lead to overestimated results. There are also limitations of the FABQ, which could explain the weak associations in

all our analyses of fear-avoidance beliefs in Paper 3. It has been suggested that FABQ has a limited ability to detect fear-avoidance beliefs as a single construct and instead reflects a multidimensional psychological measure [148, 149]. Furthermore, previous studies have shown that FABQ has poor responsiveness to change [125, 150], which may negatively impact its ability to detect longitudinal associations and, in turn, provide underestimated results.

In Paper 2, the primary outcome was ODI, which is commonly used to measure functional disability in LBP and has acceptable reliability and validity [129, 151]. However, ODI has been shown to have large floor and ceiling effects and, therefore, would not be ideal for patients with scores at the end of the spectrum [152] and may be less accurate in detecting change in patients who have a minor disability [129]. In our study population, the ODI scores were in the lower range of the scale (mean = 23.4 points), which limits the ability to improve on ODI over time and, in turn, influence the ability to detect associations between the independent variables and disability. In the secondary aim of Paper 2, we defined clinically meaningful improvement of disability, pain intensity, and quality of life after three months by predefined cut-off change scores for each outcome. The major limitation caused by using cut-offs is that the ability to achieve successful improvement is dependent on the patients' baseline level of the outcomes. Standardised cut-off scores have not been established for common outcome measures used for LBP research, and the definition of outcomes after treatment is, therefore, dependent on the researcher's preferred definition, which, in turn, will influence the results and reduce the ability to compare results between studies [153]. In this thesis, we attempted to utilise common and recommended cut-offs as far as possible.

In Paper 3, motion sensors provided exact measures of spinal range-of-motion and peak velocity. It is possible that the data from the motion sensors were influenced by measurement errors, due to either the technical equipment or the patients' performance; however, the testing procedure was described in detail to reduce the risk of measurement error. The standardised instruction of the movement may have contributed toward a standard way of performing the task, i.e., by ignoring symptoms of pain or fear to please the researcher and perform the task appropriately. However, the standardised task may also minimise the risk of performance bias by limiting the patients' movement options, thus enabling us to compare the performance both within and across

individuals. It should also be noted that other movement tasks may be relevant when evaluating persons with LBP and may be more strongly associated with the outcomes. However, we believe that if persons have pain and fear when they perform spinal movements, impaired kinematics will be prominent regardless of the specific task performed [154]. Spinal flexion is a simple and commonly utilised clinical test frequently used in clinical studies [4] and is essential for basic activities of daily living. Furthermore, a recent study identified that visualising and thinking of forward bending and lifting was associated with fear [155], which supports that spinal flexion was an appropriate test for the purpose of our research question.

Random errors

Random errors can be described as the variability in the data. Such errors is not easily explained and is related to the precision of the results [138]. CIs were used to evaluate the amount of random errors (precision) in this thesis. The degree of random errors is inversely proportional to the size of the study population. A strength in Paper 1 is the possibility to utilize the large database from the HUNT Study and, thus, increase the precision of the results. Papers 2 and 3 were smaller clinical studies and the chance of random errors are correspondingly higher.

Reverse causation

The prospective design in Paper 1 has the advantage of evaluating causal relations since the exposure of interest was measured prior to the outcome. However, we cannot disregard the possibility of reverse causation, which is when the outcome of interest precedes the exposure [139]. The definition of reverse causation is challenging. For instance, in some cases, the outcome does not precede the exposure *per se*, but there might be some underlying traits among persons with the lowest probability of recovery that caused the exposure. An example of reverse causation in Paper 1 could be that persons with the lowest probability of recovery from LBP had some underlying attributes (e.g., previous pain episodes, other physical health conditions, undetected disease) prior to baseline that caused the exposures (e.g., number of pain sites, pain-related disability, psychological distress, and self-rated general health). For instance, persons who reported LBP at follow-up in HUNT3 might have had previous and fluctuating pain episodes that influence number of pain sites, psychological distress, or disability at baseline in HUNT2. It is therefore possible that the observed associations in

our studies are overestimated. Unfortunately, we had no information about previous pain episodes at HUNT2, but we tried to reduce the risk of reverse causation by adjusting for other physical health conditions reported in HUNT2 in sensitivity analyses. The adjustment of other physical health conditions had minor influence on the results. Furthermore, we excluded persons with BMI <18.5 kg/m^2 to reduce the risk of reverse causation due to undetected disease.

6.3 Evaluations of clinical importance

Clinical importance is central when interpreting our results. The point estimates observed in our studies indicate the estimated strength of the associations. In Paper 3, No clear associations were found between kinematic measures, fear-avoidance beliefs, and self-reported outcomes, indicating that the clinical importance is limited. The results imply that it would require a major increase in range-of-motion to accomplish a clinically meaningful change of >10 point on the ODI [134] after nine months. The required increase in range-of-motion would in some cases be impossible to achieve due to the anatomical structure of the spine and pelvis.

6.4 Interpretation of main results

6.4.1 Multisite pain

Few studies have investigated the effect of the number of pain sites on LBP prognosis. A previous study showed that upper-body pain accompanied by LBP was associated with an increased risk of poor outcomes [5], and a recent study investigated prognostic factors across different musculoskeletal pain sites and found that widespread pain was associated with poor outcome related to pain and disability regardless of the primary pain site [156]. Our findings extend on these studies by showing a dose-response relationship between the number of pain sites and the long-term probability of recovery from LBP (Paper 1) as well as a short-term longitudinal association between increased number of pain sites with increased disability, higher pain intensity, and reduced quality of life (Paper 2).

The underlying mechanisms of multisite pain and associations with LBP prognosis are not well understood, but one possible explanation is that localised and non-localised

musculoskeletal pain are two separate conditions. Non-localised pain may be a more complex condition, including co-complaints, such as sleep problems [63, 64, 157], psychological symptoms [7, 63], and poor self-reported health [63, 64], which, in turn, may influence the LBP prognosis [5, 158]. Furthermore, in some cases, multisite pain is classified as fibromyalgia, which has shown to have more psychological [159] and neurological symptoms [160], altered pain processing [161], and poorer health status [159] compared to persons without fibromyalgia diagnosis. Although localised LBP also may be a complex condition, it is more often of shorter duration and lower intensity [162], thus, the co-complaints may be less prominent. It is unclear whether common co-complaints in non-localised pain, such as self-reported health, sleep problems, or psychological symptoms are a consequence or a cause of LBP due to the cross-sectional nature of these associations [7, 63, 64]. However, they have previously been identified as prognostic factors for LBP in some studies [5, 158], and therefore, it is conceivable that these co-complaints contribute to the persistence of pain and disability. Our analyses of statistical interaction did not identify a synergistic effect of co-complaints and multisite pain on the prognosis of LBP; however, the results showed that persons with ≥4 pain sites had poorer prognosis of recovery within all strata of pain-related disability and psychological distress. Although we did not identify any interaction in our study, it is conceivable that there exists a biological interaction, for instance, between pain and psychological distress [163].

Knowledge on modifiable factors that influence LBP prognosis can potentially improve LBP management and may be used for targeted physiotherapy interventions. Large long-term population-based studies performed in Norway found that the mean number of pain sites was relatively stable over time [164, 165]. However, our results in Paper 2 show that the mean number of pain sites was reduced by 0.4 sites after three months. Furthermore, a reduction of one or more pain sites from baseline to three months was associated with clinically meaningful improvement in disability (OR: 2.3, 95% CI 0.7 to 7.4) at three months compared to no improvement or an increase in number of pain sites. Even though the estimate was imprecise, the association indicated that number of pain sites was modifiable in these patients. We are unaware of any other studies that have specifically investigated whether reducing the number of pain sites influences the prognosis of LBP, thus, improved knowledge is necessary to recommend management for other pain sites parallel to LBP management.

6.4.2 Kinematics

Theories focusing on biomechanical and kinematic factors as an independent or leading cause of LBP have gradually been challenged, as they alone cannot fully explain the underlying mechanisms of LBP [39, 166-170]. This is in line with our results, indicating that measures of peak velocity and range-of-motion have limited influence on LBP and accompanying disabilities.

We found no clear associations between kinematic variables with disability, pain intensity, or work ability, with the exception of weak associations between improved range-of-motion and reduced disability over a nine-month period. It is uncertain whether the kinematic measures would have influenced disability, work ability, or pain intensity differently if the biomechanical aspects were specifically addressed during the treatment period in our study. However, the effect of specific movement control exercises on functional- and pain-related outcomes in LBP seems limited [170]. Several studies have shown that intervention of spinal- and core exercises show no additional effect over other treatments for LBP [168, 170-172].

Our findings in Paper 3 are in line with previous studies that found no associations between changes in peak velocity and changes in function, work status, or pain intensity [78, 79]. The lack of association between kinematic measures and self-reported outcomes in our studies and previous research are somewhat surprising, considering the body of evidence indicating impaired spinal movement in persons with LBP compared to healthy controls [4, 154, 173, 174] and that specific exercises may improve spinal movement [175]. A possible explanation is that it is a large variation within the normal range of how movement tasks are performed. It is possible that the large variation in movement performance may cause underestimated results and that subgroup analyses may be more informative. However, impaired spinal movement is not exclusive for persons with LBP [71, 176] and movement impairment is not always present in persons with LBP [176], which may indicate that movement performance has limited influence on functional- and pain-related outcomes in LBP populations in general. A recent review concluded that due to large individual differences, no currently available kinematic measure can clearly distinguish between a healthy spine and degenerated spine [177]. Subgrouping patients with LBP based on kinematic variables has been suggested in the literature [77, 178]. Some studies have demonstrated favourable outcomes of pain and disability in patients who received matching and individualised

exercises based on subgroups of spinal movement dysfunction [179, 180]; however, conflicting results have also been reported [168, 181]. A possible explanation for the conflicting results is that the improvements in pain and function may be influenced by improvements in psychosocial factors, which is partly supported by our findings in Paper 3 (discussed below). Psychosocial factors as mediators in the relation between spinal kinematics and functional- and pain-related outcomes are not disentangled in the studies above and should be further investigated.

As a secondary aim of Paper 3, we investigated whether fear-avoidance beliefs could explain some of the mechanisms underlying the impaired movement observed in persons with LBP. Interestingly, we found an association between FABQ-PA and peak velocity at the initial phase of a standing flexion movement. This indicates that the initiation of a movement may be more susceptible to fear of movement, and may reflect the anticipation of pain, which is in line with the fear-avoidance model. Only a few previous studies have investigated the association between the fear of movement and kinematic measures in persons with LBP, and the results are inconsistent [94-96]. However, similar findings have been identified in patients with neck pain [182, 183], which supports that concurrent evaluations of fear-avoidance beliefs would supplement measurements of spinal kinematic.

6.4.3. Psychological distress, fear-avoidance beliefs, and self-rated general health

The finding that persons with concurrent symptoms of anxiety and depression had reduced probability of recovery from LBP after ~10-11 years and that psychological distress was longitudinally associated with disability, pain intensity, and quality of life during three months follow-up, is in line with a previous study reporting that depressive symptoms were predictive of recovery from LBP at six-month follow-up [184]. However, previous studies of anxiety and depression as independent predictors of LBP prognosis have provided inconsistent results [8, 185, 186]. In a review of psychosocial risk factors for prognosis of LBP, depression and psychological distress were identified to be predictive for LBP prognosis in some studies; however, the predictive ability was evaluated as modest [8]. These inconsistent findings may be explained by the individual variation of psychological symptoms in persons with LBP [80, 115, 187]. The presence of psychological co-complaints in LBP may be different between individuals [115], and

it is conceivable that the severity of symptoms may influence the association between psychological symptoms and prognosis of LBP [187]. The large patient heterogeneity may lead to biased and underestimated results, thus, investigating subgroups of patients with LBP within different level of psychological distress may provide more valid results [115]. We tried to test the robustness of our results by performing sensitivity analyses where we excluded persons with the lowest score on FABQ, but the results remained largely similar. Furthermore, the initial level of psychological distress may influence the findings as persons with higher levels of distress have a greater potential for improvement. In our study, the level of distress was low, which may reduce the ability to identify associations in the current study population. The mean HADS value in the HUNT LBP cohort was 4.0 points for depression and 5.0 points for anxiety, and in the clinical cohorts, the mean Hopkins symptom checklist value was 1.7 points for the FYSIOPRIM cohort and 1.6 points for the Lab cohort. According to recommended cut-offs for presence of psychological symptoms [121, 123], only 4-9% of the participants scored above the cut-off on the HADS (>8 points) or Hopkins symptom checklist (>1.85 points) in our study populations. The suggested mechanisms behind the relation between pain and depression are shared biological pathways and neurotransmitters, such as norepinephrine and serotonin, which may influence pain signal processing [145]. A common belief is that psychological distress develops as a consequence of chronic pain, but elevated distress is also identified in persons with acute LBP [80], and studies have suggested that there is a bidirectional relationship between pain and depression [146]. Thus, based on our results and previous studies, it is conceivable that psychological distress influence LBP in both a short- and long-term perspective.

In paper 3, we investigated the influence of fear-avoidance beliefs on functional- and pain-related outcomes. According to the fear-avoidance model of pain [50], symptoms of pain-related fear are included as a part of the cyclic relationship between pain, catastrophising and disability. It is important to mention that the fear-avoidance model of pain has been criticised: although current evidence supports associations between separate components in the model, there is a lack of evidence supporting the direction of the pathway between pain, fear, and disability [188, 189]. Our within-person analyses showed that FABQ-PA was longitudinally associated with disability and pain intensity, and that FABQ-W was longitudinally associated with work ability. However, All the observed associations between fear-avoidance beliefs and the outcomes were weak,

which may be due to limitations of the FABQ, as described in paragraph 6.2.2 'information bias'. Our results extend on previous cross-sectional studies that found associations between fear-avoidance beliefs and pain and disability [190, 191]. However, the temporality of the association needs further investigation.

Reporting poor or not so good self-reported general health reduced the probability of recovery from LBP by 27-34% (Paper 1). This finding is unsurprising as the variable may incorporate the physical, psychological and social aspects of health and, thus, reflect an overall evaluation of the persons' health and well-being [126]. In concordance with our results, self-reported health has previously been associated with poor LBP prognosis [5] and a transition from acute to chronic LBP [8].

6.4.4 Work ability

Our study shows that persons with higher work ability have less disability, less pain, and a higher quality of life. This is in line with previous studies supporting the importance of work to persons' lives and general well-being [10, 15, 101, 106]. Further, high work ability has been associated with reduced risk of work absence in persons with LBP [192] and were predictive of disability pensions in a working population [105]. Our study lends further support to this notion. In contrast, we did not find an association between the single question on work disability due to LBP on the probability of recovery from LBP in Paper 1. The persons included in Paper 1 (without specific connection to health care services) may represent a different population than the patients in Paper 2, and the follow-up time is largely different, which may explain the contrasting results. Furthermore, the definition of work ability is different in the two studies. The question of work disability in Paper 1 was dichotomised into 'no disability' and 'disability'. Dichotomising work disability may result in reduced specificity (i.e., reduced ability to detect the severity of the work disability) and valuable information may be lost. In contrast, the question regarding work ability in Paper 2 was reported on an 11-point likert scale, which may provide more nuanced information.

Interestingly, improved work ability over a three-month period was the only variable consistently associated with all outcome measures, which further highlights the importance of work ability in persons with LBP. The average improvement in work ability was 0.9 points at the three-month follow-up. Despite the small degree of

improvement, the results indicate that work ability is potentially modifiable, and the change in the present study corresponds to a previous observational study of women on sick leave [106]. By using change scores, we can identify potential modifying effects; however, we need further insight into how work ability should be addressed to facilitate improvement, and the effects on outcomes should be further investigated in impact studies.

A growing body of evidence supports the promising effect of work-related interventions, for example, increased work ability and increased days without sick leave in persons with mental disorders [193] and in persons with neck or back pain [194]. However, conflicting results have also been reported [195]. Our results indicate that receiving physiotherapy for LBP may enhance work ability and that work ability is connected to several aspects of a persons' daily life, including physical disability, pain, and quality of life. Furthermore, a previous study found that workers with LBP report concerns about the ability to work and a lack of reassurances that work participation is favourable [196], which may indicate that addressing work ability is a relevant and necessary part of LBP management.

In this thesis we used work ability as a single measure to represent the social domain which do not fully cover the diversity of the domain. However, the ability to work represent a significant part of the social domain by having large influence on a person's social belonging [15] and it has been shown that social exclusion is associated with increased pain [197]. Furthermore, it is important to recognise that work ability is a multidimensional concept and may include physical, psychological, and social aspects. Further investigation of the social domain is necessary, for example, investigating the influence of economic stress [198], work participation, and social interactions [199, 200] on prognosis of LBP.

6.5 A holistic biopsychosocial assessment

Pain relief is not the only reason that people seek health care for LBP, but problems with daily activities, social participation, and ability to do normal work are common motivations for contacting the health services [201]. Our findings support that LBP should be treated with a more holistic health approach. The ability of single treatments to affect multiple factors and relations between the factors is limited, and interaction

between prognostic factors across the biopsychosocial domains may explain why single or symptomatic treatments have largely failed [98]. Currently, there is still an overwhelming focus on biological factors in clinical physiotherapy practice. Our findings, together with current evidence, indicate that biomechanics is not a primary element in LBP and suggest that psychosocial factors should receive increased clinical attention. In line with our studies, it is suggested that the definition of pain, published by the International association for the study of pain [37], needs an update to be consistent with the biopsychosocial model, and should include 'cognitive and social components' as part of the definition [202]. It is important to acknowledge that all the domains may have individual importance and should be addressed. Although the variables in our study are organised within specific domains, they are not limited to that domain and may overlap. Thus, based on our findings, we cannot determine the individual or absolute importance of each domain, but rather increase our knowledge of the specific variables.

6.6 Clinical Implications

The findings in our studies indicate that screening of presence of possible modifiable co-complaints, such as psychological distress, fear-avoidance beliefs and work ability in persons with LBP may be contribute to evaluation of LBP prognosis and may be useful targets for physiotherapy treatment. Work ability appeared to be an important factor for patients with LBP and change in work ability was associated with improvement in both disability, pain intensity, and quality of life. Clinical assessment of a person's ability to work is an accessible and feasible approach and may be useful to provide specific and targeted treatment goals.

Based on our results, we cannot recommend that assessing spinal kinematics is of importance in LBP management. Each individual may have different movement strategies and although these strategies may change if persons experience pain, the influence on prognosis and severity of LBP may be insignificant. Nevertheless, spinal movement may be associated with psychological factors such as fear-avoidance beliefs. Thus, if assessment of spinal kinematics is included in the management of LBP, concurrent assessment of fear-avoidance beliefs may inform management tailoring. Furthermore, fear-avoidance beliefs have proven to be modifiable in previous studies of

physiotherapy management of LBP [203] and neck pain [204], indicating that targeting fear regarding physical activity and work is feasible in physiotherapy interventions.

6.7 Future perspectives

Although considerable amount of research has been done on LBP the past decades, the disability and societal burden following LBP keep rising [18, 205]. The results from this study provides new knowledge on prognostic and associated factors on LBP outcomes. To design effective secondary prevention strategies, we need to evaluate the clinical usefulness of the prognostic and associated factors and to investigate how patients with these characteristics respond to specific treatments. Stratified care based on patient subgroups have received increased attention in LBP research the recent years and allow clinicians to target treatment to subgroups of patients based on established modifiable characteristics and prognostic factors [14, 206]. However, there is still a knowledge gap on subgroup treatment effects [207]. Furthermore, moving beyond subgroups, personalised and tailored management of musculoskeletal pain may be a direction for future research [208-210]. A patient's individual combination of characteristics may influence the treatment response. Profiling and assessing prognostic factors in patients at hand would provide individual treatment recommendations and inform clinical decision making. Observational studies based on large databases, electronic health records, and machine learning could provide further insight into smaller subgroups and individual cases of patients with LBP and the response to specific interventions provided in primary or secondary health care [211]. Such studies will represent the large variability of patients seeking health care [212] and can perform subgroup analyses due to large statistical power, which contrasts with the current gold standard RCT's of pooled heterogeneous patient samples. Finally, including biopsychosocial variables in clinical practice require improved clinical competence on biopsychosocial factors and increased confidence to utilise this knowledge in LBP management [13, 213].

7 Conclusions

Multisite pain and the presence of psychological distress were associated with poor long-term prognosis of LBP in the general LBP population and influenced function, pain, and quality of life negatively in LBP patients attending physiotherapy. No statistical interaction was found between multisite pain and the other co-complaints on the association with probability of recovery from LBP in the general LBP population. Work ability was associated with disability, pain intensity, and quality of life in LBP patients, and change in work ability, as the only variable, was associated with clinically meaningful improvement in disability, pain intensity, and quality of life after three months.

No clear longitudinal associations were found between kinematic measures and self-reported outcomes. Increased range-of-motion was weakly associated with reduced disability over time, but no associations were found between peak velocity and disability, work ability, or pain intensity. Peak velocity at the initiation of a spinal flexion was weakly associated with higher FABQ-PA. Furthermore, higher FABQ-PA were associated with higher disability and higher pain intensity, and higher FABQ-W were associated with lower work ability.

8 References

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Paper 1

BMJ Open

The influence of multisite pain and psychological comorbidity on prognosis of chronic low back pain: longitudinal data from the Norwegian HUNT Study

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ABSTRACT

Objectives This study aimed to investigate the prospective influence of multisite pain, depression, anxiety, self-rated health and pain-related disability on recovery from chronic low back pain (LBP).

Setting The data is derived from the second (1995–1997) and third (2006–2008) wave of the Nord-Trøndelag Health Study (HUNT) in Norway.

Participants The study population comprises 4484 women and 3039 men in the Norwegian HUNT Study who reported chronic LBP at baseline in 1995–1997.

Primary outcome measures The primary outcome was recovery from chronic LBP at the 11-year follow-up. Persons not reporting pain and/or stiffness for at least three consecutive months during the last year were defined as recovered. A Poisson regression model was used to estimate adjusted risk ratios (RRs) with 95% CIs.

Results At follow-up, 1822 (40.6%) women and 1578 (51.9%) men reported recovery from chronic LBP. The probability of recovery was inversely associated with number of pain sites (P-trend<0.001). Compared with reporting 2–3 pain sites, persons with only LBP had a slightly higher probability of recovery (RR 1.10, 95% CI 0.98 to 1.22 in women and RR 1.10, 95% CI 1.01 to 1.21 in men), whereas people reporting 6–9 pain sites had substantially lower probability of recovery (RR 0.58, 95% CI 0.52 to 0.63 in women and RR 0.70, 95% CI 0.63 to 0.79 in men). Poor/not so good self-rated general health, symptoms of anxiety and depression, and pain-related disability in work and leisure were all associated with reduced probability of recovery, but there was no statistical interaction between multisite pain and these comorbidities.

Conclusions Increasing number of pain sites was inversely associated with recovery from chronic LBP. In addition, factors such as poor self-rated health, psychological symptoms and pain-related disability may further reduce the probability of recovery from chronic LBP.

Strengths and limitations of this study

- The strengths of the current study are the large and unselected population of women and men with chronic low back pain (LBP), the prospective design and the possibility of adjusting for several potential confounding factors.
- A limitation is the lack of information about the course of LBP and the other variables between the Nord-Trøndelag Health 2 (HUNT2) and HUNT3 Study.
- Furthermore, we cannot rule out that changes in lifestyle differed between those who experienced remission of symptoms and those who did not, for example, individuals with a high number of pain sites at baseline could be less prone to adopt a healthy lifestyle during the follow-up period because of the pain-related disability.

INTRODUCTION

Low back pain (LBP) is a common cause of disability and is ranked as the most burdensome disease globally.[1 2] LBP is the fourth most common diagnosis (after upper respiratory infection, hypertension and coughing) seen in primary care[3] and approximately every fifth adult suffers from chronic LBP.[4] Thus, in addition to the suffering experienced by affected individuals, LBP represents a substantial economic burden to the society. This underscore the importance of increased knowledge about factors that can improve the prevention and management of chronic LBP.

Chronic LBP rarely exists as a separate entity and co-occurrence of multisite pain and other comorbidities are common.[5–9] A large case-control study comprising more than 100 000 people showed that individuals with chronic LBP had higher occurrence of other musculoskeletal conditions, depression, anxiety and sleep disorders compared with controls without chronic LBP.[10] In particular, other chronic pain conditions are very prevalent among people with chronic LBP.[5] Number of pain sites by itself has been suggested to bedose-dependently related to reduced physical and mental function[11 12] and there are data to support the notion that generalised pain differs markedly from conditions with only one or a few pain sites with

respect to other risk factors.[13] Currently, there is a lack of longitudinal studies addressing how the extent of multisite pain influences the prognosis of chronic LBP. Moreover, it is unclear to what extent multisite pain interacts with other comorbid factors such as poor self-rated general health, pain-related disability and poor mental health to influence the prognosis of chronic LBP.

The main objective of this study was therefore to prospectively investigate the influence of common somatic and psychological comorbidities on prognosis of chronic LBP. We hypothesised (1) that multisite chronic pain, poor self-rated general health, pain-related disability and poor psychological health are factors that are inversely and independently related to the probability of recovery from chronic LBP and (2) that the possible association between number of pain sites and prognosis of LBP is modified by other somatic and psychological comorbidities.

METHODS

Study population

In Nord-Trøndelag county, Norway, all inhabitants aged 20 years or older were invited to participate in three health surveys (the Nord-Trøndelag Health Study (the HUNT Study)), the first in 1984–1986 (HUNT1), the second in 1995–1997 (HUNT2) and the last in 2006–2008 (HUNT3). The current study is based on data from HUNT2 and HUNT3. Of 93 898 eligible participants, 65 237 (65.5%) accepted the invitation to participate in HUNT2. In HUNT3, a total of 93 860 participants were invited, and 50 807 (54.1%) accepted the invitation. More detailed information about selection procedures, participation and questionnaires used in the HUNT Study can be found at http://www.ntnu.edu/hunt.

Information on lifestyle and health-related factors were collected by questionnaires and a clinical examination at both HUNT2 and HUNT3. For the purpose of this study, we included data from the 37 070 people who participated at both surveys. We excluded 15 062 women and 12 861 men who reported to be free from chronic LBP at HUNT2. Moreover, we excluded 1557 persons with missing information on musculoskeletal pain at HUNT3 and 23 persons without complete values on body mass index (BMI) from the clinical examination. Further, 44 persons defined as underweight (BMI <18.5 kg/m^2) were additionally excluded from the analyses to reduce the possibility for reverse causation due to undetected disease. Thus, the prospective analyses were based on 4484 women and 3039 men. Each participant signed a written consent, and the study was approved by the Regional Committee for Ethics in Medical Research (project no. 2014/2044 REK midt, Norway).

Chronic LBP

The questions about musculoskeletal pain were adopted from the Standardised Nordic Questionnaire.[14] The participants were asked "During the last year, have you had pain and/or stiffness in your muscles and joints that lasted for at least three consecutive months?" Response options were 'yes' and 'no'. If answering 'yes', the participants were asked to indicate the affected body area(s), that is, up to nine body areas (neck, shoulders/upper arms, upper back, elbows, low back, wrists/hands, hips, knees and ankles/feet). Chronic LBP was in both surveys defined by 'yes' to the first question and low back indicated as an affected body area by the second question. Persons who responded 'yes' to the first question but did not indicate low back as an affected body area were considered to be free from chronic LBP. Number of chronic pain sites were estimated by adding together pain-afflicted body areas, of which the total number of pain sites includes LBP. The primary outcome was recovery from chronic LBP at the 11-year follow-up. Persons categorised with chronic LBP at HUNT2 responding 'no' at HUNT3 to the question "During the last year, have you had pain and/or stiffness in your muscles and joints that lasted for at least three consecutive months?" were defined as recovered.

Pain-related comorbidities

The participants' self-rated general health was evaluated using the question "How is your health at the moment?", with response options 'very good', 'good', 'not so good' and 'poor'. The answers were dichotomised into two groups: 'very good/good' and 'not so good/poor' in line with previous studies.[15]

Pain-related disability was evaluated separately for work ability and leisure time activity. The question about work ability was: "Have the pain and/or stiffness reduced your ability to work during the last year?" with four possible responses: 'no', 'not significantly', 'to some degree', 'significantly' and 'don't know'. The first and last response options were merged and categorised as 'no disability', and the two middle categories as 'work disability'. For leisure time activity, the question was: "Have the pain/or stiffness reduced your leisure activity?" with possible responses: 'yes' and 'no'. The responses on disability due to musculoskeletal symptoms were then categorised into four groups: 'no disability', 'work disability', 'leisure disability' and 'work and leisure disability'.

Symptoms of anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS). HADS is a validated and well-established self-rating questionnaire including seven questions on anxiety and seven questions on depression.[16]As recommended, the cut-off score value was set to ≥8 on both anxiety and depression and were dichotomised as presence or no presence of anxiety and/or depression.[16 17] In addition, a mixed HADS variable was constructed consisting of four groups: 'no depression or anxiety', 'only depression', 'only anxiety' and 'both depression and anxiety'.[18] Symptoms of only depression or only anxiety were defined by a HADS score ≥8 on the respective subscales, whereas symptoms of both depression and anxiety were defined by a HADS score ≥8 on both subscales.

Possible confounders

All estimated associations were adjusted for possible confounders. Age was categorised in 20–29, 30–39,…≥ 60years. BMI was calculated as weight divided by the square of height (kg/m^2) by standardised measurements of height and weight from the clinical examination, and classified into BMI groups according to the suggestions by the WHO (normal weight, overweight and obesity).[19] Physical work demands were assessed by the question: " If you have paid or unpaid work, how would you describe your work?" with the possible responses: 'mostly sedentary', 'much walking', 'much walking and lifting' or 'heavy physical work'. Leisure time physical activity was assessed by the question: "How much of your leisure time have you been physically active during the last year?" where the participants reported number of hours of light and/or hard activity. Four categories were constructed based on this information; 'inactive' (no light or hard activity), 'low activity' (<3 hours of light and no hard activity), 'moderate activity' (≥3 hours light and/or <1 hours of hard activity) and 'high activity' (any light and ≥1 hour of hard activity). Further, education was assessed by the question "what is your highest level of education?", and were divided in four categories: 'primary school', 'high school', 'college ≤4 years' and 'college >4 years'. Smoking was assessed by questions about past or present use of cigarettes, and were divided in three categories: 'never-smoker', ' previous smoker' and 'current smoker'.

Statistical analysis

We used a generalised linear model of the Poisson family to estimate the relative probability of recovery from chronic LBP as risk ratios (RRs) with 95% CIs. An RR >1.0 indicates higher probability of recovery compared with the reference category, whereas a RR <1.0 indicates a reduced probability of recovery. All estimated associations were adjusted for age, BMI, physical activity, education, smoking and physical work demands. All main analyses were conducted separately for men and women. Furthermore, a test for linear trend (ie, dose response) across categories of number of pain sites was conducted by treating the categories as an ordinal variable in the regression model.

In addition, we conducted analyses combining number of pain sites (<4 vs 4–9 sites) and comorbid conditions in relation to the probability of recovery from chronic LBP. Previous studies have shown that reporting of ≥4 pain sitesis associated with a markedly poorer prognosis of pain relief,[20] as well as increasing likelihood of healthcare utilisation and sickness absence.[21] Statistical interaction was evaluated by likelihood ratio tests of a product term of number of pain sites and each of the comorbid factors (self-reported health, pain-related disability and HADS). All statistical analyses were performed using Stata for Windows V.13.1.

RESULTS

Table 1 presents the baseline characteristics of the study population according to number of chronic pain sites. At baseline, 66.4% of the women and 47.2% of the men reported ≥4 pain sites. Of the 4484 women and 3039 men who reported chronic LBP at baseline (HUNT2), 1822 (40.6%) women and 1578 (51.9%) men were reported recovered from chronic LBP at the 11-year follow-up (HUNT3).

Table 2 shows the association between number of pain sites, pain-related disability, psychological symptoms and self-rated general health with the probability of recovery from chronic LBP at follow-up. Increasing number of pain sites was inversely associated with the probability of recovery (P-trend <0.001 in both women and men). In specific, women and men who reported 6–9 pain sites had substantially lower probability of recovery (RR 0.58, 95% CI 0.52 to 0.63 and RR 0.70, 95% CI 0.63 to 0.79, respectively), compared with women and men who reported 2–3 pain sites. People with only LBP had a

Table 1 Baseline characteristics of the study population stratified by gender and number of chronic pain sites

	Women		Men	
	<4 pain sites	4–9 pain sites	<4 pain sites	4–9 pain sites
No of persons (%)	1506 (33.6)	2978 (66.4)	1605 (52.8)	1434 (47.2)
Age (years), mean (SD)	47.9 (13.6)	50.7 (11.9)	48.4 (12.1)	51.8 (11.4)
Body mass index (kg/m^2), mean (SD)	26.1 (4.1)	27.0 (4.5)	26.5 (3.3)	27.0 (3.4)
Physically inactive, n (%)	82 (5.4)	208 (7.0)	96 (6.0)	103 (7.2)
Education ≤13 years, n (%)	1142 (75.8)	2470 (82.9)	1244 (77.5)	1220 (85.1)
Current smoker, n (%)	427 (28.4)	1021 (34.3)	416 (25.9)	412 (28.7)
Poor/not so good self-rated health, n (%)	443 (29.4)	1786 (60.0)	461 (28.7)	831 (57.9)
Pain-related disability, work and leisure, n (%)	726 (48.2)	2034 (68.3)	784 (48.8)	970 (67.6)
HADS score depression >8, n (%)	65 (4.3)	187 (6.3)	96 (6.0)	124 (8.6)
HADS score anxiety >8, n (%)	149 (9.9)	425 (14.3)	110 (6.9)	147 (10.3)

HADS, Hospital Anxiety and Depression Scale.

Table 2 Relative probability of recovery from chronic low back pain at 11-year follow-up according to number of chronic pain sites, pain-related disability, the HADS score and self-rated general health at HUNT2

	Women				Men			
	No of persons	No of cases	Crude RR	Multi adjusted* RR (95% CI)	No of persons	No of cases	Crude RR	Multi adjusted* RR (95% CI)
No of pain sites								
1	326	189	1.13	1.10 (0.98 to 1.22)	454	284	1.11	1.10 (1.01 to 1.21)
2–3	1180	608	1.00	1.00 (reference)	1151	651	1.00	1.00 (reference)
4–5	1330	557	0.81	0.83 (0.76 to 0.90)	873	422	0.85	0.86 (0.79 to 0.94)
6–9	1648	468	0.55	0.58 (0.52 to 0.63)	561	221	0.70	0.70 (0.63 to 0.79)
Pain-related disability								
No disability	649	355	1.00	1.00 (reference)	487	304	1.00	1.00 (reference)
Work disability	591	271	0.84	0.87 (0.78 to 0.98)	430	249	0.93	0.94 (0.85 to 1.05)
Leisure disability	257	131	0.93	0.94 (0.82 to 1.08)	250	143	0.92	0.90 (0.79 to 1.02)
Work and leisure disability	2760	964	0.64	0.68 (0.62 to 0.74)	1754	818	0.75	0.76 (0.70 to 0.83)
HADS								
No depression or anxiety	2572	1103	1.00	1.00 (reference)	2050	1110	1.00	1.00 (reference)
Depression	252	90	0.83	0.90 (0.76 to 1.07)	220	101	0.85	0.85 (0.73 to 0.99)
Anxiety	574	215	0.87	0.88 (0.78 to 0.98)	257	120	0.86	0.88 (0.77 to 1.01)
Depression and anxiety	342	107	0.73	0.77 (0.66 to 0.91)	195	80	0.76	0.79 (0.67 to 0.94)
Self-rated general health								
Very good/good	2208	1099	1.00	1.00 (reference)	1730	1017	1.00	1.00 (reference)
Poor/not so good	2229	704	0.64	0.66 (0.61 to 0.71)	1292	551	0.73	0.72 (0.67 to 0.78)

*Adjusted for age (19–29, 30–39, 40–49, 50–59 and >60 years), education (primary school and lower secondary school, upper secondary school, higher education <4 years, higher education >4 years and unknown), body mass index (normal weight, overweight and obesity), physical activity (inactive, low activity, moderate activity, high activity and unknown), smoking (never-smoker, previous smoker, current smoker and unknown) and physical work demands (mostly sedentary, much walking, much walking and lifting, heavy physical work and unknown).
HADS, Hospital Anxiety and Depression Scale; HUNT, Nord-Trøndelag Health Study; RR, risk ratio.

slightly higher probability of recovery (RR 1.10, 95% CI 0.98 to 1.22 in women and RR 1.10, 95% CI 1.01 to 1.21 in men) compared with women and men who reported 2–3 pain sites. Pain-related disability that influenced both work ability and leisure activity was associated with reduced probability of recovery in both women (RR 0.68, 95% CI 0.62 to 0.74)) and men (RR 0.76, 95% CI 0.70 to 0.83). HADS score ≥8 on both depression and anxiety subscales was associated with reduced probability of recovery in both women (RR 0.77, 95% CI 0.66 to 0.91) and men (RR 0.79, 95% CI 0.67 to 0.94). Persons reporting poor or not so good general health had a markedly reduced probability of recovery, both in women (RR 0.66, 95% CI 0.61 to 0.71) and men (RR 0.72, 95% CI 0.67 to 0.78), compared with those reporting good or very good general health.

Table 3 presents the combined effect of number of pain sites and pain-related disability, psychological symptoms and self-rated general health on the probability of recovering for chronic LBP. We did not observe any statistical interaction between number of pain sites and pain-related disability, psychological symptoms or self-rated health (p≥0.24 for all tests). However, stratified analysis within categories of the exposure variables showed that reporting ≥4 pain sites was associated with lower probability of recovery independently of level of pain-related disability and psychological symptoms. Within strata of pain-related disability, persons who reported ≥4 pain sites had 16%–27% lower probability of remission compared with persons with 1–3 pain sites in the same pain-related disability categories. Likewise, within the different strata of psychological symptoms, persons with ≥4 pain sites had 25%–35% lower probability of recovery compared with persons with 1–3 pain sites.

DISCUSSION

In this large population-based study, we found that musculoskeletal comorbidity, reduced self-rated general health and psychological symptoms were independently associated with reduced probability of recovery from chronic LBP at 11-year follow-up. The factors with the strongest association with poor prognosis were widespread chronic pain (6–9 pain sites) and poor or not so good self-rated general health. The strength of the associations between the various comorbidities and pain prognosis was fairly similar for women and men. Probability of recovery from chronic LBP was inversely associated with increasing number of chronic pain sites. Although there was no interaction between number of chronic pain sites and other comorbidities, we observed in the combined analysis that persons with ≥4 pain sites were associated with lower probability of recovery from chronic LBP within all strata of pain-related disability and symptoms of depression and/or anxiety. The current findings indicate that musculoskeletal comorbidity has a strong and independent influence on long-term prognosis of chronic LBP.

It is noteworthy that about 66% of the women and 47% of the men in this study reported ≥4 chronic pain sites at baseline. This supports the view that co-occurrence of musculoskeletal pain is very common in chronic LBP.[5 6] To our knowledge, this is the first population-based study to investigate the prospective influence of graded musculoskeletal comorbidity on the prognosis of chronic LBP. The dose–response association between number of chronic pain sites and reduced probability of recovery from chronic LBP suggests that musculoskeletal comorbidity should be considered an important predictor in identifying target groups for public health secondary prevention. This was also supported by our combined analysis, showing that number of pain sites was the main driving factor for predicting persistence of chronic LBP.

More than 40% of the women and 50% of the men in the current study reported recovery from chronic LBP at 11-year follow-up. Interestingly, a previous study showed that the prevalence of chronic LBP was relatively stable from HUNT2 to HUNT3 with about 26% of women and 20% of men reporting chronic LBP at both surveys.[22] Thus, our results indicate that during an 11-year period a substantial proportion of the population shift from having chronic LBP to remission, but that a substantial proportion also develops pain in the same period. Similar large fluctuations in reporting of chronic LBP at the individual level have also been observed by others.[23 24] Thus, our findings lend further support to the notion that chronic LBP on the individual level may fluctuate substantially over time while the population prevalence remains relatively stable. The current study adds to this knowledge by showing that individuals who shift from having chronic LBP symptoms to remission of symptoms are more likely to have fewer chronic pain sites, less pain-related disability, better self-rated health and no major symptoms of anxiety or depression.

Increasing number of chronic pain sites were inversely associated with probability of recovery, that is, women and men who reported ≥6 pain sites had about 30%–40% lower probability of recovery from chronic LBP compared with women and men with 2–3 pain sites. Previous cross-sectional studies have indicated a dose–response association between number of pain sites and a range of negative health outcomes such as psychological distress, poor sleep, poor self-rated health, reduced social and functional ability,[11] as well as increased sickness absence and healthcare utilisation.[25]The current prospective study extends this body of knowledge showing that number of chronic pain sites have a strong dose–response influence on prognosis of chronic LBP. Although we observed no interaction between number of chronic pain sites and other comorbid factors, the probability of relief from chronic LBP was consistently lower for the group with multisite pain within all strata of pain-related disability and psychological symptoms scores. These findings support the long-held view that it may be useful to classify patients with chronic LBP into 'back pain alone' or 'back pain plus other pain' to improve clinical decision-making.[26]

Table 3 Relative probability of recovery from chronic low back pain at 11-year follow-up according to the combined effect of number of chronic pain sites and pain-related disability, score on the HADS and self-rated general health at HUNT2

	1–3 pain sites			4–9 pain sites			
	No of persons	No of cases	Multi adjusted* RR (95% CI)	No of persons	No of cases	Multi adjusted* RR (95% CI)	p Value†
Pain-related disability							
No disability	714	448	1.00 (reference)	422	211	0.84 (0.75 to 0.94)	0.002
Work disability	466	270	0.94 (0.85 to 1.03)	555	256	0.77 (0.69 to 0.86)	0.002
Leisure disability	271	172	0.98 (0.88 to 1.09)	236	102	0.71 (0.61 to 0.83)	<0.001
Work and leisure disability	1510	756	0.81 (0.75 to 0.87)	3004	1026	0.59 (0.54 to 0.64)	<0.001
HADS							
No depression or anxiety	2151	1225	1.00 (reference)	2471	988	0.75 (0.70 to 0.80)	<0.001
Depression	161	84	0.92 (0.79 to 1.07)	311	107	0.66 (0.56 to 0.77)	0.002
Anxiety	259	142	1.00 (0.89 to 1.12)	572	193	0.65 (0.58 to 0.73)	<0.001
Depression and anxiety	138	69	0.92 (0.77 to 1.09)	399	118	0.58 (0.49 to 0.68)	<0.001
Self-rated general health							
Very good/good	2187	1302	1.00 (reference)	2617	838	0.57 (0.53 to 0.61)	<0.001
Not all good/poor	904	417	0.78 (0.72 to 0.85)	1751	814	0.82 (0.77 to 0.87)	0.301

*Adjusted for age (19–29, 30–39, 40–49, 50–59 and >60 years), education (primary school and lower secondary school, upper secondary school, higher education <4 years, higher education >4 years and unknown), body mass index (normal weight, overweight and obesity), physical activity (inactive, low activity, moderate activity, high activity and unknown), gender, smoking (never-smoker, previous smoker, current smoker and unknown) and physical work demands (mostly sedentary, much walking, much walking and lifting, heavy physical work and unknown).
†p Value from stratified analysis of number of pain sites by general health, physical disability and HADS score.
HADS, Hospital Anxiety and Depression Scale; HUNT, Nord-Trøndelag Health Study; RR, risk ratio.

The current finding of a dose–response association between number of chronic pain sites and prognosis of chronic LBP may indicate that the extent of musculoskeletal comorbidity could provide additional complementary information to improve classification in stratified care approaches. The idea that assessment of multisite pain can assist clinical judgement of prognosis and improve targeted treatment has been proposed before,[6] and the current data lend further support to this idea. Furthermore, since number of chronic pain sites per se seem to be a strong prognostic factor in chronic LBP it may also be useful to consider this variable when recruiting subjects into research studies to facilitate baseline comparisons.

Although previous data indicate that psychological symptoms are more common in patients with LBP than in comparable controls,[10] our results do not indicate that such symptoms strongly influence the prognosis of chronic LBP. However, another study of subjects with neck and/or LBP in HUNT3 showed that symptoms of mental distress were significant determinants for seeking healthcare, which could have moderated the associations.[27] Our findings are in line with Dunn *et al*[28] who found no significant association between depression, and only a modest association between anxiety, and the risk of disabling LBP at 12 months follow-up in patients presenting with LBP in general practice. In the same study, it was observed that self-rated health had a relatively strong impact on prognosis of LBP with patients who rated their health as poor having more than twofold increased risk of disabling back pain. Very few individuals in our study population rated their health as poor and we were, therefore, not able to estimate probability for recovery among these individuals. However, we observed that women and men who rated their health as less than good (ie, poor or not so good) had about 30% lower probability of recovery from chronic LBP compared with those who rated their health as good or very good.

The strengths of the current study are the large and unselected population of women and men with chronic LBP, the prospective design and the possibility of adjusting for several potential confounding factors. The questions on chronic musculoskeletal pain used in HUNT2 have acceptable reliability and validity.[14 29 30] Likewise, the HADS Scale has been shown to be at a valid indicator of possible depression and anxiety in clinical practice as well as in the general population.[16 17 31] A limitation is the lack of follow-up information about the course of LBP and the other variables between the HUNT2 and HUNT3 Study. Thus, any changes occurring during the follow-up period could not be taken into account in the analyses. For example, information regarding treatment during the follow-up period or information on changes in lifestyle could be of interest. A healthy lifestyle has been associated with improved long-term outcome in individuals with recurrent LBP episodes.[32] Thus, it may be possible that individuals who changed their lifestyle during the follow-up period also altered their course of chronic LBP. Furthermore, we cannot rule out that such changes in lifestyle were differential between participants who experienced remission of symptoms versus those who did not, for example, individuals with a high number of pain sites at baseline could be less prone to adopt a healthy lifestyle during the follow-up period because of pain-related disability.

In conclusion, the current study indicates that multisite chronic pain is independently and inversely associated with the probability of recovery from chronic LBP. Poor self-rated health, psychological symptoms and pain-related disability might further reduce the probability of recovery from chronic LBP. There was no interaction between number of chronic pain sites and other comorbidities, including pain-related disability, psychological symptoms and self-rated general health. These findings underscore the importance of taking comorbid symptoms into account, and in particular number of chronic pain sites, when designing management programmes or treatment for secondary prevention of chronic LBP.

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Competing interests None declared.

Patient consent Obtained.

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Paper 2

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Paper 3

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Original article

Longitudinal associations of kinematics and fear-avoidance beliefs with disability, work ability and pain intensity in persons with low back pain

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A B S T R A C T

Background: Impaired lumbar movement has cross-sectionally been associated with low back pain (LBP); however, the consequence of impaired movement on disability and pain in persons with LBP is poorly understood. Furthermore, fear-avoidance beliefs (FAB) may influence spinal movement, but the relation between fear-avoidance and kinematics is unclear.
Objectives: To investigate the longitudinal associations of kinematics and FAB with disability, work ability and pain in patients with LBP. Further, to explore associations between FAB and kinematics.
Design: Prospective observational study.
Method: Kinematic measures were performed on 44 persons with LBP at baseline, three and nine months. Motion sensors identified range-of-motion and velocity during a spinal flexion/extension. FAB, disability, work ability and pain were reported at all time points using questionnaires.
Results: Increased range-of-motion was weakly associated with less disability (−0.14 points, 95% CI -0.22 to −0.06). Velocity was not associated with disability, work ability or pain. Higher FAB of physical activity were associated with more disability (1.50 points, 95% CI 0.51 to 2.49) and pain (0.37 points, 95% CI 0.11 to 0.62). Higher work-related FAB was associated with lower work ability (−0.37 points, 95% CI -0.68 to −0.05). Moreover, higher FAB showed weak associations with lower velocity in the initial movement phase (−3.3°/s, 95% CI -6.1 to −0.5).
Conclusions: Of the kinematic measures, only range-of-motion was related to disability. Higher FAB was weakly associated with all self-reported outcomes and with lower velocity only at the initial flexion phase. However, the magnitude of these associations suggest marginal clinical importance.

1. Introduction

Altered lumbar kinematics and fear-avoidance beliefs have been associated with low back pain (LBP) (Laird et al., 2014; Wertli et al., 2014a). Measures of lumbar kinematics have been found to differentiate persons with and without LBP, for instance by reduced range-of-motion and reduced angular velocity in persons with LBP (Laird et al., 2014; Dieën et al., 2018; Laird et al., 2018). However, the consequences of altered lumbar kinematics on physical- and work related disability and on pain intensity over time among persons with LBP is not clear.

In addition to lumbar kinematics, fear-avoidance beliefs may negatively influence performance and function in persons with LBP (van Abbema et al., 2011; Vlaeyen and Linton, 2000), and are believed to influence the prognosis of LBP (Vlaeyen and Linton, 2000; Wertli et al., 2014b; Linton and Shaw, 2011). Thus, it is conceivable that fear-avoidance beliefs may influence lumbar kinematics. High pain-related fear has been associated with lower peak velocity of the lumbar spine in participants recently recovered from LBP (Thomas et al., 2008) although this is not found in participants with ongoing chronic LBP (Jette et al., 2016). It remains unclear if persons with more fear-avoidance beliefs have correspondingly reduced range-of-motion and velocity during spinal flexion over time. During a task specific movement, pain-related fear may manifest itself in different phases of the movement, e.g., in the initiation, intermediary or end phase of the movement. A cross sectional study reported that lower range-of-motion and velocity were associated with more anxiety, fear of movement and catastrophizing during the start phase of spinal movements in persons with chronic LBP (Vaisy et al., 2015). However, further studies are needed to understand how lumbar kinematics, fear-avoidance beliefs and self-reported outcomes relate to each other over time.

The aim of this study was therefore longitudinally to investigate if lumbar kinematic measures in segments of a standing flexion/extension

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movement and fear-avoidance beliefs are associated with disability, work ability and pain intensity within patients with LBP receiving physiotherapy treatment. We also examined within-person associations over time between fear-avoidance beliefs and lumbar kinematic measures.

2. Materials and methods

2.1. Participants/study population

We performed a longitudinal, observational study of 44 patients with non-specific LBP receiving primary care physiotherapy in the period from May 2014 until March 2017. Eligible patients were invited to participate in the study when they first contacted the clinic seeking treatment for LBP. Kinematic measures and questionnaires were completed before the first consultation with the physiotherapist and at three and nine months follow-up. Inclusion criteria were current non-specific LBP of any duration as primary complaint, and age over 16 years. The exclusion criteria were insufficient language capabilities, severe neurologic signs, pregnancy and recent back surgery (in the preceding six months). For 10 persons, the baseline measurements of kinematic data were excluded due to technical problems. The current study was approved by the Regional Committee for Ethics in Medical Research (project no. 2013/2244 REK Mid-Norway), and the participants provided written informed consent. The study was carried out according to the Declaration of Helsinki.

2.2. Outcome variables

Primary outcome was disability measured by Oswestry Disability Index (ODI) (Fairbank and Pynsent, 2000; Roland and Fairbank, 2000). The ODI ranges from zero (not disabled at all) to 100 (completely disabled). Secondary outcomes were work ability and pain intensity. Work ability was measured by a single item question obtained from the Work Ability Index (Ahlstrom et al., 2010). The question: 'describe your current work ability compared with the lifetime best' was scored on an 11-point numerical rating scale (0–10), where zero represents 'completely unable to work' and 10 represent 'work ability at its best'. Pain intensity was measured on an 11-point Numeric Pain Rating Scale (Childs et al., 2005) (0–10, where zero represents no pain and 10 represent worst possible pain), where the participant were asked to report average pain intensity the last two weeks.

2.3. Kinematic measures

To assess range-of-motion (degrees from start to end of the movement) and peak angular velocity (degrees per second) of a sagittal spinal movement, the participants were instructed to perform a simple spinal flexion in standing position. The participants were instructed to stand with shoulder width distance between the feet, and arms along the side. They were asked to perform flexion as far as possible with the knees extended, and return to upright position (extension). They were not given any instruction on speed of the movement.

2.4. Kinematic data acquisition

Kinematic data during the flexion and extension were recorded by motion sensors attached to the skin over the spinous process Th6, using a Liberty motion tracker system (Polhemus, Inc, Colchester, Vermont, USA). Detailed information on the Liberty system can be found on the manufacturers' homepage (https://polhemus.com/motion-tracking/all-trackers/liberty). The system's source placed above the patients' head creates an electromagnetic field and captures the position and orientation of the body-worn sensors, related to other sensors or to the source, with a sampling rate of 240 Hz. Spinal motion was defined as movement of the sensor on Th6 relative to the source. Raw data were low pass filtered at 20 Hz using a second order Butterworth filter. A custom-built software program in Matlab was used to record the data and compute the kinematic variables.

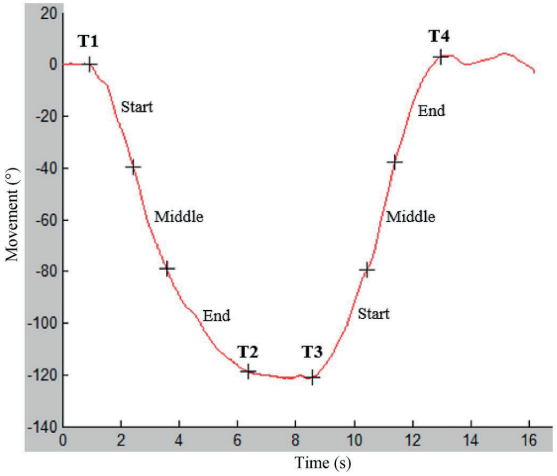

Fig. 1. An example of a curve of range-of-motion during standing flexion and extension (return from flexion to upright position). Zero on the y-axis represent the marker position at the point where the recording started. Start and end of spinal flexion (T1 and T2), and start and end of extension (T3 and T4) were defined as the points the velocity exceeded or fell below 5% of maximum speed, respectively. The flexion and extension phases were divided into three equal range segments: start-, middle- and end phase, based on range-of-motion between T1 and T2, and between T3 and T4.

2.5. Kinematic data analysis

Start and end of spinal flexion (T1 and T2) and extension (T3 and T4) were defined as the points when the velocity exceeded or fell below 5% of maximum velocity, respectively (Fig. 1). Range-of-motion was calculated as degrees of movement between T1 to T4. Peak angular velocity of the trunk was obtained separately from the flexion and extension phase of the spinal movement. To obtain a more detailed description of peak velocity in the flexion and extension movement phases, we split each movement in three equal segments based on the range-of-motion in each phase. The three equal range segments in the flexion and extension phases were labeled as start-, middle- and end phase between T1 and T2, and between T3 and T4. The split segments were analyzed separately.

2.6. Questionnaires

The Fear-Avoidance Beliefs Questionnaire (FABQ) (Waddell et al., 1993) was used to quantify negative fear-avoidance beliefs regarding pain. The questionnaire is divided into two subscales to address fear-avoidance beliefs related to physical activity (FABQ-PA) and work (FABQ-W). The total score on FABQ-PA (range 0–24) was calculated based on four items, and FABQ-W (range 0–42) based on seven items. Higher numbers indicate more fear-avoidance beliefs. The two subscales were transformed to relative scores (patient score/maximum score) in the longitudinal analyses to be able to compare the strength of the association with the outcomes.

2.7. Other variables

We obtained information on age (years), body height (cm) and weight (kg), education, work status and number of pain sites by

questionnaire. Level of education was determined by the question "what is your highest level of education?", with four possible categories: 'primary school', 'high school', 'college ≤4 years' and 'college > 4 years'. Current work status was categorized into 'paid work', unpaid work', 'retired', 'unemployed', 'student', 'sick leave' or 'disability pension'. Patients reported number of pain sites by marking pain-affected areas on a pain diagram (Kuorinka et al., 1987), with nine possible musculoskeletal pain areas: neck, shoulders/upper arms, upper back, elbows, low back, wrists/hands, hips, knees, and ankles/feet.

2.8. Statistical analyses

We estimated group changes in kinematic measures, FABQ-PA, and FABQ-W from baseline to three and nine months using mixed effects models with random intercept, which accounts for the dependency of observations within persons and utilize all available data for each person irrespective of missing data at some time points. The normality assumptions for random intercepts and residuals were assessed by histogram and QQ plots. We also performed fixed effects analyses to estimate the within-person longitudinal associations between each single kinematic variable and fear-avoidance beliefs with the three outcome variables disability, work ability and pain intensity. Here, each person serves as her/his own control, and confounding by time invariant factors such as age, gender and socioeconomic status were thus accounted for by design (Rabe-Hesketh and Skrondal, 2012; Allison, 2009). The within-person associations (presented in Tables 3 and 4) are interpreted as mean change with 95% confidence intervals of the outcome variables for each unit increase in the exposure variables compared to that person's exposure level at another time point. The within-person analyses of velocity were adjusted for range-of-motion due to a potential dependency between movement velocity and range of the spinal movement. It is not clear if pain intensity could confound the longitudinal associations, and we thus performed supplementary analyses with additional adjustment for pain intensity (except when pain intensity was the main variable of interest). Furthermore, we performed three sensitivity analyses where we (i) excluded 14 participants without complete follow-up information; (ii) included only persons who reported pain duration longer than nine months to assess whether long-term pain influenced the estimates (n = 23); and (iii) excluded participants with values < 8 points on FABQ-PA (n = 19) and < 10 points on FABQ-W (n = 18) at baseline, to investigate the associations among persons with more severe fear-avoidance beliefs. The cut off were based on median values of each subscale of the FABQ. Precision of the estimated associations was assessed by a 95% confidence interval. The statistical analyses were performed using Stata version 15.1.

3. Results

Characteristics of the participants at baseline, and at three and nine months follow-up are reported in Table 1. Nine per cent of the participants were lost to follow-up at three months, and 32 per cent at nine months follow-up. Twenty-eight out of 44 included participants were female (64%), total mean age was 42.8 years (range 16–74) and 62% reported to have had pain > 9 months.

Table 2 shows that range-of-motion increased from baseline to three months by 10.3° (95% CI 1.4 to 19.2) and from baseline to nine months by 8.0° (95% CI -1.6 to 17.6). Overall, peak velocity increased from baseline to three and nine months follow-up, and the flexion phase of the movement showed greatest change (16–24°/s). FABQ-PA and FABQ-W decreased 2.7 points (95% CI -4.5 to −1.3) and 2.1 points (95% CI -4.0 to −0.2) at three months, and decreased 3.4 points (95% CI -5.2 to −1.6) and 3.6 points (95% CI -5.8 to −1.5) at nine months, respectively. The change in all variables mainly occurred within three months.

Longitudinal within-person analyses is interpreted as the mean change in the outcome variables for each unit increase in the exposure variables compared to that person's exposure level at another time point. Table 3 shows that a one degree increase in range-of-motion compared to that person's range-of-motion at any other time point was weakly associated with less disability (−0.14 points, 95% CI -0.22 to −0.06). Peak velocity was not associated with either disability, work ability or pain intensity in analyses adjusted for range-of-motion. A 10% higher score in the FABQ-PA was associated with higher disability (1.50 points, 95% CI 0.51 to 2.49) and more pain (0.37 points, 95% CI 0.11 to 0.62) compared to that person's score at any other time points. A 10% higher score in the FABQ-W was associated with lower work ability (−0.37 points, 95% CI -0.68 to −0.05). When pain intensity was included as a covariate, the associations between FABQ-PA and disability, and between FABQ-W and work ability became weaker and

Table 1
Participant characteristics at each time of follow-up (baseline, three months, and nine months).

Characteristics	Baseline	3 months	9 months
Number of persons	44	40	30
Female (%)	28 (64%)	25 (63%)	17 (57%)
Age, mean (SD)	42.8 (14.8)	42.3 (15.4)	45.1 (14.7)
BMI, mean (SD)	25.4 (4.9)	25.5 (5.0)	26.1 (5.1)
Underweight, n (%)	1 (2%)	1 (3%)	0 (0%)
Normal weight, n (%)	20 (45%)	19 (48%)	15 (50%)
Overweight, n (%)	18 (41%)	15 (38%)	11 (37%)
Obese, n (%)	4 (9%)	4 (10%)	3 (10%)
Education ≤ 13 years[a], n (%)	24 (55%)	20 (50%)	14 (47%)
Average pain (0–10)[b], mean (SD)	5.4 (2.2)	2.9 (2.1)	2.6 (2.3)
Disability (0–100)[c], mean (SD)	23.6 (12.4)	14.4 (12.1)	12.5 (10.7)
Work ability (0–10)[d], mean (SD)	6.1 (2.4)	7.4 (2.5)	7.9 (2.3)
Pain sites (1–9), mean (SD)	2.9 (1.6)	3.0 (1.6)	2.6 (1.4)
On sick leave or disability leave, n (%)	6 (14%)	6 (15%)	2 (7%)

Abbreviations: BMI = body mass index.
[a] High school or below.
[b] 0 = 'no pain', and 10 = 'worst possible pain'.
[c] Measured by Oswestry Disability Index. Zero = 'not disabled at all', and 100 = 'completely disabled'.
[d] 0 = 'completely unable to work', and 10 = 'work ability at its best'.

Table 2
Kinematic measures during a standing spinal flexion/extension and fear-avoidance beliefs at baseline, as well as change from baseline to three and nine months follow-up (positive change values indicate an increase, whereas negative values indicate a decrease from baseline to each time point).

Measures (Th6 vs source)	Baseline mean (SD)	Mean (95% CI) change at 3 months[a]	Mean (95% CI) change at 9 months[a]
Range-of-motion[b], °	119.0 (25.1)	10.3 (1.4–19.2)	8.0 (−1.6 to 17.6)
Peak flexion velocity[c], °/s			
Start phase	61.0 (22.6)	18.7 (10.4–27.1)	23.9 (14.9–32.9)
Middle phase	62.8 (25.4)	17.9 (9.4–26.4)	24.3 (15.2–33.4)
End phase	47.2 (22.6)	16.1 (7.8–24.5)	20.5 (11.6–29.5)
Peak extension velocity[c], °/s			
Start phase	61.1 (23.9)	11.7 (2.7–20.7)	13.0 (3.3–22.7)
Middle phase	70.6 (26.1)	11.6 (2.9–20.4)	17.0 (7.6–26.4)
End phase	66.4 (32.8)	13.5 (3.3–23.7)	17.8 (6.9–28.8)
FABQ-PA, 0-24	8.8 (5.3)	−2.7 (−4.5 to −1.3)	−3.4 (−5.2 to −1.6)
FABQ-W, 0-42	11.3 (10.4)	−2.1 (−4.0 to −0.2)	−3.6 (−5.8 to −1.5)

Abbreviations: FABQ-PA = Fear-avoidance beliefs of physical activity; FABQ-W = Fear-avoidance beliefs of work; SD = standard deviation; CI = confidence interval.
[a] From baseline.
[b] From neutral position.
[c] The flexion and extension movement is divided in three equal segments: start-, middle- and end phase of the movement. Start- and endpoint of the movement were defined as where the movement reached 5% of maximum speed.

Table 3
Within-person changes in disability, work ability and pain intensity associated with fear-avoidance beliefs and kinematic measures during a standing spinal flexion/extension. All variables were measured at baseline, three and nine months. Estimates reflect changes per unit increase of the kinematic or FABQ variables.

Kinematic measures	Mean (95% CI) change in disability[a]	Mean (95% CI) change in work ability[b]	Mean (95% CI) change in pain intensity[c]
Range-of-motion[d], °	−0.14 (−0.22 to −0.06)	0.01 (−0.01 to 0.03)	−0.01 (−0.03 to 0.02)
Peak flexion velocity, °/s			
Start phase[e]	−0.08 (−0.18 to 0.02)	0.00 (−0.02 to 0.02)	−0.02 (−0.04 to 0.01)
Middle phase[e]	−0.05 (−0.16 to 0.05)	−0.01 (−0.03 to 0.01)	−0.02 (−0.05 to 0.01)
End phase[e]	−0.04 (−0.14 to 0.06)	−0.01 (−0.03 to 0.01)	−0.03 (−0.06 to 0.00)
Peak extension velocity, °/s			
Start phase[e]	0.01 (−0.08 to 0.10)	−0.01 (−0.03 to 0.01)	−0.01 (−0.03 to 0.02)
Middle phase[e]	0.00 (−0.10 to 0.10)	−0.01 (−0.03 to 0.01)	−0.01 (−0.03 to 0.02)
End phase[e]	−0.03 (−0.11 to 0.06)	−0.01 (−0.03 to 0.01)	−0.02 (−0.04 to 0.01)
FABQ-PA, pr 10% increase[f]	1.50 (0.51–2.49)	−0.11 (−0.30 to 0.08)	0.37 (0.11–0.62)
FABQ-W, pr 10% increase[f]	1.22 (−0.46 to 2.90)	−0.37 (−0.68 to −0.05)	0.33 (−0.09 to 0.76)

Abbreviations: FABQ-PA = Fear-avoidance belief questionnaire of physical activity; FABQ-W = Fear-avoidance belief questionnaire of work; CI = confidence interval.
[a] Measured by Oswestry Disability Index, range zero = 'not disabled at all' to 100 = 'completely disabled'.
[b] Range 0 = 'completely unable to work' to 10 = 'work ability at its best'.
[c] Average pain the last two weeks, range 0 = 'no pain' to 10 = 'worst possible pain'.
[d] From neutral position.
[e] Adjusted for range-of-motion.
[f] FABQ were transformed to relative scores of maximum score (patient score/maximum score) for each subscale, and where a one unit increase in FABQ represents 10% of the scale.

the confidence intervals included the null-value, i.e., 0.77 points (95% CI -0.17 to 1.70) and −0.27 points (95% CI -0.58 to 0.04) respectively.

Table 4 presents the longitudinal within-person associations between fear-avoidance beliefs and kinematic measures. A 10% higher score in the FABQ-PA showed weak associations with lower peak velocity at the start phase of the flexion movement (−3.3°/s, 95% CI -6.1 to −0.5). We found no associations between fear-avoidance beliefs and any of the kinematic measures in the extension movement phase (not shown in table). In supplementary analyses adjusting for pain intensity, the association became slightly weaker (−3.2°/s, 95% CI -6.3 to −0.1).

3.1. Sensitivity analyses

In the sensitivity analyses where we i) only included participants with complete follow-up information in the analyses, ii) excluded participants with pain duration less than nine months, and iii) excluded participants with the lowest score on FABQ, the associations remained largely similar, although with lower precision indicated by wider 95% confidence intervals.

4. Discussion

Of the kinematic measures, only larger range-of-motion during standing flexion/extension was longitudinally associated with reduced disability, albeit weakly. We found no associations between peak velocity and disability, work ability or pain intensity over time. Higher scores on the fear-avoidance subscale of physical activity were longitudinally associated with more severe disability and more pain, and higher scores on the subscale of work were associated with reduced work ability. Moreover, for this specific task and instruction, we found that fear-avoidance beliefs were not associated with range-of-motion, but with peak velocity at the start phase of the flexion movement. However, the overall clinical importance of these effects are likely small.

4.1. Kinematic measures

There is a large body of evidence suggesting that persons with LBP have impaired spinal movement compared to healthy controls (Laird et al., 2014; Gombatto et al., 2017). Whether the impairments are of clinical importance in relation to patient outcomes remains unclear. The present study suggested weak within-person associations between improved range-of-motion and reduced disability over time. Somewhat in line with this, correlation between change in range-of-motion and clinically important change in back pain and disability has previously been reported in a subgroup of patients with back pain only (Mieritz et al., 2014). Since we examined concurrent changes in range-of-motion and disability, the temporal relationship remains uncertain. Nevertheless, it is conceivable that range-of-motion could be a therapeutic target to reduce disability among people with LBP.

Change in peak velocity in the present study was not associated with changes in disability, work ability nor pain. Our results are in

Table 4
Within-person changes in kinematic measures during a standing spinal flexion associated with fear-avoidance beliefs of physical activity and work. All variables were measured at baseline, three and nine months. Estimates reflect changes per unit increase of the FABQ variables.

	Mean (95% CI) change in range-of-motion[a],°	Mean (95% CI) change in peak flexion velocity[b], °/s		
		Start phase	Middle phase	End phase
FABQ-PA, pr 10% increase[c]	0.5 (−3.0 to 4.1)	−3.3 (−6.1 to −0.5)	−2.4 (−5.2 to 0.4)	−2.5 (−5.4 to 0.5)
FABQ-W, pr 10% increase[c]	1.1 (−5.1 to 7.2)	−1.4 (−6.0 to 3.3)	−0.5 (−5.1 to 4.1)	1.1 (−3.6 to 5.8)

Abbreviations: FABQ-PA = Fear-avoidance belief questionnaire of physical activity; FABQ-W = Fear-avoidance belief questionnaire of work; CI = confidence interval.
[a] From neutral position.
[b] Adjusted for range-of-motion.
[c] FABQ were transformed to relative scores of max score (patient score/maximum score) for each subscale, and where a one unit increase in FABQ represents 10% of the scale.

concordance with previous studies that failed to identify an association between change in peak velocity and change in function, work status and pain intensity in patients with back pain (Mieritz et al., 2014; Poitras et al., 2000). Thus, along with previous findings, our results do not indicate that evaluating objective measures of peak velocity is relevant in a clinical setting. However, it should be noted that we only measured spinal kinematics during a flexion/extension movement, and that other movements could be more strongly associated with the outcome measures. Furthermore, we cannot rule out that subjective interpretation of the movement instructions may have influenced the participants' performance and thus the kinematic measures.

4.2. Fear-avoidance beliefs

Pain-related fear is considered an important psychological factor in development (Vlaeyen and Linton, 2012) and maintenance (Woby et al., 2004) of pain-related disability, and previous results indicate that fear-avoidance beliefs play an intermediate role in the relationship between spinal pain and disability (Lee et al., 2015). In line with this, our study found that higher score of fear-avoidance beliefs was associated with more severe self-reported disability, reduced work ability and more pain over time. Albeit modestly, fear-avoidance beliefs were consistently associated with all self-reported outcomes, thus our findings support that fear-avoidance beliefs are of importance in persons with LBP.

When we included pain intensity as a covariate in the model, the associations were further reduced, suggesting the importance of pain intensity in the relation between fear-avoidance beliefs and physical- and work related outcomes. The direction of the pathway between fear-avoidance beliefs and pain intensity is unclear, thus we cannot determine whether the reduced estimates are explained by either confounding or by mediating effect of pain intensity on the relation between fear-avoidance beliefs and disability and work ability. The initial low level of fear-avoidance beliefs in the present study may have influenced the results. However, we performed supplementary analyses on persons with moderate or high fear-avoidance beliefs only, which did not influence the conclusion of the study.

Few studies have previously investigated the associations between fear-avoidance beliefs and kinematic measures in persons with LBP, and the results are inconsistent (Thomas et al., 2008; Jette et al., 2016; Vaisy et al., 2015). There are some comparable studies of persons with neck pain, indicating that more fear of movement was associated with reduced peak velocity in sagittal neck movement (Meisingset et al., 2015; Vikne et al., 2013), which support our findings. However, none of these studies has investigated the associations between fear of movement and kinematics over time, and may therefore not be directly comparable to our study. The fear-avoidance model propose that the avoidance behavior occurs due to the person's anticipation of pain after an initial injury as well as response to pain (Vlaeyen and Linton, 2000, 2012). Hence, the initiating phase of the movement could be more susceptible to higher fear-avoidance beliefs. Together with previous findings (Vaisy et al., 2015), this is in line with our finding that higher score in fear-avoidance beliefs was associated with lower peak velocity only at the start phase of the movement.

4.3. Strengths and limitations

The main strength of this study was the repeated measure design with objective measures of lumbar kinematics at baseline, three and nine months follow-up. The measurement system used in the present study provided objective measures of spinal movement, and we obtained detailed information by dividing the movement into segments. The standing flexion/extension movements were performed with the participant's preferred speed, which is reported to produce more consistent measures of kinematics (McGregor and Hughes, 2000). Another strength of the present study was the estimation of within-person associations. The analysis method focuses on change within participants, in contrast to estimating the participants at group-level, which correspond to a clinical setting where the clinician typically performs individual assessments. Each person function as its own control, thus the estimates will not be confounded by measured or unmeasured time-invariant factors which otherwise can be difficult to account for.

It should be noted that the heterogeneity of the participants in the present study may influence the results, and must be considered in the interpretation. The present study included both acute, subacute and chronic LBP patients. However, we performed supplementary analyses on 23 persons with long-term pain only (more than nine months), which did not change the conclusion of the study. Furthermore, the patients reported low severity of disability, moderate work ability and low fear-avoidance beliefs at baseline, thus the results may be influenced by the relatively healthy study population. However, excluding 19 participants with low score of fear-avoidance beliefs for physical activity and 18 persons with low score of fear-avoidance beliefs for work did not change the estimates noteworthy. Finally, the relatively small sample size and high loss to follow-up resulted in low statistical power and wide confidence intervals for some of the associations in the present study. Complete case analyses (n = 30) did not change the results of the study.

4.4. Clinical implications

Physical therapists still have a largely biomechanical approach to treating LBP (Gardner et al., 2017). The present study does not support the clinical importance of evaluating detailed kinematic measures in relation to functional outcomes; however, we cannot rule out that the kinematics would have affected the outcome more convincingly if these aspects had been addressed specifically. Although the clinical importance is debatable, fear-avoidance beliefs were consistently associated with all self-reported outcomes, suggesting that addressing fear of movement in relation to self-reported outcomes may be of relevance. Finally, we cannot disregard that the relation between objectively measured kinematics and self-reported physical- and work related disability and pain intensity is complex, and a laboratory setting, as in the present study, may not truly uncover the complexity. Thus, generalizing the results into a clinical setting must be done with caution.

5. Conclusion

Of the kinematic measures, only range-of-motion showed within-person longitudinal associations, albeit weakly, with self-reported disability. Higher fear-avoidance beliefs of physical activity was longitudinally associated with higher self-reported disability and pain, whereas higher fear-avoidance beliefs of work was longitudinally associated with lower work ability. Further, higher fear-avoidance beliefs of physical activity were weakly associated with lower peak velocity in the start phase of the spinal flexion movement. However, due to the modest strength of the associations in the present study, the clinical importance remain unclear.

Conflicts of interest

None declared.

Ethical approval

The current study was approved by the Regional Committee for Ethics in Medical Research (project no. 2013/2244 REK Mid-Norway), and the participants provided written informed consent. The study was carried out according to the Declaration of Helsinki.

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